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PCT

Organizacion y Digitalizacion CSA Ltda

Industria y Comercio
SUPERINTENDENCIA
PROPIEDAD INDUSTRIAL
República de Colombia
Ministerio de Comercio, Industria y Turismo

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PARA EFECTOS DE CONSULTA
INVENTARIO

SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No. 10-69276

54. TITULO: **COMPUESTOS QUE CONTIENEN QUINOXALINA COMO INHIBIDORES DEL VIRUS DE LA HEPATITIS C**

52. CLASIFICACION INTERNACIONAL: **A01N 43/60, A61K 31/495**

71. SOLICITANTE: **ENANTA PHARMACEUTICALS, INC.**

DOMICILIO: **500 Arsenal Street, Watertown, MA 02472, ESTADOS UNIDOS DE AMERICA**

74. APODERADO: **Dra. MARGARITA CASTELLANOS A.**

22. BOGOTA, D.C., - 9 JUN. 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-069276- -00000-0000

Fecha: 2010-06-09 14:07:29 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 532

Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO
ADMISION A TRAMITE - NUEVAS CREACIONES

PATENTE DE INVENCION [ ] **MODELO DE UTILIDAD** [ ] **Art. 33 Decisión 486/00**

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

Completa [ ] Incompleta [ ]

PATENTE DE INVENCION PCT [X] **MODELO DE UTILIDAD PCT** [ ] **Art. 33 Decisión 486/00 Circular Única**

- [X] Indicación que se solicita una PCT
- [X] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [X] Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- [ ] Dibujos de ser estos pertinentes
- [X] Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [X] Incompleta [ ]

DISEÑO INDUSTRIAL [ ] **(Art. 119 Decisión 486/00)**

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

Completa [ ] Incompleta [ ]

ESQUEMA DE TRAZADO [ ] **(Art. 92 Decisión 486/00)**

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

Completa [ ] Incompleta [ ]

000001

PETITO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-069276- -00000-0000
Fecha: 2010-06-09 14:07:29 Dep: 2020 DIR NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 532

dicación

FORMULARIO UNICO DE SOLICITUD DE PATENTES PCT ENTRADA EN FASE NACIONAL

SOLICITUD DE:

(1)

[X] **Patente de Invención.** [ ] **Patente de Modelo de Utilidad.**

[X] **Capítulo I** [ ] **Capítulo II**

(2) **SOLICITANTE (71)**

Nombre: **ENANTA PHARMACEUTICALS, INC.**
Dirección: **500 Arsenal Street**
Watertown, MA 02472
ESTADOS UNIDOS DE AMERICA
Nacionalidad o Domicilio: **Watertown, MA**
ESTADOS UNIDOS DE AMERICA
Lugar de Constitución: **Delaware, ESTADOS UNIDOS DE AMERICA**

Teléfono: Fax:
E-mail:

IDENTIFICACIÓN
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Número ____ Cual ____

(3) **REPRESENTANTE O APODERADO**

Nombre: **MARGARITA CASTELLANOS A.**
Dirección: **CALLE 94A No. 7A-09**
Teléfono: **7560770** Fax: **7550158**
E-mail: info@castellanosvco.com

IDENTIFICACIÓN
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ] Cual ____
Número **39'779.654** TPA **70.819**

(4) **INVENTOR (ES) (72)**

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ZHE WANG
67 Westwoods Blvd.
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ESTADOS UNIDOS DE AMERICA

(5) **PCT (86)**

Solicitud Internacional No. **PCT/US2008/083541** Fecha **14/11/2008**

Publicación Internacional No. **WO 2009/064975 A1** Fecha **22/05/2009**

(6) **Título (54)** **COMPUESTOS QUE CONTIENEN QUINOXALINA COMO INHIBIDORES DEL VIRUS DE LA HEPATITIS C**

(7) **Clasificación Internacional (51)** **A01N 43/60, A61K 31/495**

(8) **Prioridad** SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	14/11/2007	60/987,958
US	01/02/2008	61/025,458

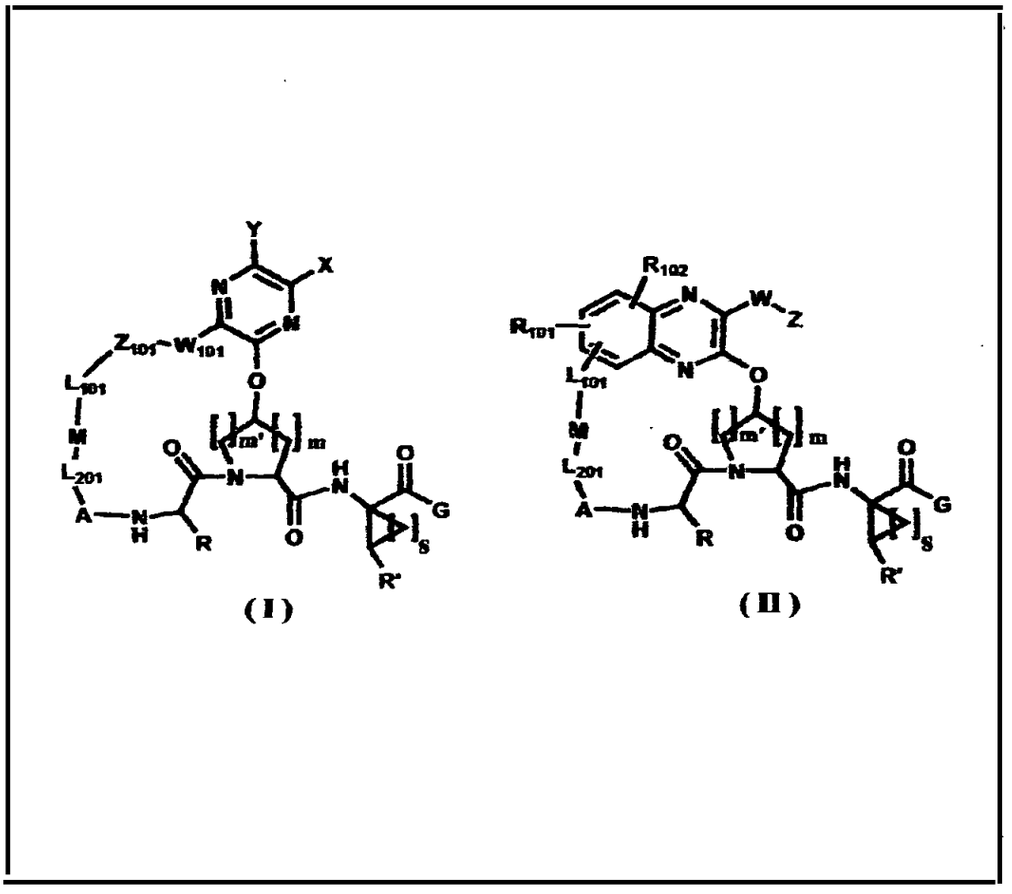
(9) **Comprobantes de pago Nos.** **10-4,574, 10-44,843, 10-15,973 y 10-41,093** **Fecha** **Mayo 28, Junio 2, Marzo 1 y Mayo 20, 2010**

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, junto con la sustitución del mismo a mi favor
- [ ] 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 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: **Tarjeta Propietario, Extracto para la publicación**

(11) FIGURA CARACTERISTICA:



(12) Solicito la concesión de la patente,

NOMBRE: **MARGARITA CASTELLANOS ABONDANO**

FIRMA:

C.C. No. 39'779.654 Usaquén - TPA 70.819 C.S.J.

- 9 JUN. 2010

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página. - MCA/gcb - P1976

000003

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 10 - 43,574
FECHA : MAYO 28 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-069276- -00000-0000

Fecha 2010-06-09 14 07:29 Dep. 2020 DIR NUEVASCR
Tra 11 PATENTEIYII Eve 378 FASENACIONALI
Act 411 PRESENTACION Folios 532

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	324715635	28/05/2010	3,290,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	111	PTC SOLICITUD DE PATENTE DE MODEL	325,000.00
			TOTAL : $	325,000.00

SON: TRESCIENTOS VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

000004

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 44,843
FECHA : JUNIO 2 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-069276- -00000-0000
Fecha: 2010-06-09 14:07:29 Dep: 2020 DIR NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 532

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	324715613	02/06/2010	5,753,000.00

***** 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 AÑO ANTR	229,000.00
			TOTAL : $	229,000.00

SON: DOSCIENTOS VEINTINUEVE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

000005

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 15,973
FECHA : MARZO 1 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-069276- -00000-0000
Fecha 2010-06-09 14 07 29 Dep 2020 DIR NUEVASCR
Tra 11 PATENTEIYII Eve: 378 FASENACIONALI
Act 411 PRESENTACION Folios: 532

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	325591405	01/03/2010	2,377,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54 INFORMACION DETALLADA DE UN TRAMI	26,000.00
		TOTAL : $	26,000.00

SON: VEINTISEIS MIL PESOS

RESPONSABLE: _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

000006

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 41,093
FECHA : MAYO 20 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-069276- -00000-0000
Fecha: 2010-06-09 14:07:29 Dep: 2020 DIR NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 532

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	353132301	20/05/2010	17,063,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
19	50005-01-01 SOLICITUDES	*** REIVINDICACION UNITARIA ADICIONAL	494,000.00
		TOTAL : $	494,000.00

SON: CUATROCIENTOS NOVENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 May 2009 (22.05.2009)

PCT

(10) International Publication Number
WO 2009/064975 A1

000007

(51) International Patent Classification:
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(21) International Application Number:
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(22) International Filing Date:
14 November 2008 (14.11.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/987,958 14 November 2007 (14.11.2007) US
61/025,458 1 February 2008 (01.02.2008) US

(71) Applicant *(for all designated States except US)*: **ENANTA PHARMACEUTICALS, INC.** [US/US]; 500 Arsenal Street, Watertown, MA 02472 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GAI, Yonghua** [US/US]; 13 Valley View Drive, North Grafton, MA 01536 (US). **OR, Yat, Sun** [US/US]; 169 Fayette Street, Watertown, MA 02472 (US). **WANG, Zhe** [US/US]; 67 Westwoods Blvd., Hockessin, DE 19707 (US).

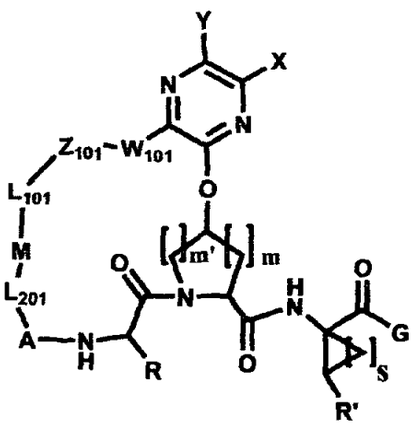
(74) Agents: **HARLAN, Edgar, W.** et al.; Elmore Patent Law Group, PC, 515 Groton Road, Unit 1R, Westford, MA 01886 (US).

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

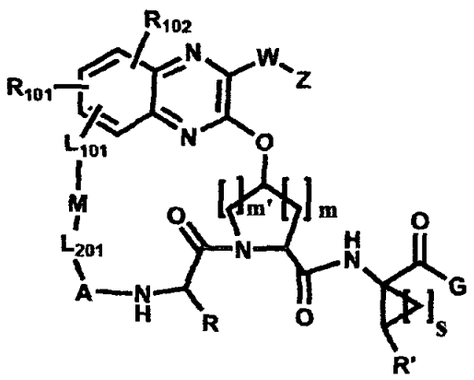
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS,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

Published:
— *with international search report*

(54) Title: QUINOXALINE-CONTAINING COMPOUNDS AS HEPATITIS C VIRUS INHIBITORS



(I)



(II)

(57) Abstract: The present invention discloses compounds of formula I and II or pharmaceutically acceptable salts, esters, or prodrugs thereof which inhibit serine protease activity, particularly the activity of hepatitis C virus (HCV) NS3-NS4A protease. Consequently, the compounds of the present invention interfere with the life cycle of the hepatitis C virus and are also useful as antiviral agents. The present invention further relates to pharmaceutical compositions comprising the aforementioned compounds for administration to a subject suffering from HCV infection. The invention also relates to methods of treating an HCV infection in a subject by administering a pharmaceutical composition comprising the compounds of the present invention.

WO 2009/064975 A1

QUINOXALINE-CONTAINING COMPOUNDS AS HEPATITIS C VIRUS INHIBITORS

RELATED APPLICATIONS

This application claims the benefit of US provisional application number 60/987,958 filed on November 14, 2007 and US provisional application number 61/025,458 filed on February 1, 2008. The contents of the above applications are incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to novel hepatitis C virus (HCV) protease inhibitor compounds having antiviral activity against HCV and useful in the treatment of HCV infections. More particularly, the invention relates to quinoxaline-containing compounds, compositions containing such compounds and methods for using the same, as well as processes for making such compounds.

BACKGROUND OF THE INVENTION

HCV is the principal cause of non-A, non-B hepatitis and is an increasingly severe public health problem both in the developed and developing world. It is estimated that the virus infects over 200 million people worldwide, surpassing the number of individuals infected with the human immunodeficiency virus (HIV) by nearly five fold. HCV infected patients, due to the high percentage of individuals inflicted with chronic infections, are at an elevated risk of developing cirrhosis of the liver, subsequent hepatocellular carcinoma and terminal liver disease. HCV is the most prevalent cause of hepatocellular cancer and cause of patients requiring liver transplantations in the western world.

There are considerable barriers to the development of anti-HCV therapeutics, which include, but are not limited to, the persistence of the virus, the genetic diversity of the virus during replication in the host, the high incident rate of the virus developing drug-resistant mutants, and the lack of reproducible infectious culture systems and small-animal models for HCV replication and pathogenesis. In a majority of cases, given the mild course of the infection and the complex biology of the liver, careful consideration must be given to antiviral drugs, which are likely to have significant side effects.

Only two approved therapies for HCV infection are currently available. The original treatment regimen generally involves a 3-12 month course of intravenous interferon-α (IFN-α), while a new approved second-generation treatment involves co-treatment with IFN-α and the general antiviral nucleoside mimics like ribavirin. Both of these treatments suffer from interferon related side effects as well as low efficacy against HCV infections. There exists a need for the development of effective antiviral agents for treatment of HCV infection due to the poor tolerability and disappointing efficacy of existing therapies.

In a patient population where the majority of individuals are chronically infected and asymptomatic and the prognoses are unknown, an effective drug would desirably possess significantly fewer side effects than the currently available treatments. The hepatitis C non-structural protein-3 (NS3) is a protcolytic enzyme required for processing of the viral polyprotein and consequently viral replication. Despite the huge number of viral variants associated with HCV infection, the active site of the NS3 protease remains highly conserved thus making its inhibition an attractive mode of intervention. Recent success in the treatment of HIV with protease inhibitors supports the concept that the inhibition of NS3 is a key target in the battle against HCV.

HCV is a flaviridae type RNA virus. The HCV genome is enveloped and contains a single strand RNA molecule composed of circa 9600 base pairs. It encodes a polypeptide comprised of approximately 3010 amino acids.

The HCV polyprotein is processed by viral and host peptidase into 10 discreet peptides which serve a variety of functions. There are three structural proteins, C, E1 and E2. The P7 protein is of unknown function and is comprised of a highly variable sequence. There are six non-structural proteins. NS2 is a zinc-dependent metalloproteinase that functions in conjunction with a portion of the NS3 protein. NS3 incorporates two catalytic functions (separate from its association with NS2): a serine protease at the N-terminal end, which requires NS4A as a cofactor, and an ATP-ase-dependent helicase function at the carboxyl terminus. NS4A is a tightly associated but non-covalent cofactor of the serine protease.

The NS3-NS4A protease is responsible for cleaving four sites on the viral polyprotein. The NS3-NS4A cleavage is autocatalytic, occurring in cis. The remaining three hydrolyses, NS4A-NS4B, NS4B-NS5A and NS5A-NS5B all occur in trans. NS3 is a

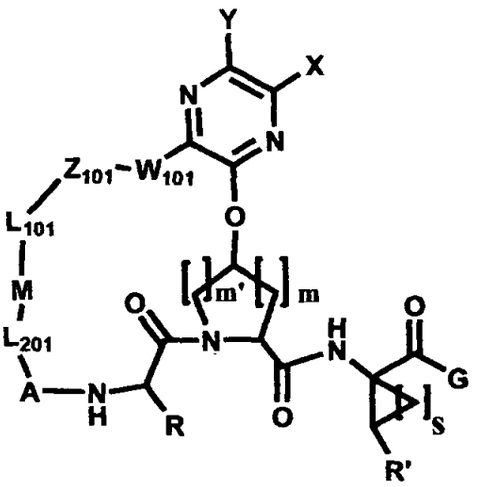
serine protease which is structurally classified as a chymotrypsin-like protease. While the NS serine protease possesses proteolytic activity by itself, the HCV protease enzyme is not an efficient enzyme in terms of catalyzing polyprotein cleavage. It has been shown that a central hydrophobic region of the NS4A protein is required for this enhancement. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficacy at all of the sites.

A general strategy for the development of antiviral agents is to inactivate virally encoded enzymes, including NS3, that are essential for the replication of the virus. Current efforts directed toward the discovery of NS3 protease inhibitors were reviewed by S. Tan, A. Pause, Y. Shi, N. Sonenberg, Hepatitis C Therapeutics: Current Status and Emerging Strategies, *Nature Rev. Drug Discov.* 1, 867-881 (2002).

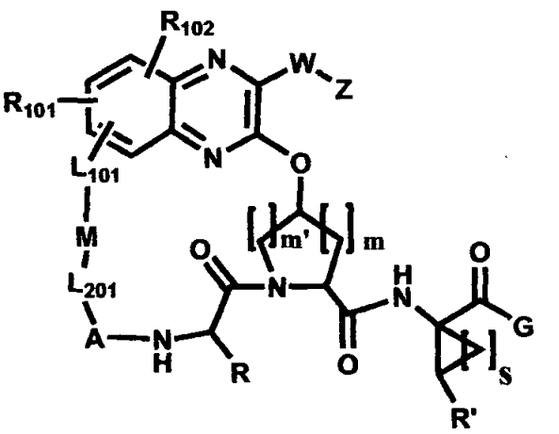
SUMMARY OF THE INVENTION

The present invention relates to quinoxaline-containing compounds and pharmaceutically acceptable salts, esters or prodrugs thereof, and methods of using the same to treat hepatitis C infection in a subject in need of such therapy. Compounds of the present invention interfere with the life cycle of the hepatitis C virus and are also useful as antiviral agents. The present invention further relates to pharmaceutical compositions comprising the aforementioned compounds, salts, esters or prodrugs for administration to a subject suffering from HCV infection. The present invention further features pharmaceutical compositions comprising a compound of the present invention (or a pharmaceutically acceptable salt, ester or prodrug thereof) and another anti-HCV agent, such as interferon (e.g., alpha-interferon, beta-interferon, consensus interferon, pegylated interferon, or albumin or other conjugated interferon), ribavirin, amantadine, another HCV protease inhibitor, or an HCV polymerase, helicase or internal ribosome entry site inhibitor. The invention also relates to methods of treating an HCV infection in a subject by administering to the subject a pharmaceutical composition of the present invention. The present invention further relates to pharmaceutical compositions comprising the compounds of the present invention, or pharmaceutically acceptable salts, esters, or prodrugs thereof, in combination with a pharmaceutically acceptable carrier or excipient.

In one embodiment of the present invention there are disclosed compounds represented by Formulas I or II, or pharmaceutically acceptable salts, esters, or prodrugs thereof:



(I)



(II)

Wherein

A is absent or selected from –(C=O)–, $-S(O)_2$, -C=N-OR_1 or –C(=N-CN);

L_{201} is absent or selected from -C_1-C_8 alkylene, –C_2-C_8 alkenylene, or –C_2-C_8 alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted –C_1-C_8 alkylene, substituted –C_2-C_8 alkenylene, or substituted –C_2-C_8 alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; –C_3-C_{12} cycloalkylene, or substituted –C_3-C_{12} cycloalkylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; –C_3-C_{12} cycloalkenylene, or substituted –C_3-C_{12} cycloalkenylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N;

M is absent or selected from O, S, SO, SO_2 or NR_1; wherein R_1 is selected at each occurrence from the group consisting of:

(i) hydrogen;

(ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

(iii) heterocycloalkyl or substituted heterocycloalkyl;

(iv) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted C_2-C_8 alkenyl, or substituted $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;

L_{101} is absent or selected from $-C_1-C_8$ alkylene, $-C_2-C_8$ alkenylene, or $-C_2-C_8$ alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkylene, substituted $-C_2-C_8$ alkenylene, or substituted $-C_2-C_8$ alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkylene, or substituted $-C_3-C_{12}$ cycloalkylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkenylene, or substituted $-C_3-C_{12}$ cycloalkenylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N;

Z_{101} is absent or selected from aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

W_{101} is absent or selected from $-O-$, $-S-$, $-NR_1-$, -C(O)- or $-C(O)NR_1-$;

X and Y taken together with the carbon atoms to which they are attached to form a carbocyclic moiety or a heterocyclic moiety. The carbocyclic or heterocyclic moiety can be selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, or substituted heterocylic;
or X and Y together can form a C_2-C_8-alkylene group or a C_2-C_8-heteroalkylene group.
R_{101} and R_{102} are independently selected from the group consisting of:

(i) hydrogen, halogen, CN, CF_3, N_3, NO_2, OR_1, SR_1, SO_2R_2, $-NHS(O)_2-R_2$, $-NH(SO_2)NR_3R_4$, NR_3R_4, CO_2R_1, COR_1, $CONR_1R_2$, $N(R_1)COR_2$;

(ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

(iii) heterocycloalkyl or substituted heterocycloalkyl;

(iv) $-C_1$-C_8 alkyl, $-C_2$-C_8 alkenyl, or $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1$-C_8 alkyl, substituted $-C_2$-C_8 alkenyl, or substituted $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3$-C_{12} cycloalkyl, or substituted $-C_3$-C_{12} cycloalkyl; $-C_3$-C_{12} cycloalkenyl, or substituted $-C_3$-C_{12} cycloalkenyl;

R and R' are each independently selected from the group consisting of:

(i) $-C_1$-C_8 alkyl, $-C_2$-C_8 alkenyl, or $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1$-C_8 alkyl, substituted $-C_2$-C_8 alkenyl, or substituted $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3$-C_{12} cycloalkyl, or substituted $-C_3$-C_{12} cycloalkyl; $-C_4$-C_{12} alkylcycloalkyl, or substituted $-C_4$-C_{12} alkylcycloalkyl; $-C_3$-C_{12} cycloalkenyl, or substituted $-C_3$-C_{12} cycloalkenyl; $-C_4$-C_{12} alkylcycloalkenyl, or substituted $-C_4$-C_{12} alkylcycloalkenyl;

(ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

(iii) heterocycloalkyl or substituted heterocycloalkyl;

(iv) hydrogen; deuterium;

or R' is C_1-C_8-alkyl substituted with one or more halogen atoms, preferably one or more fluorine, chlorine or bromine atoms. Preferably, R' is $-CHQ_1Q_2$, where Q_1 and Q_2 are independently selected from halogen; preferably F, Cl and Br;

G is selected from –OH, $-NHS(O)_2-R_2$, $-NH(SO_2)NR_3R_4$, and NR_3R_4;

R_2 is selected from:

(i) aryl; substituted aryl; heteroaryl; substituted heteroaryl

(ii) heterocycloalkyl; substituted heterocycloalkyl;

(iii) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N, substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl; heterocylic; substituted heterocyclic;

R_3 and R_4 are independently selected from:

(i) hydrogen;

(ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

(iii) heterocycloalkyl or substituted heterocycloalkyl;

(iv) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl; heterocyclic, or substitututed heterocyclic;

alternatively, R_3 and R_4 are taken together with the nitrogen they are attached to form a heterocyclic or substituted heterocyclic;

Z is selected from the groups consisting of:

(i) hydrogen;

(ii) CN;

(iii) N_3;

(iv) halogen;

(v) $-NH-N=CHR_1$;

(vi) aryl, substituted aryl;

(vii) heteroaryl, substituted heteroaryl;

(viii) $-C_3-C_{12}$ cycloalkyl, substituted $-C_3-C_{12}$ cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl;

(ix) $-C_1-C_6$ alkyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

(x) $-C_2-C_6$ alkenyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

(xi) $-C_2-C_6$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

W is absent, or selected from alkylene, alkenylene, alkynylene, –O–, –S–, $-NR_1-$, $-C(O)NR_1-$, or -C(O)–;

m is 0, 1, 2 or 3; preferably 1;

m' is 0, 1, 2 or 3; preferably 1; and

s is 1, 2, 3 or 4; preferably 1.

In one subset of the compounds of Formulas I and II:

M is absent or selected from O or NR_1;

Z_{101} is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

W_{101} is absent, or selected from –O–, –S–, –NH-, -N(Me)-, -C(O)NH-, or -C(O)N(Me)-;

X and Y taken together with the carbon atoms to which they are attached to form a cyclic moiety which selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocylic;

R_{101} and R_{102} are independently selected from the group consisting of:

(i) hydrogen, halogen, CN, CF_3, NO_2, OR_1, SR_1, $-NHS(O)_2-R_2$, $-NH(SO_2)NR_3R_4$, NR_3R_4, CO_2R_1, COR_1, $CONR_1R_2$, $N(R_1)COR_2$;

(ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

(iii) heterocycloalkyl or substituted heterocycloalkyl;

(iv) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;

R_3 and R_4 are independently selected from:

(i) hydrogen;

(ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

(iii) heterocycloalkyl or substituted heterocycloalkyl;

(iv) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl; heterocyclic, or substituted heterocyclic;

W is absent, or selected from alkylene, alkenylene, alkynylene, –O–, –S–, –NH-, -N(Me)-, -C(O)NH-, or -C(O)N(Me)-;

m = 0, 1, or 2;

m' = 1 or 2; and

s is 1.

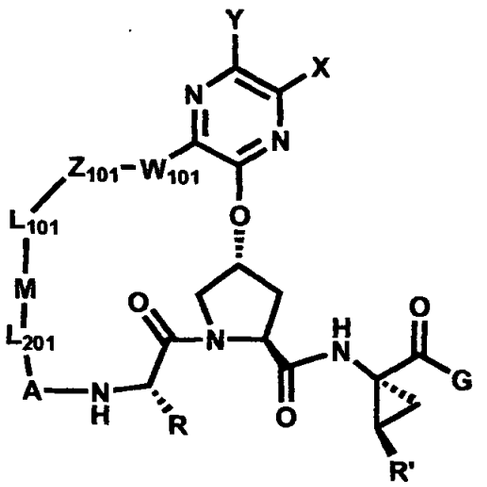
In another embodiment, the present invention features pharmaceutical compositions comprising a compound of the invention, or a pharmaceutically acceptable salt, ester or prodrug thereof. In still another embodiment of the present invention there are disclosed pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt, ester or prodrug thereof, in

combination with a pharmaceutically acceptable carrier or excipient. In yet another embodiment of the invention are methods of treating a hepatitis C infection in a subject in need of such treatment with said pharmaceutical compositions.

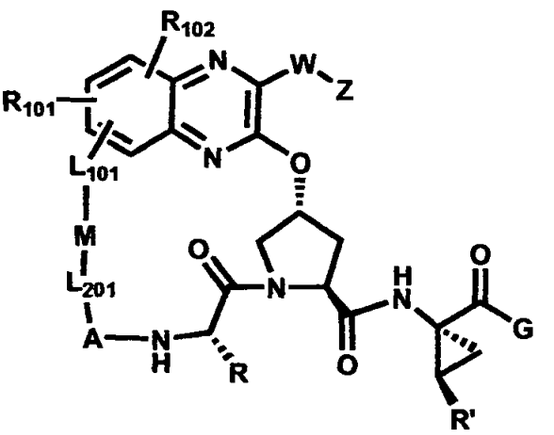
Detailed Description of the Invention

A first embodiment of the invention is a compound represented by Formula I or Formula II as described above, or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient.

Other embodiments of the invention are compounds represented by Formula III or IV:



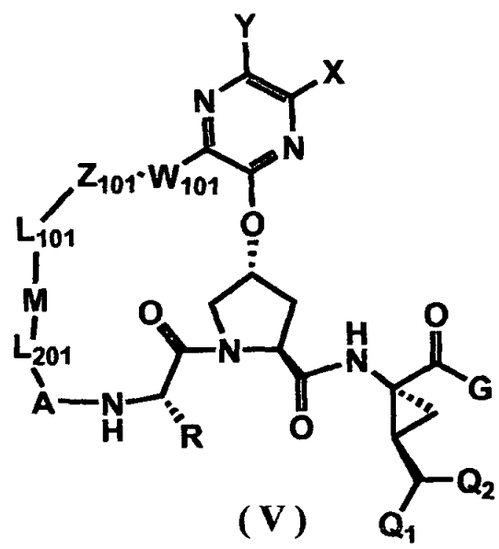
(III)



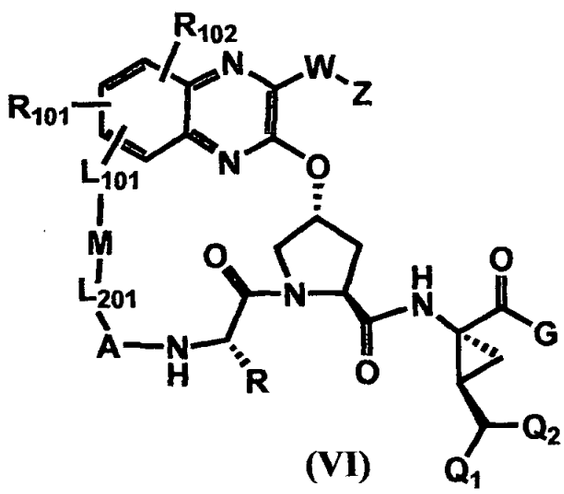
(IV)

or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where R, R', A, L_{201}, M, L_{101}, Z_{101}, W_{101}, X, Y, R_{101}, R_{102}, W, Z, and G are as previously defined.

Other embodiments of the invention are compounds represented by Formula V or VI:



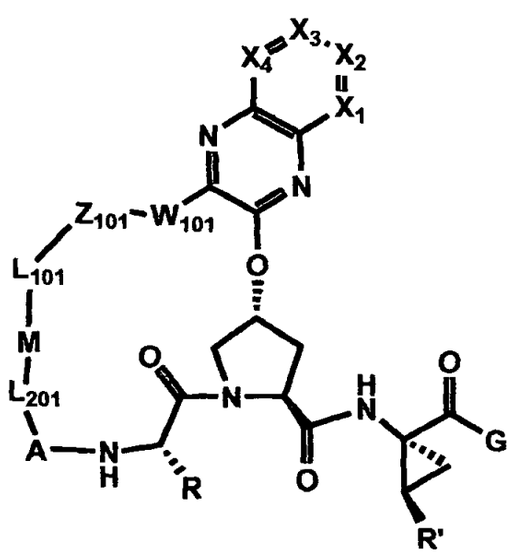
(V)



(VI)

or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where Q_1 and Q_2 are independently fluorine, chlorine or bromine, and where R, A, L_{201}, M, L_{101}, Z_{101}, W_{101}, X, Y, R_{101}, R_{102}, W, Z, and G are as previously defined. In particularly preferred embodiments, Q_1 and Q_2 are both fluorine.

Another embodiment of the invention is a compound represented by Formula VII:



(VII)

or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where X_1-X_4 are independently selected from $-CR_5$ and N, wherein R_5 is independently selected from:

(i) hydrogen; halogen; $-NO_2$; -CN; N_3; CF_3;

(ii) $-M-R_4$, M is O, S, NH;

(iii) NR_3R_4;

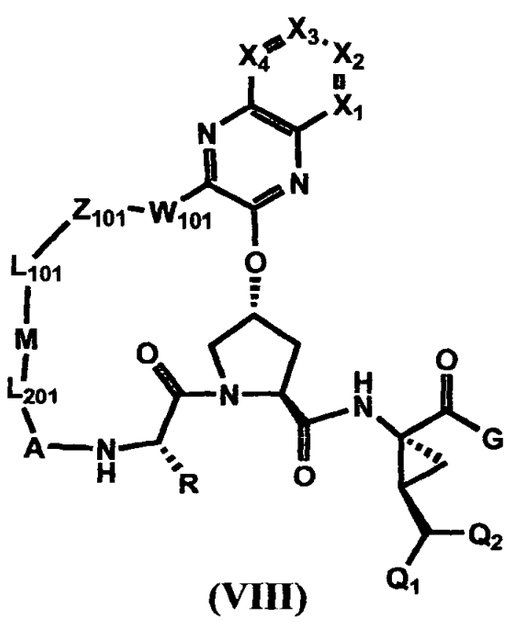
(iv) $-C_1$-C_8 alkyl, $-C_2$-C_8 alkenyl, or $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1$-C_8 alkyl, substituted $-C_2$-C_8 alkenyl, or substituted $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3$-C_{12} cycloalkyl, or substituted $-C_3$-C_{12} cycloalkyl; $-C_3$-C_{12} cycloalkenyl, or substituted $-C_3$-C_{12} cycloalkenyl;

(v) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

(vi) heterocycloalkyl or substituted heterocycloalkyl;

where R_3, R_4, R, R', A, L_{201}, M, L_{101}, Z_{101}, W_{101} and G are as previously defined.

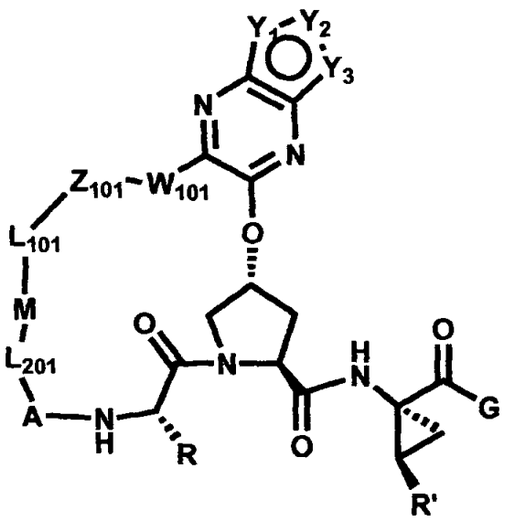
Another embodiment of the invention is a compound represented by Formula VIII:



(VIII)

or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, wherein X_1-X_4 are as defined for Formula VII, and R, A, Q_1, Q_2, L_{201}, M, L_{101}, Z_{101}, W_{101} and G are as previously defined.

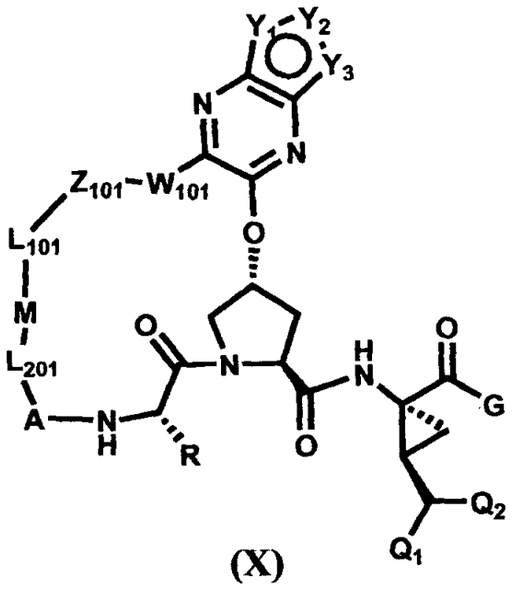
Another embodiment of the invention is a compound represented by Formula IX:



(IX)

or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where Y_1-Y_3 are independently selected from CR_5, N, NR_5, S and O; where R_5, R, R', A, L_{201}, M, L_{101}, Z_{101}, W_{101} and G are as previously defined.

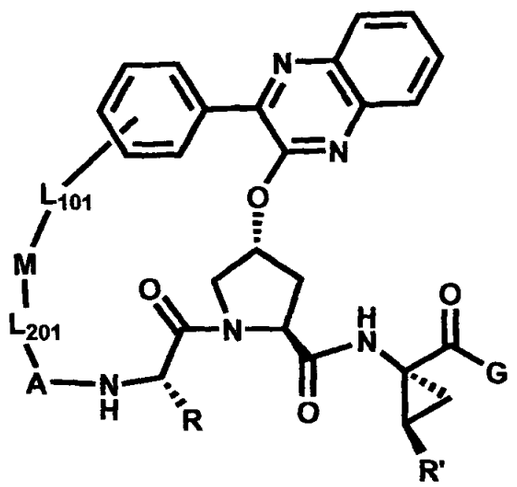
Another embodiment of the invention is a compound represented by Formula X:



(X)

a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where Y_1-Y_3 are as defined for Formula IX, and R, Q_1, Q_2, A, L_{201}, M, L_{101}, Z_{101}, W_{101} and G are as previously defined.

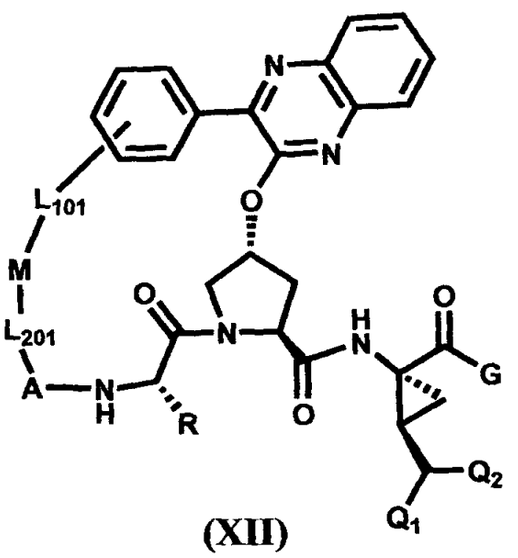
Another embodiment of the invention is a compound represented by Formula XI:



(XI)

or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where R, R', A, L_{201}, M, L_{101} and G are as previously defined.

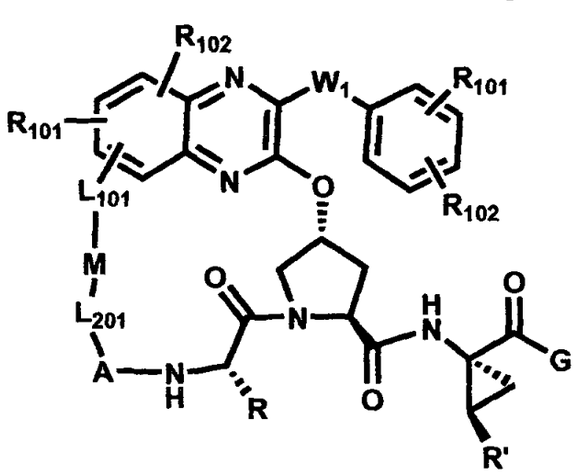
Another embodiment of the invention is a compound represented by Formula XII:



(XII)

a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where R, Q_1, Q_2, A, L_{201}, M, L_{101} and G are as previously defined.

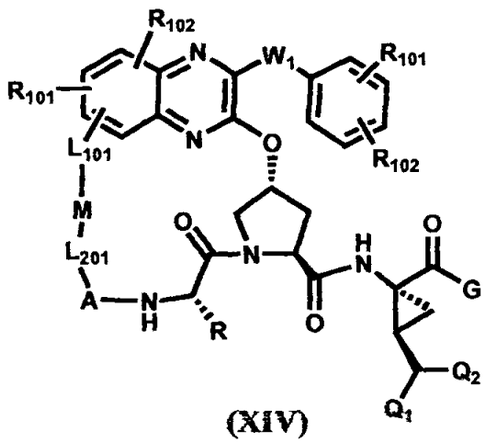
Another embodiment of the invention is a compound represented by Formula XIII:



(XIII)

or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where W_1 is absent or selected from C_1-C_4 alkylene, C_2-C_4 alkenylene, C_2-C_4 alkynylene; where R, R', A, L_{201}, M, L_{101}, R_{101}, R_{102} and G are as previously defined.

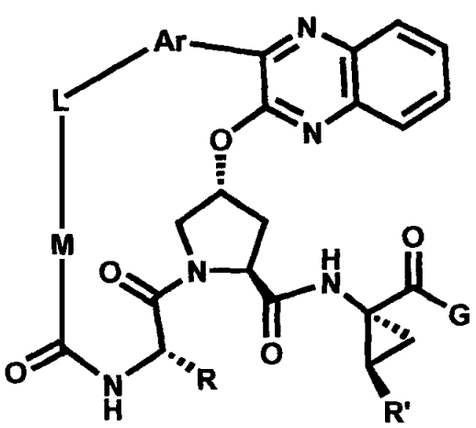
Another embodiment of the invention is a compound represented by Formula XIV:



(XIV)

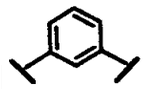
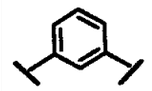
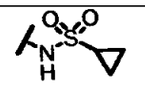
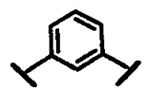
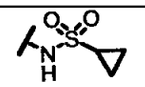
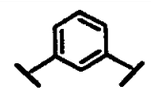
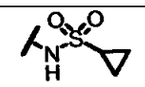
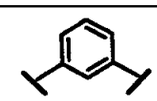
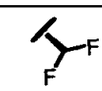
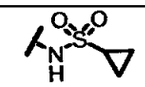
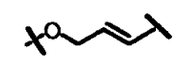
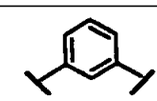
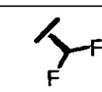
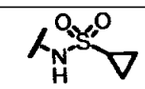
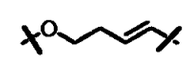
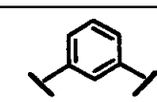
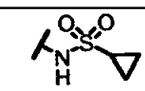
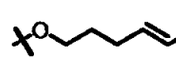
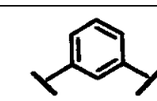
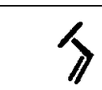
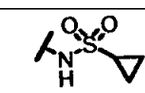
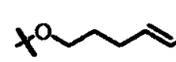
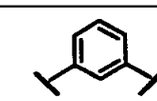
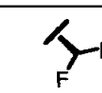
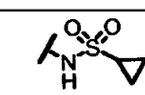
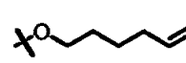
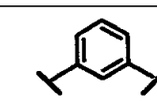
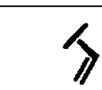
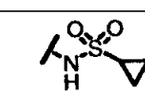
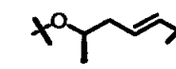
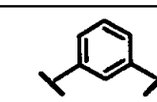
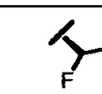
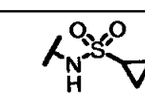
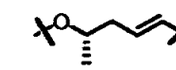
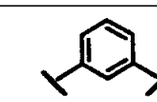
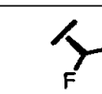
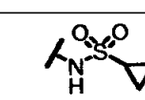
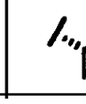
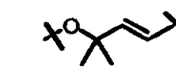
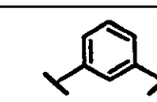
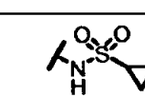
a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where W_1 is as defined for Formula XIII, and R, Q_1, Q_2, A, L_{201}, M, L_{101}, R_{101}, R_{102} and G are as previously defined.

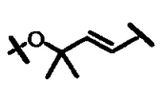
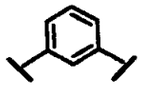
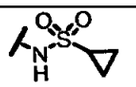
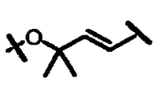
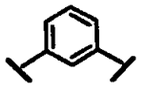
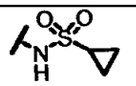
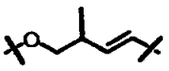
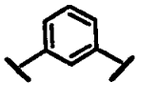
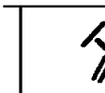
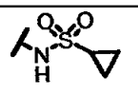
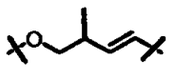
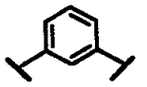
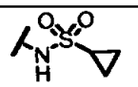
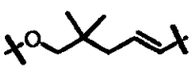
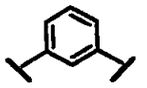
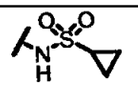
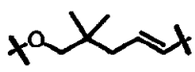
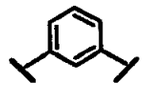
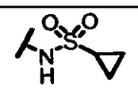
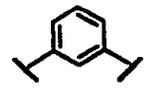
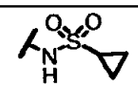
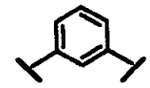
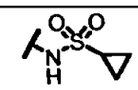
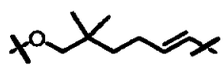
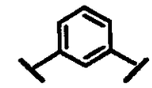
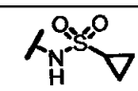
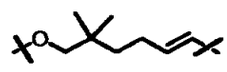
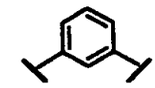
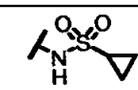
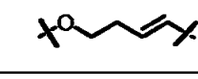
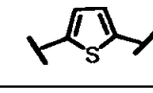
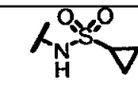
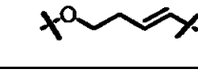
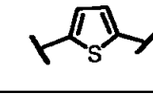
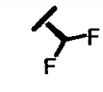
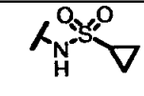
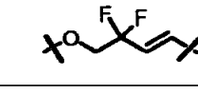
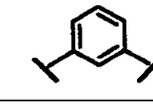
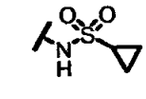
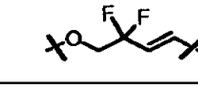
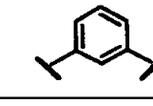
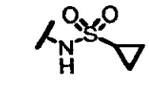
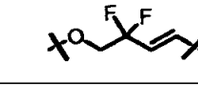
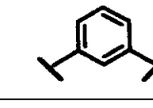
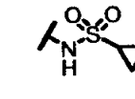
Representative compounds of the invention include, but are not limited to, the following compounds (Table 1) according to Formula XV wherein R, M-L, Ar, R' and G are delineated for each example in Table 1.

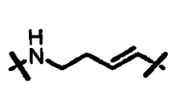
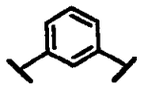
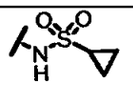
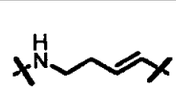
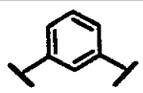
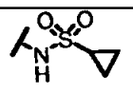
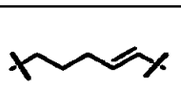
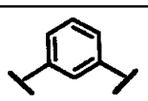
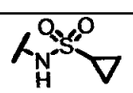
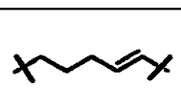
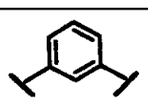
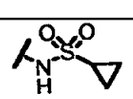
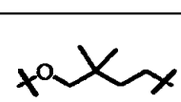
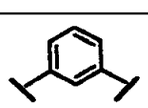
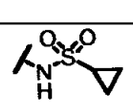
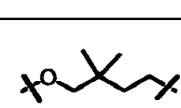
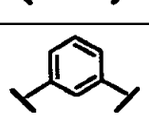
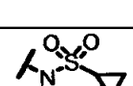
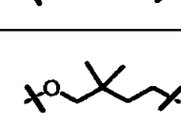
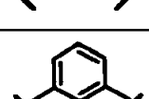
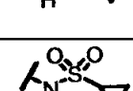
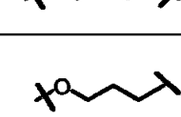
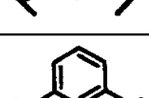
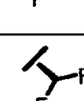
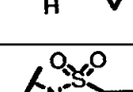
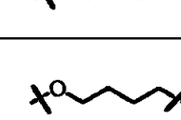
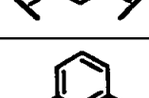
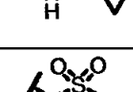
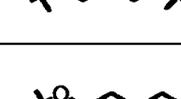
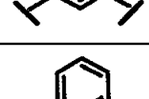
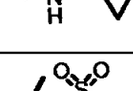
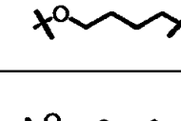
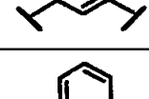
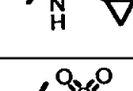
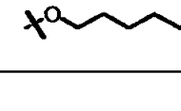
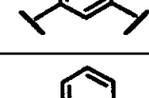
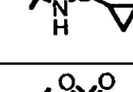
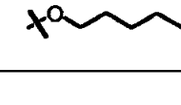
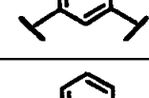
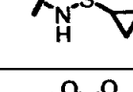
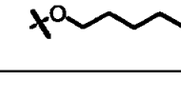
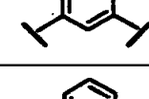
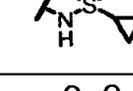
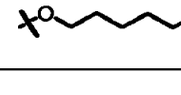
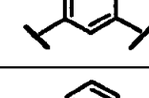
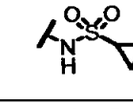


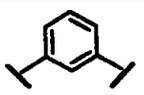
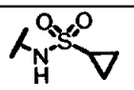
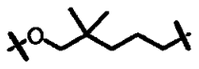
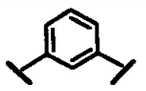
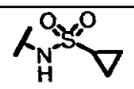
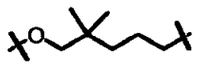
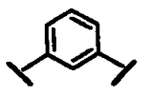
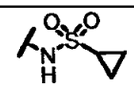
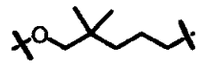
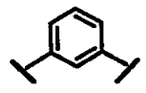
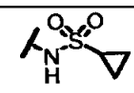
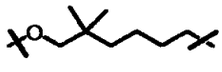
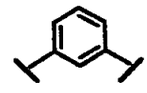
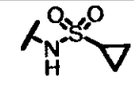
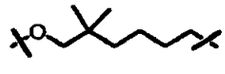
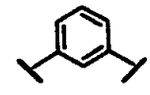
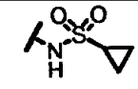
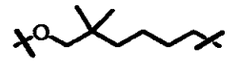
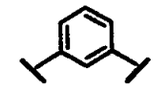
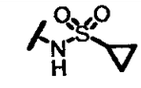
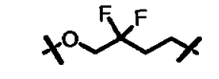
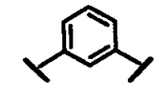
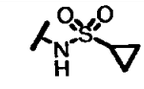
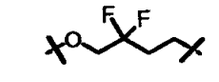
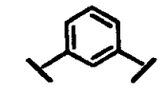
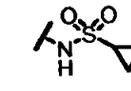
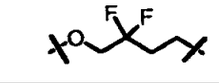
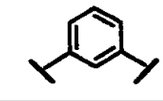
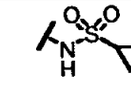
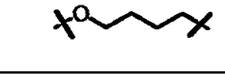
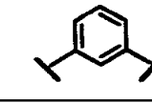
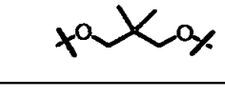
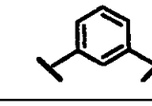
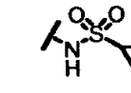
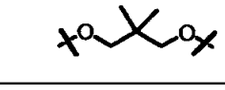
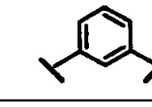
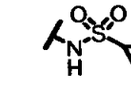
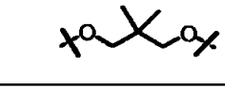
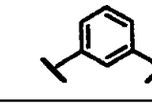
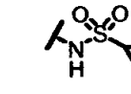
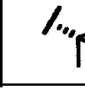
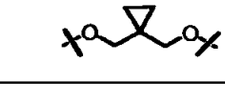
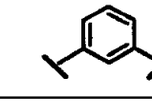
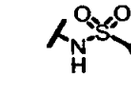
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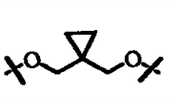
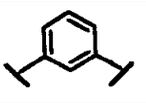
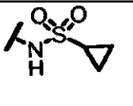
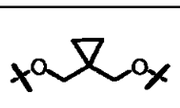
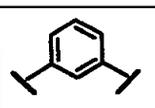
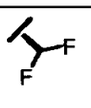
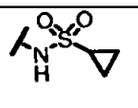
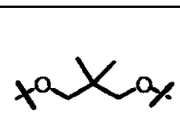
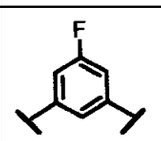
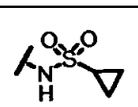
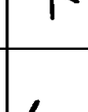
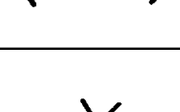
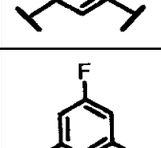
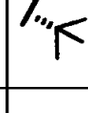
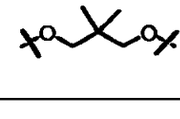
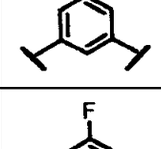
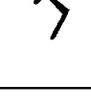
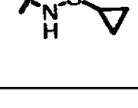
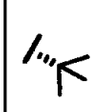
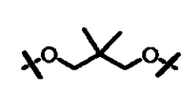
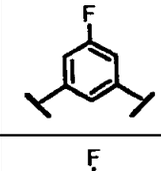
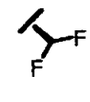
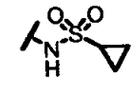
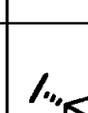
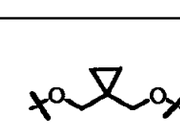
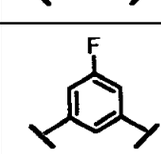
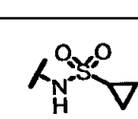
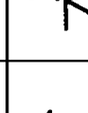
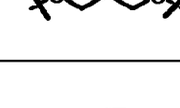
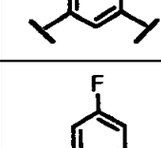
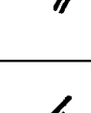
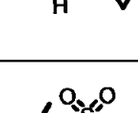
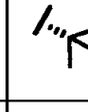
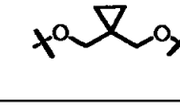
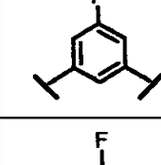
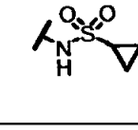
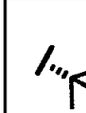
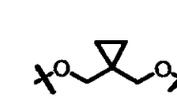
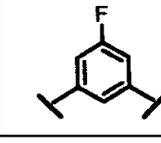
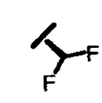
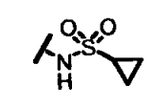
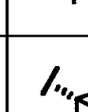
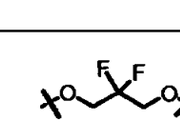
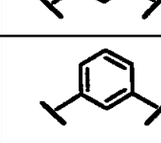
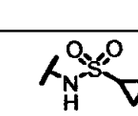
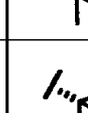
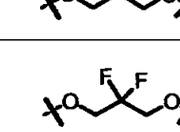
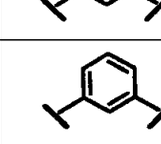
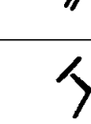
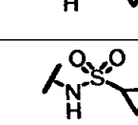
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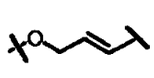
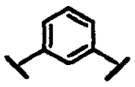
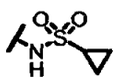
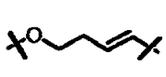
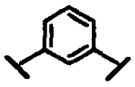
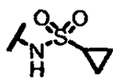
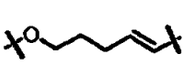
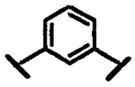
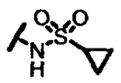
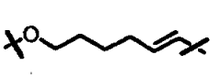
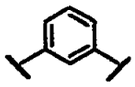
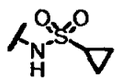
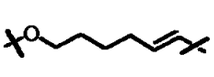
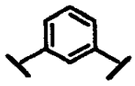
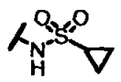
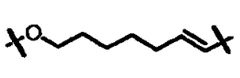
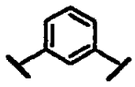
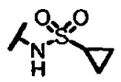
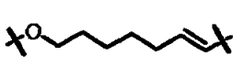
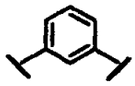
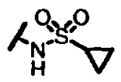
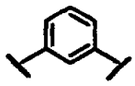
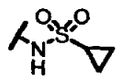
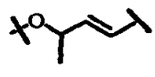
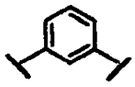
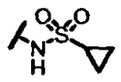
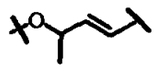
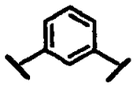
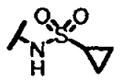
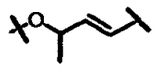
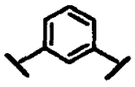
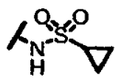
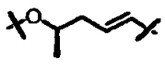
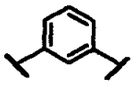
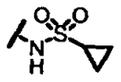
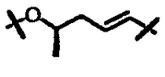
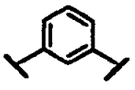
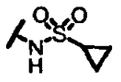
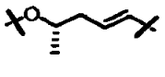
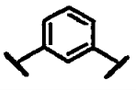
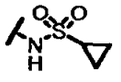
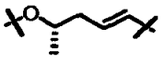
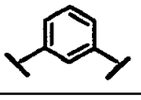
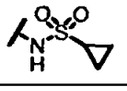
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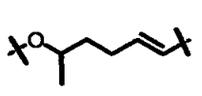
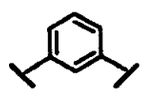
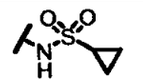
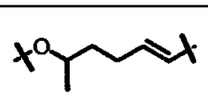
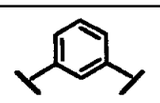
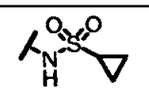
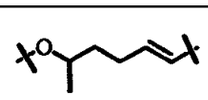
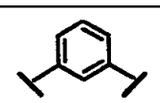
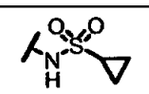
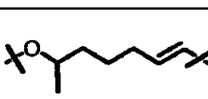
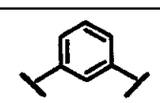
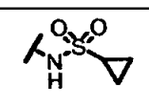
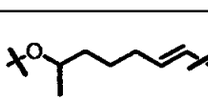
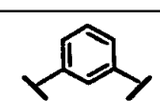
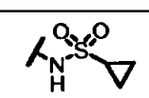
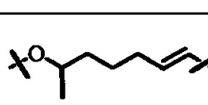
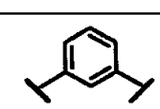
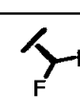
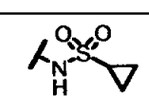
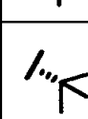
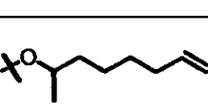
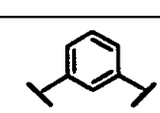
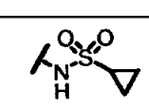
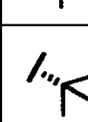
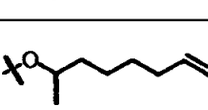
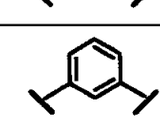
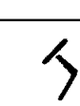
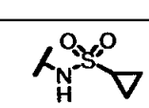
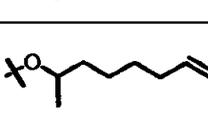
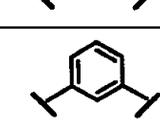
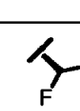
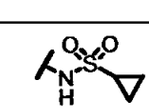
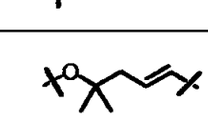
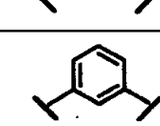
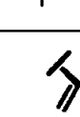
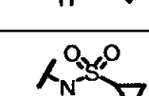
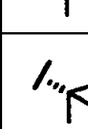
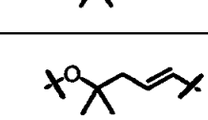
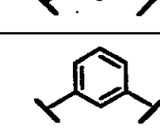
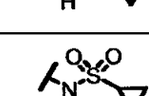
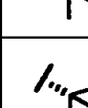
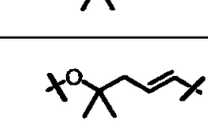
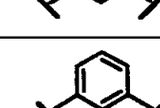
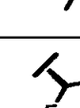
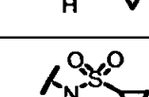
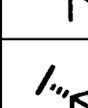
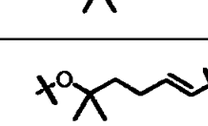
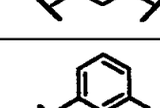
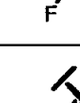
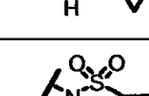
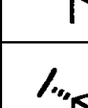
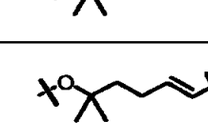
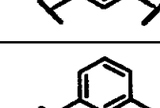
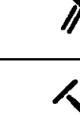
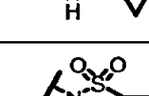
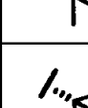
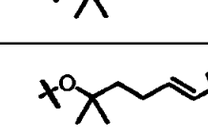
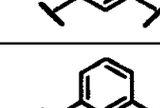
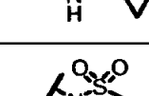
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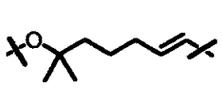
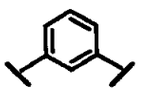
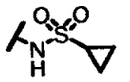
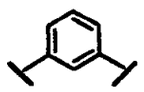
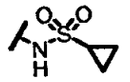
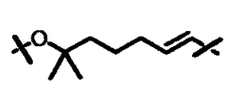
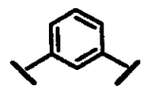
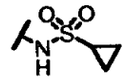
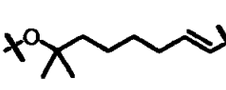
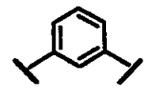
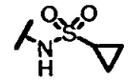
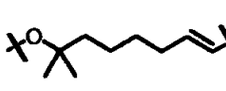
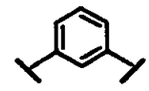
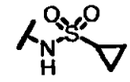
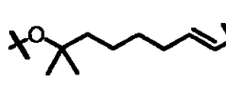
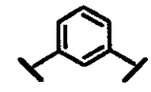
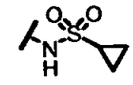
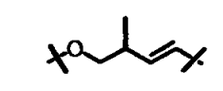
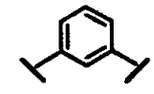
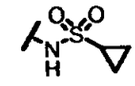
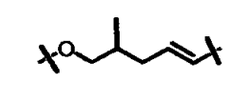
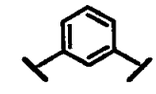
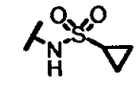
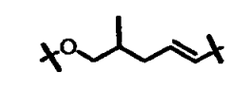
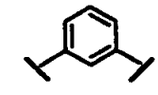
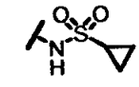
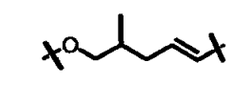
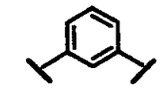
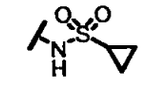
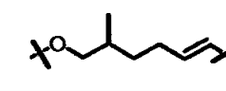
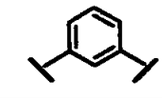
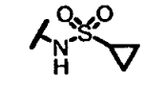
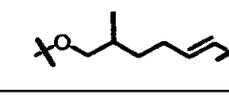
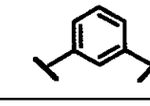
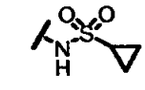
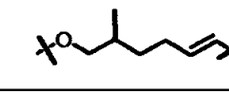
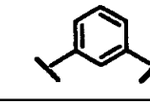
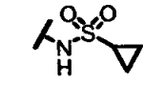
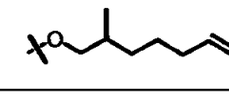
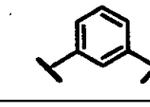
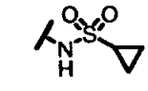
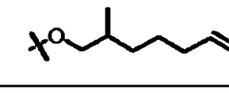
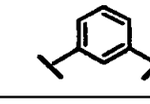
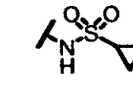
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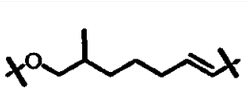
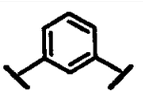
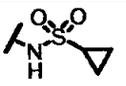
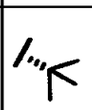
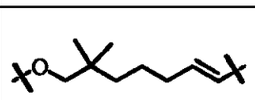
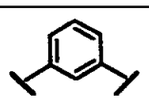
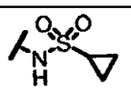
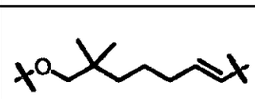
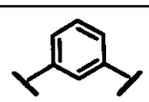
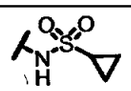
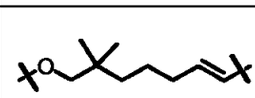
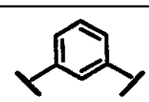
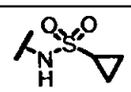
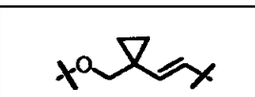
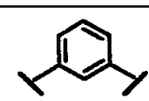
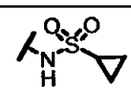
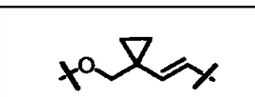
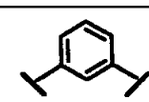
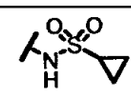
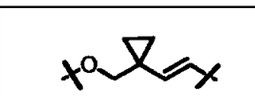
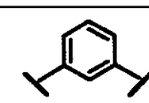
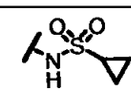
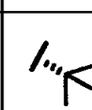
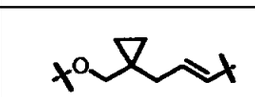
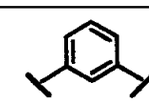
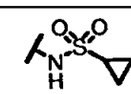
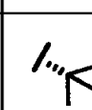
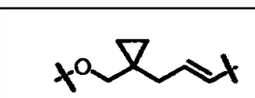
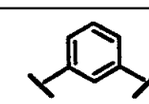
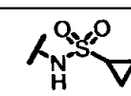
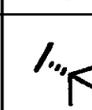
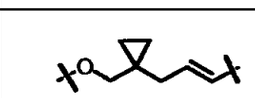
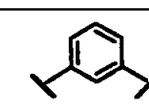
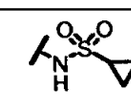
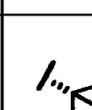
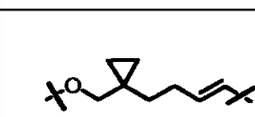
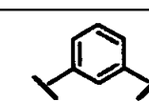
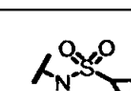
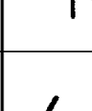
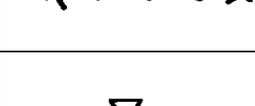
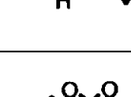
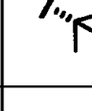
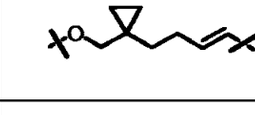
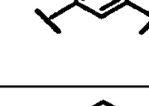
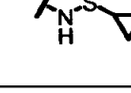
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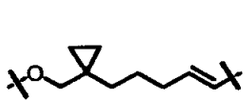
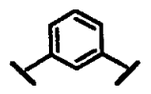
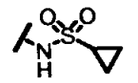
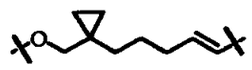
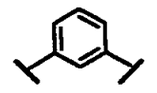
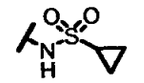
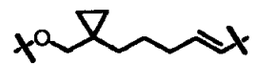
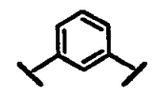
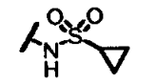
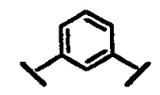
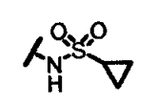
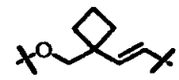
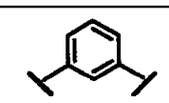
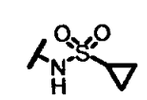
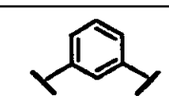
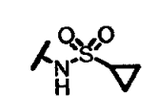
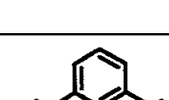
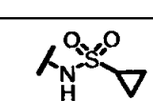
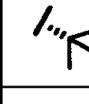
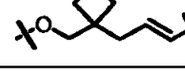
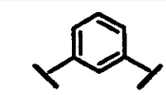
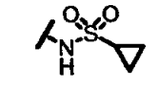
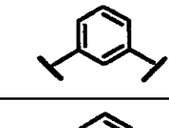
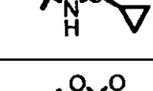
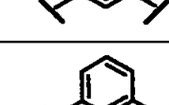
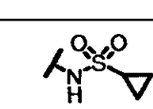
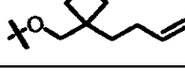
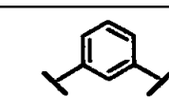
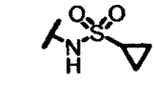
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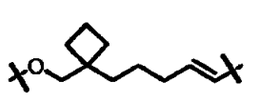
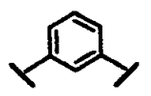
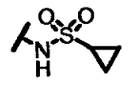
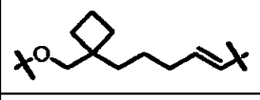
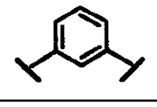
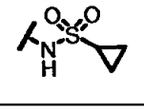
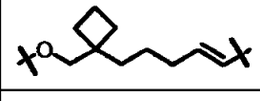
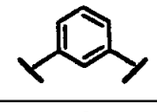
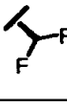
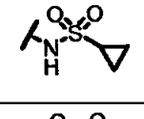
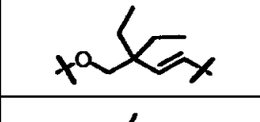
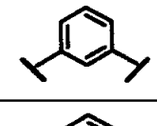
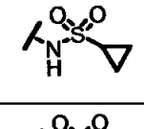
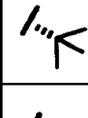
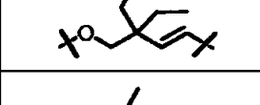
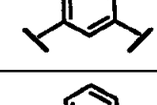
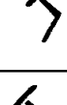
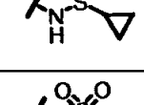
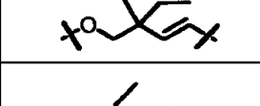
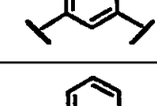
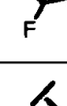
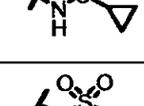
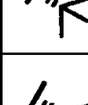
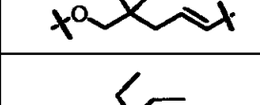
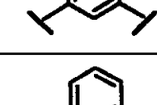
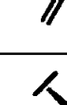
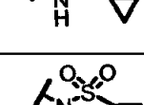
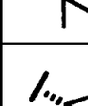
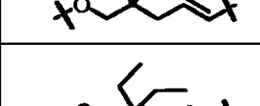
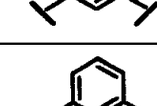
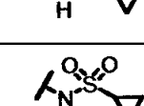
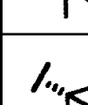
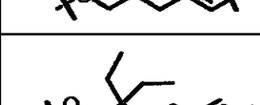
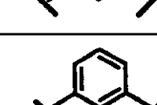
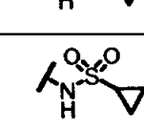
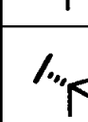
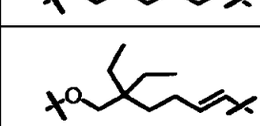
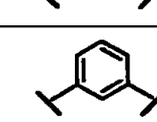
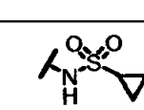
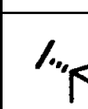
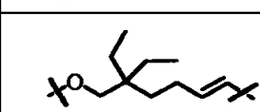
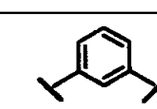
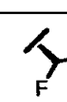
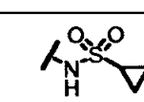
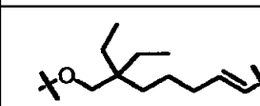
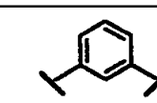
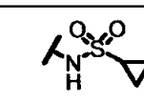
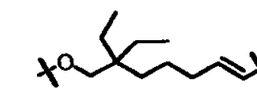
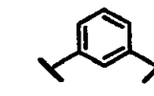
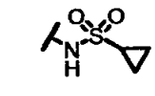
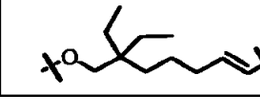
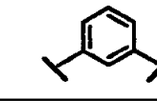
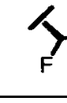
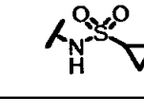
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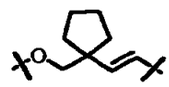
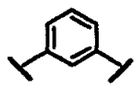
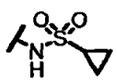
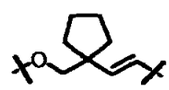
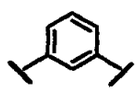
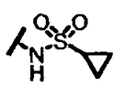
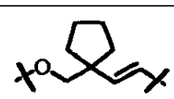
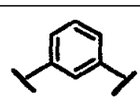
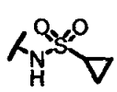
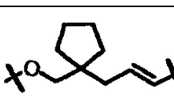
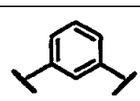
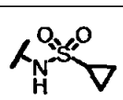
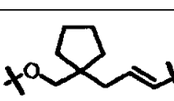
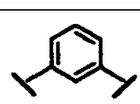
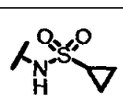
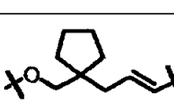
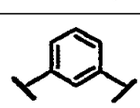
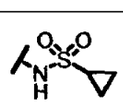
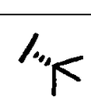
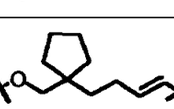
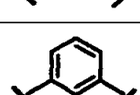
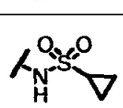
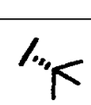
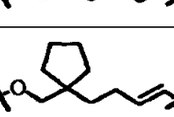
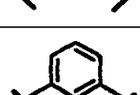
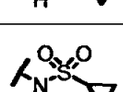
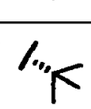
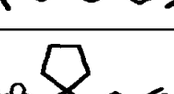
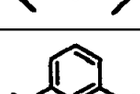
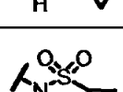
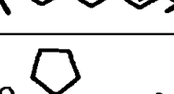
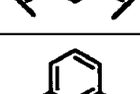
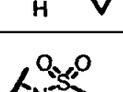
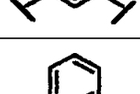
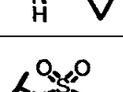
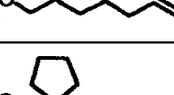
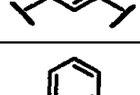
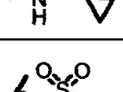
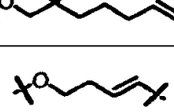
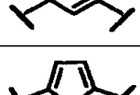
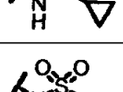
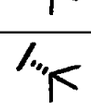
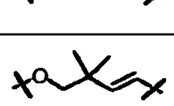
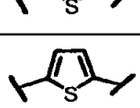
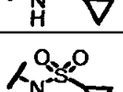
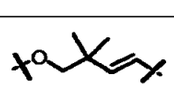
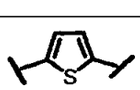
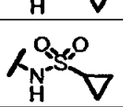
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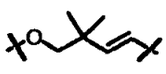
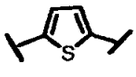
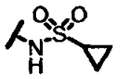
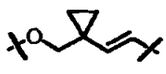
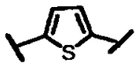
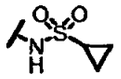
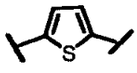
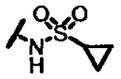
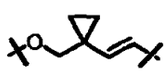
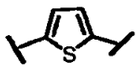
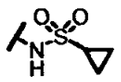
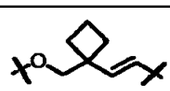
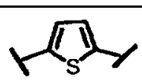
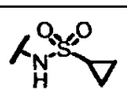
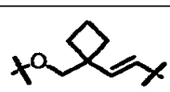
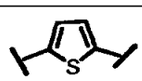
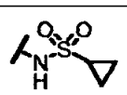
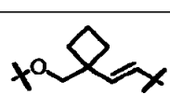
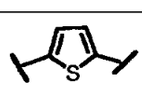
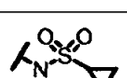
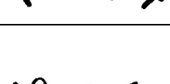
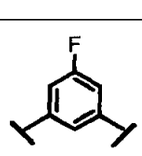
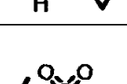
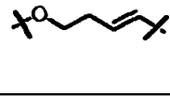
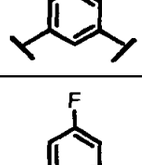
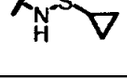
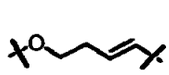
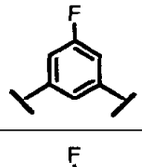
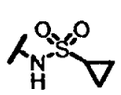
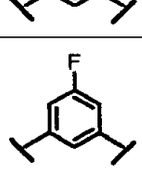
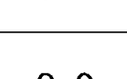
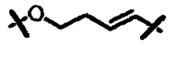
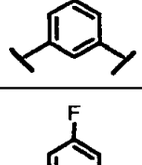
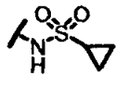
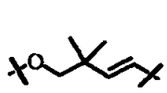
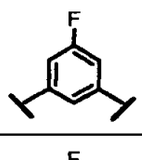
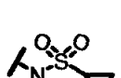
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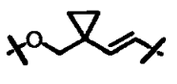
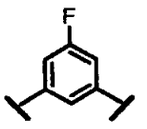
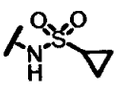
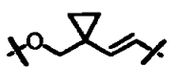
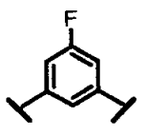
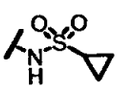
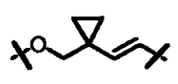
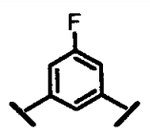
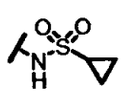
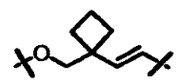
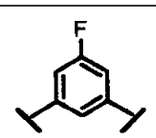
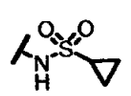
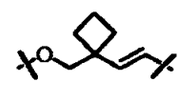
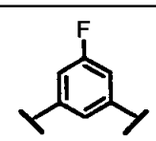
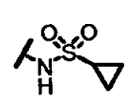
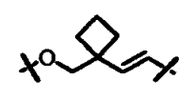
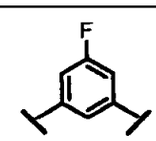
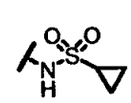
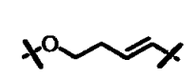
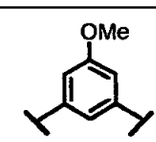
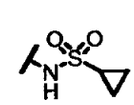
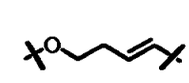
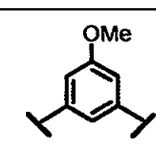
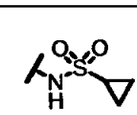
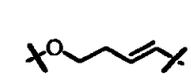
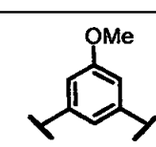
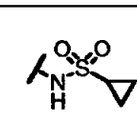
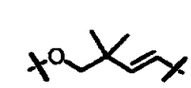
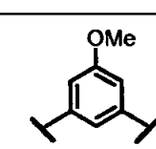
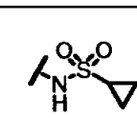
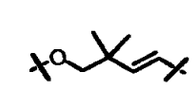
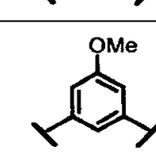
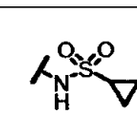
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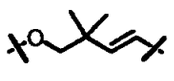
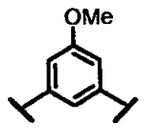
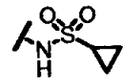
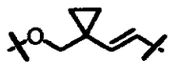
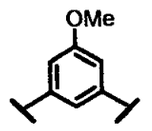
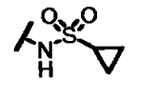
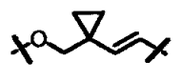
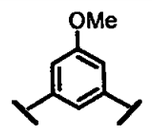
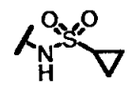
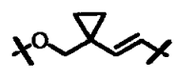
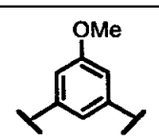
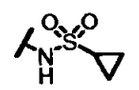
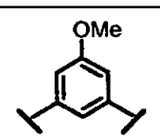
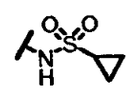
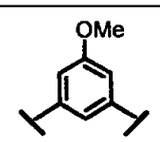
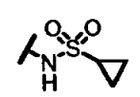
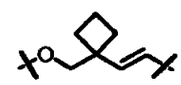
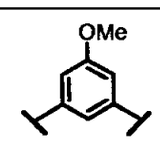
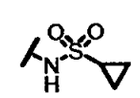
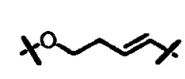
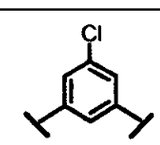
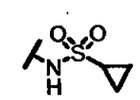
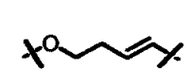
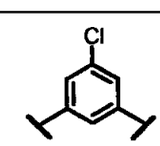
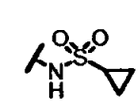
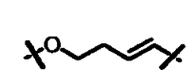
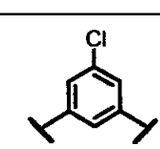
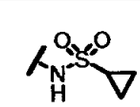
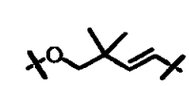
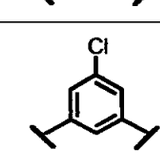
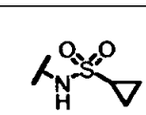
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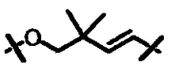
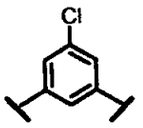
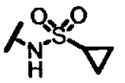
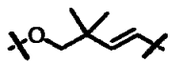
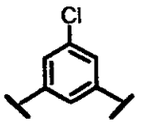
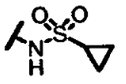
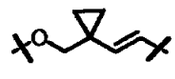
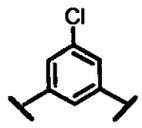
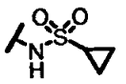
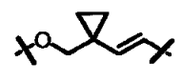
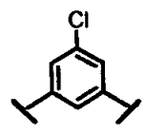
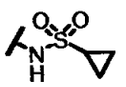
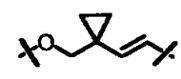
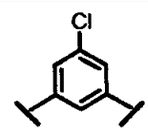
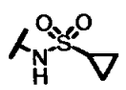
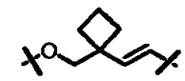
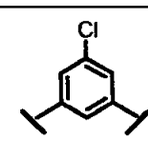
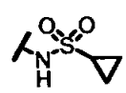
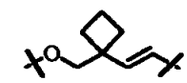
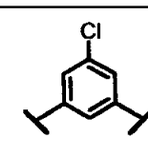
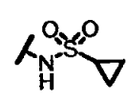
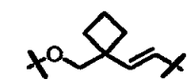
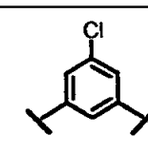
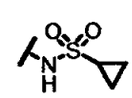
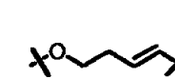
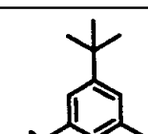
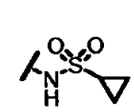
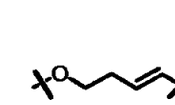
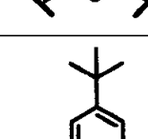
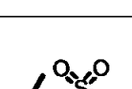
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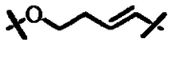
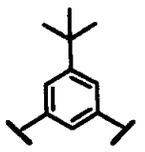
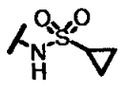
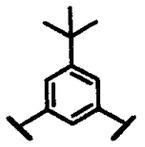
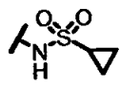
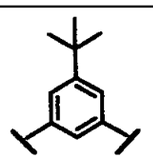
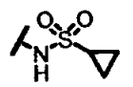
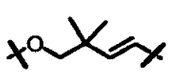
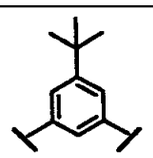
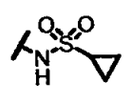
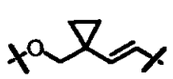
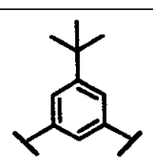
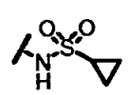
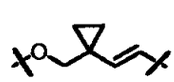
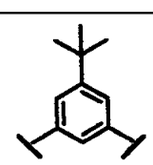
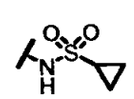
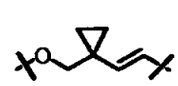
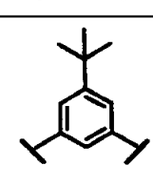
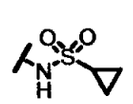
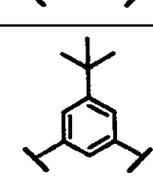
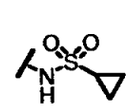
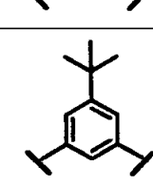
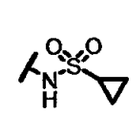
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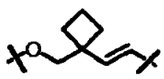
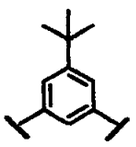
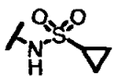
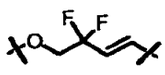
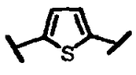
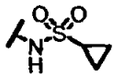
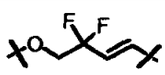
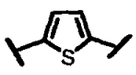
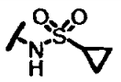
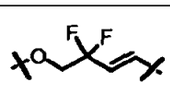
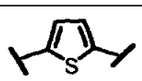
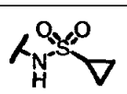
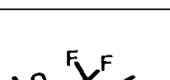
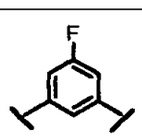
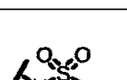
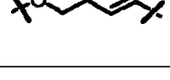
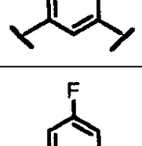
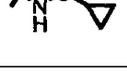
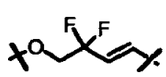
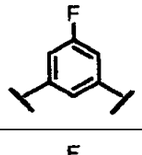
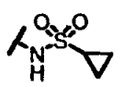
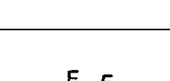
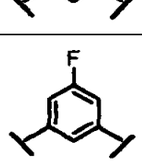
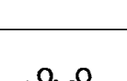
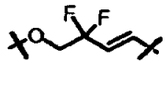
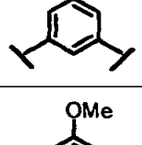
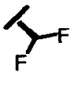
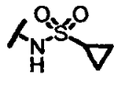
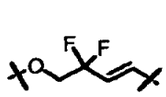
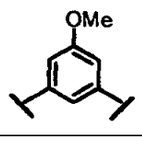
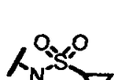
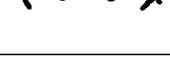
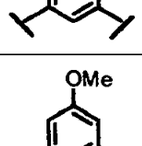
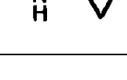
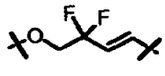
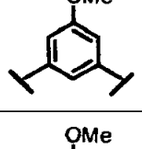
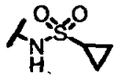
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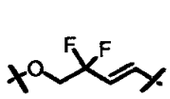
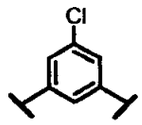
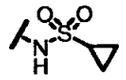
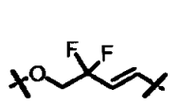
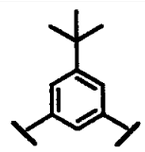
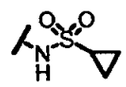
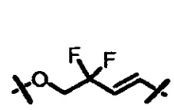
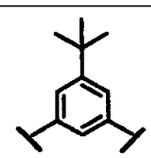
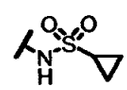
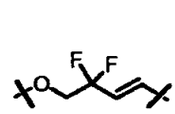
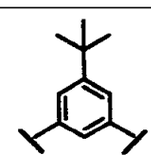
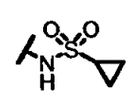
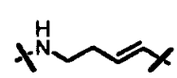
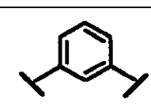
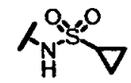
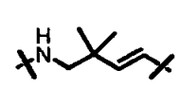
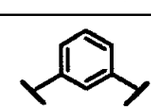
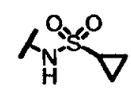
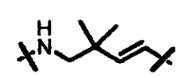
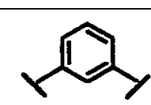
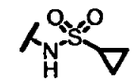
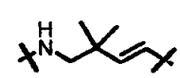
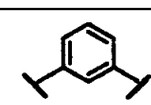
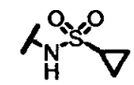
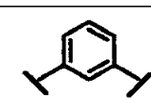
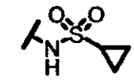
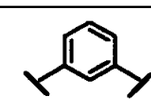
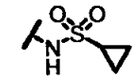
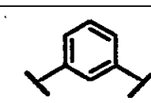
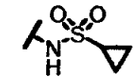
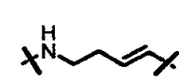
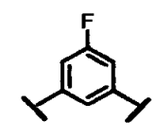
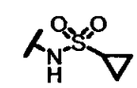
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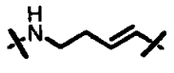
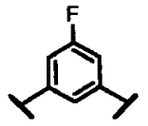
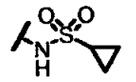
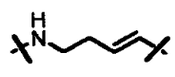
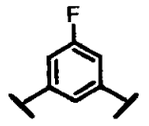
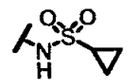
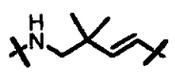
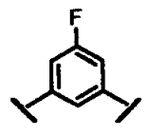
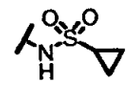
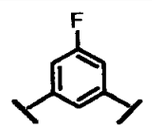
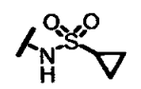
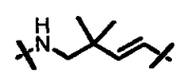
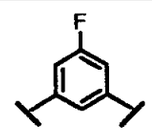
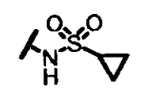
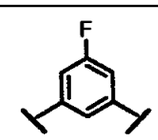
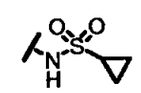
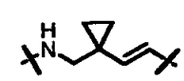
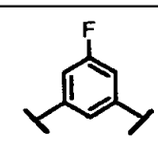
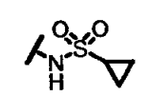
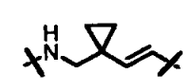
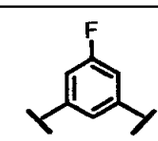
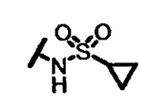
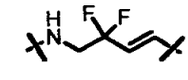
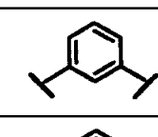
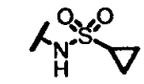
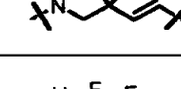
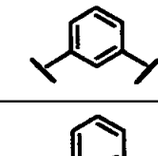
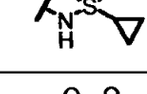
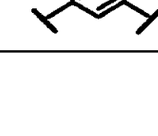
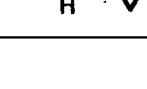
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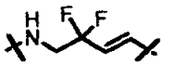
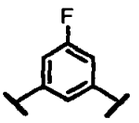
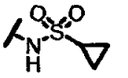
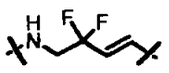
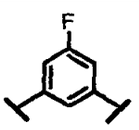
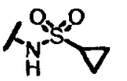
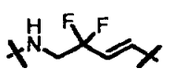
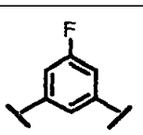
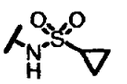
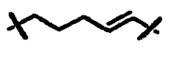
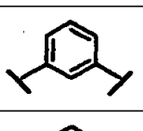
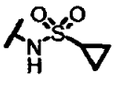
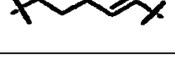
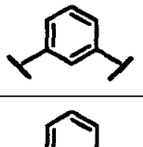
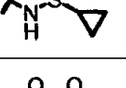
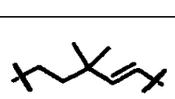
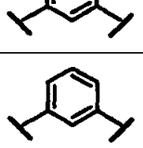
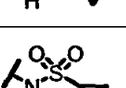
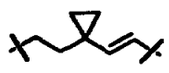
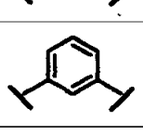
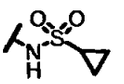
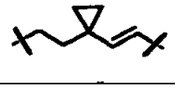
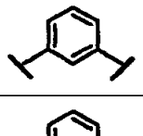
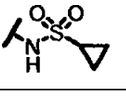
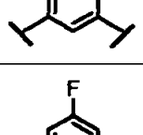
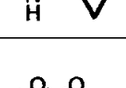
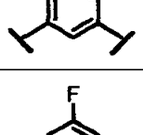
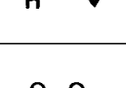
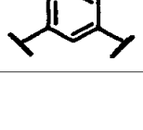
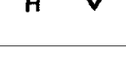
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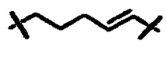
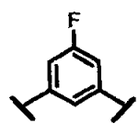
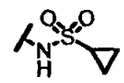
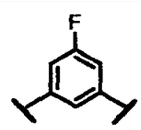
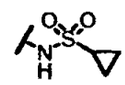
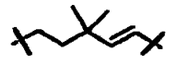
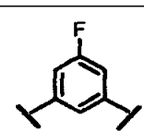
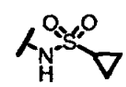
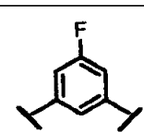
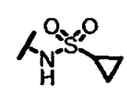
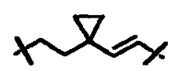
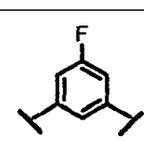
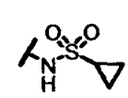
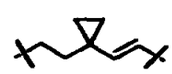
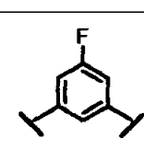
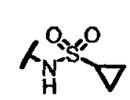
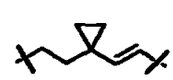
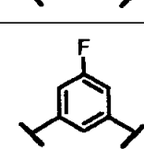
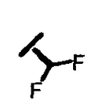
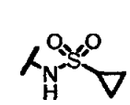
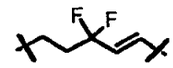
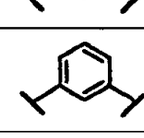
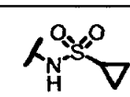
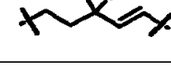
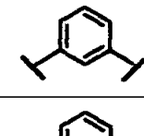
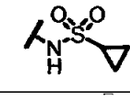
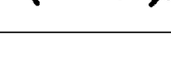
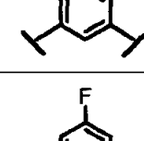
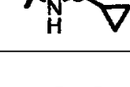
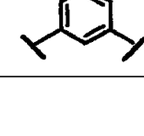
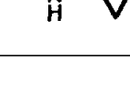
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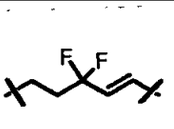
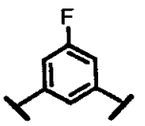
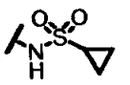
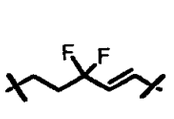
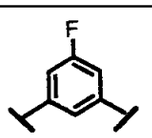
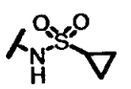
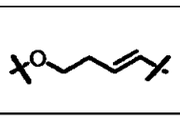
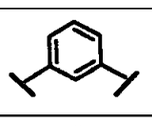
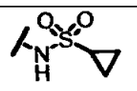
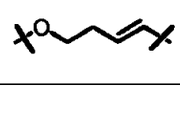
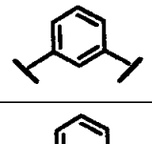
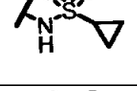
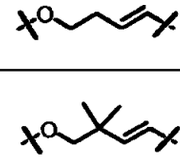
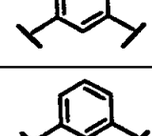
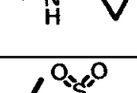
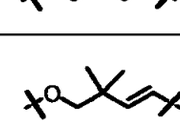
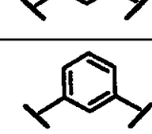
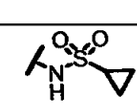
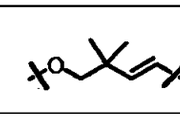
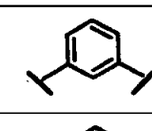
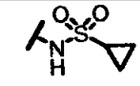
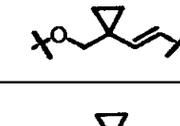
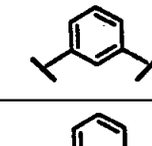
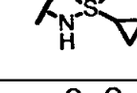
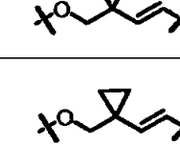
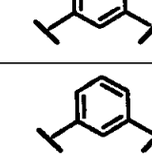
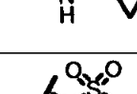
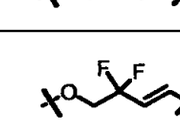
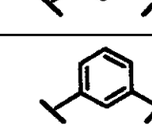
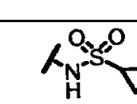
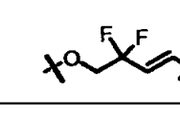
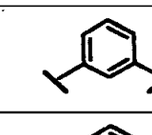
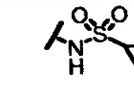
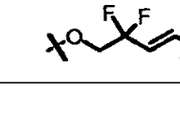
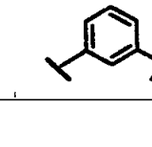
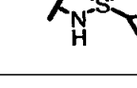
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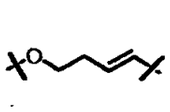
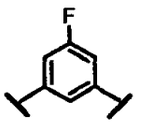
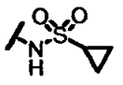
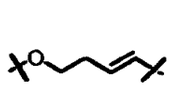
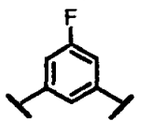
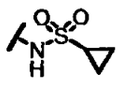
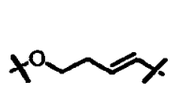
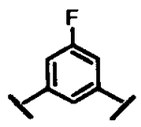
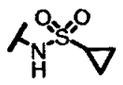
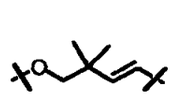
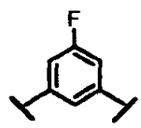
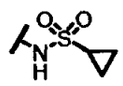
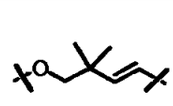
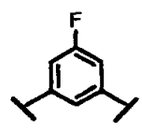
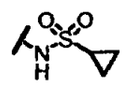
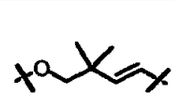
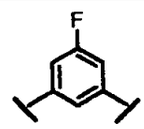
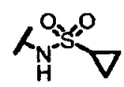
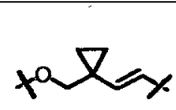
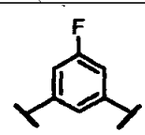
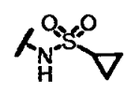
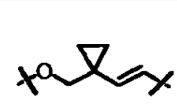
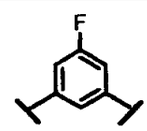
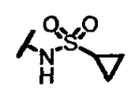
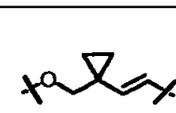
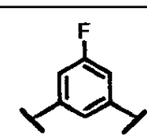
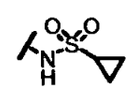
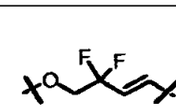
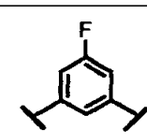
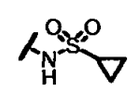
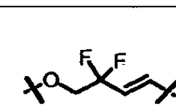
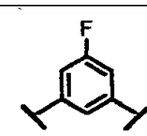
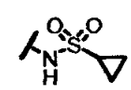
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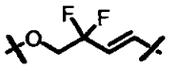
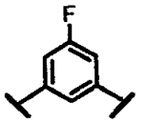
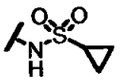
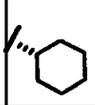
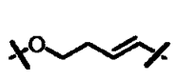
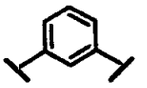
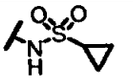
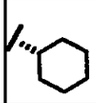
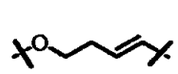
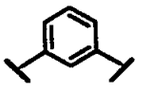
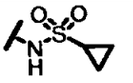
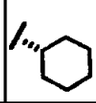
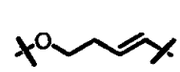
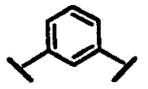
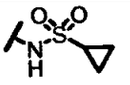
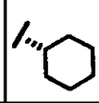
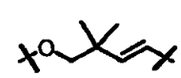
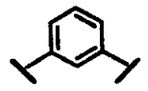
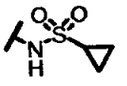
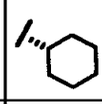
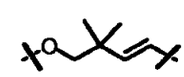
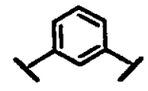
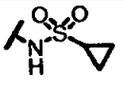
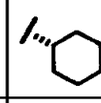
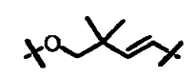
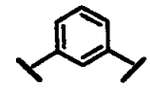
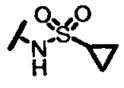
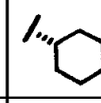
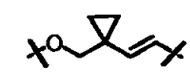
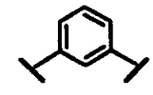
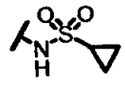
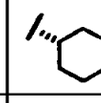
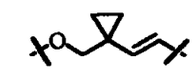
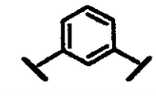
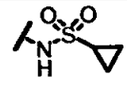
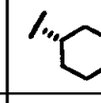
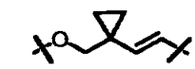
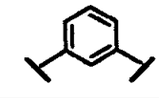
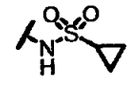
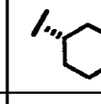
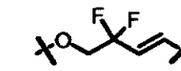
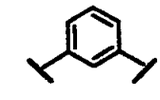
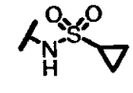
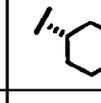
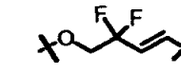
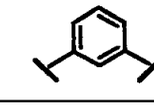
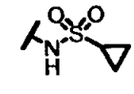
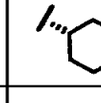
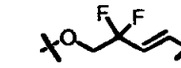
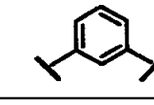
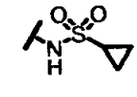
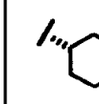
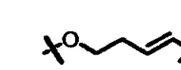
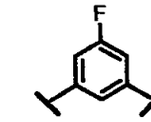
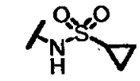
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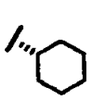
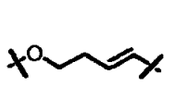
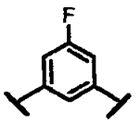
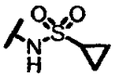
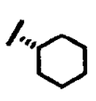
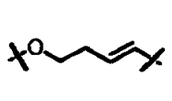
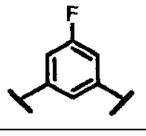
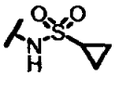
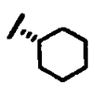
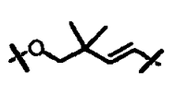
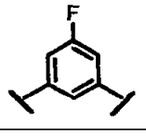
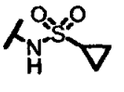
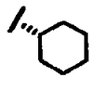
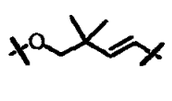
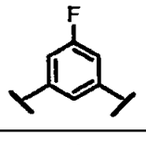
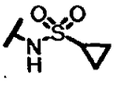
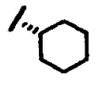
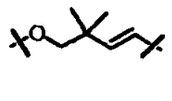
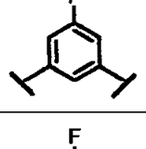
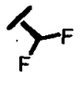
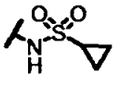
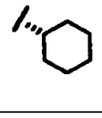
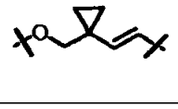
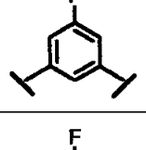
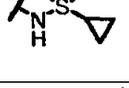
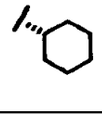
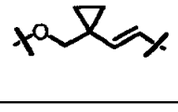
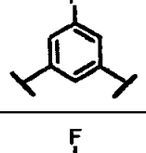
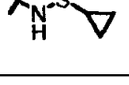
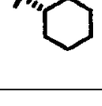
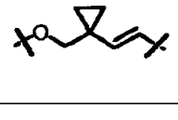
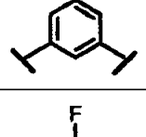
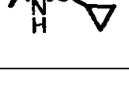
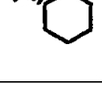
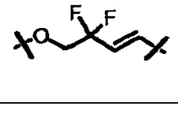
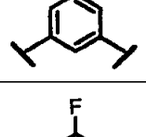
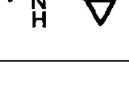
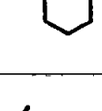
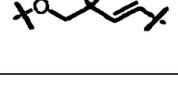
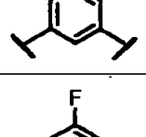
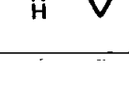
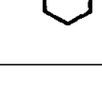
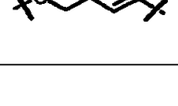
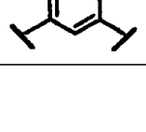
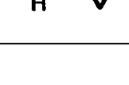
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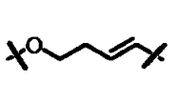
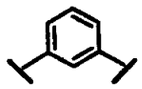
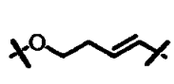
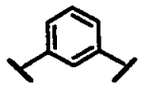
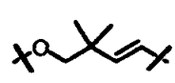
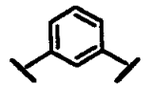
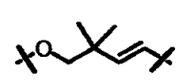
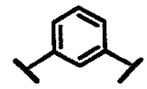
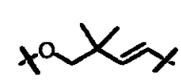
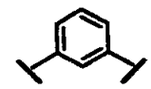
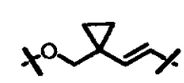
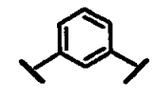
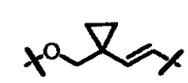
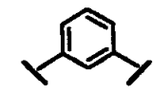
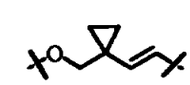
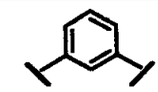
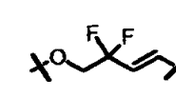
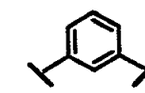
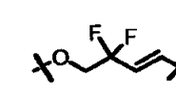
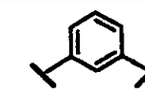
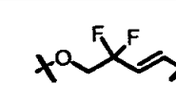
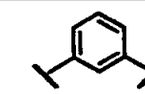
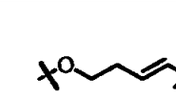
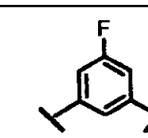
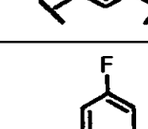
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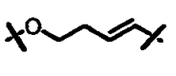
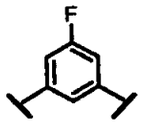
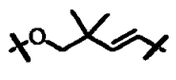
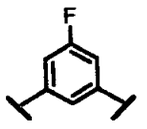
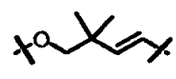
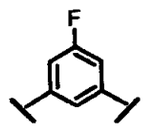
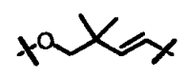
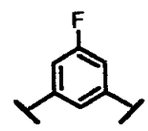
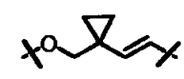
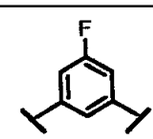
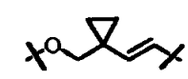
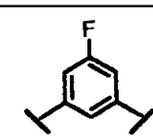
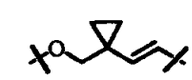
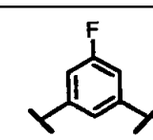
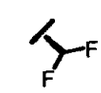
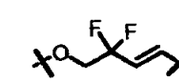
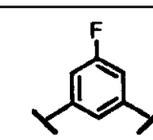
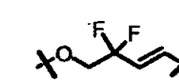
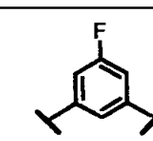
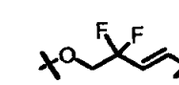
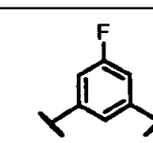
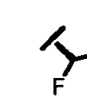
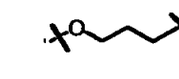
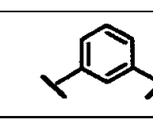
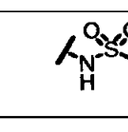
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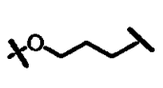
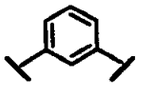
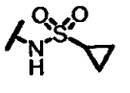
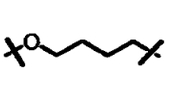
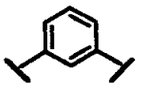
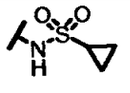
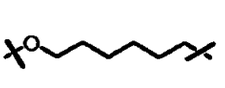
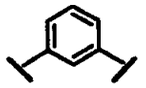
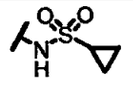
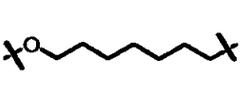
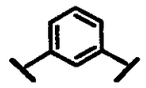
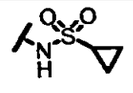
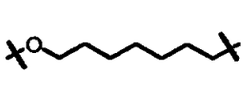
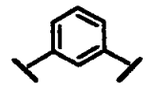
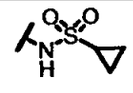
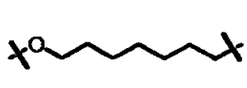
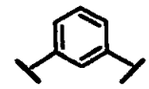
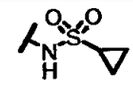
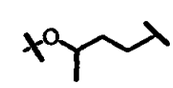
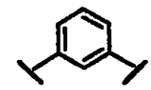
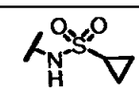
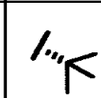
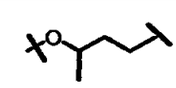
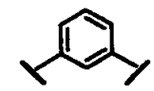
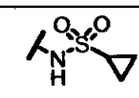
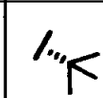
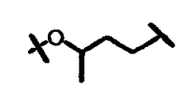
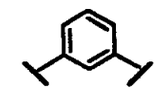
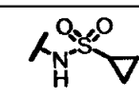
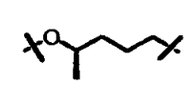
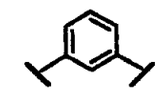
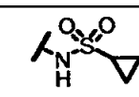
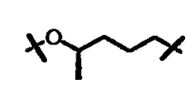
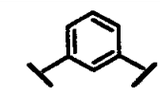
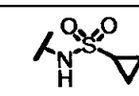
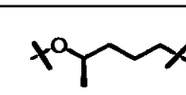
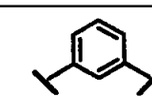
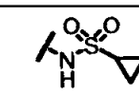
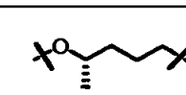
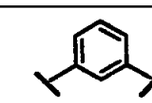
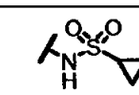
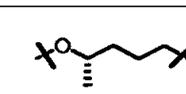
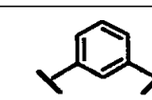
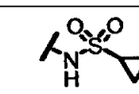
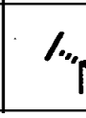
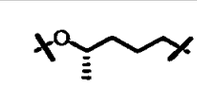
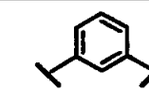
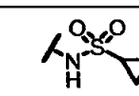
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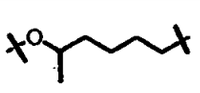
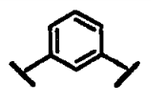
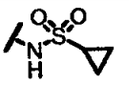
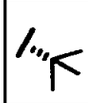
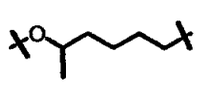
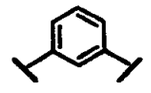
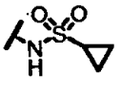
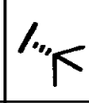
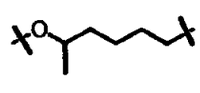
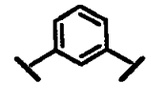
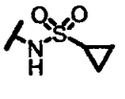
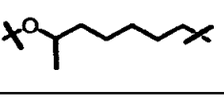
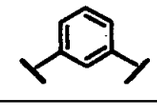
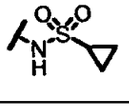
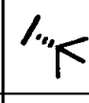
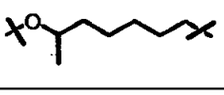
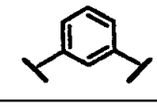
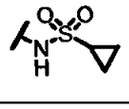
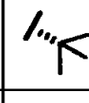
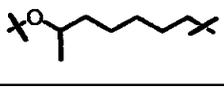
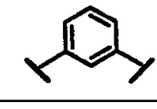
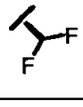
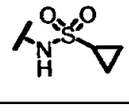
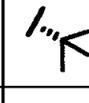
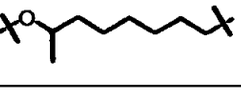
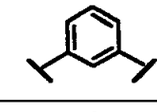
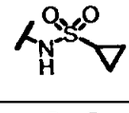
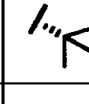
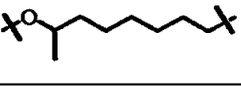
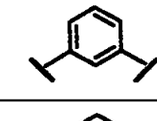
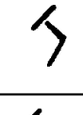
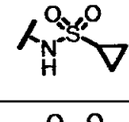
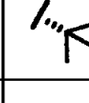
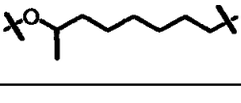
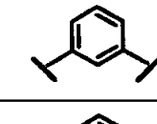
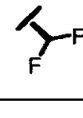
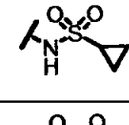
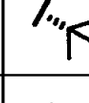
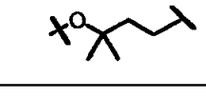
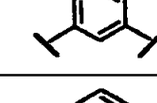
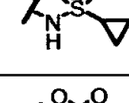
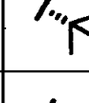
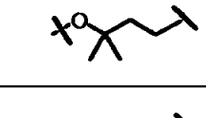
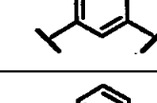
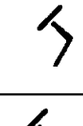
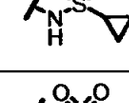
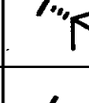
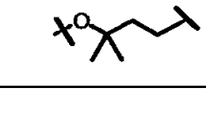
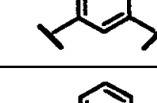
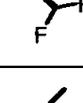
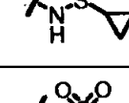
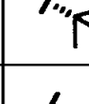
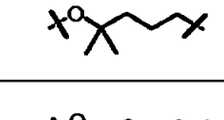
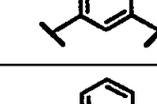
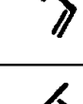
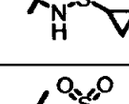
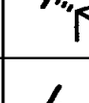
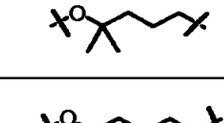
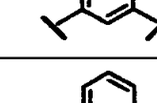
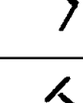
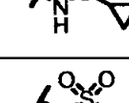
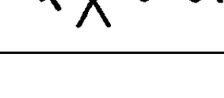
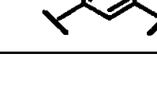
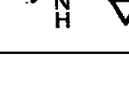
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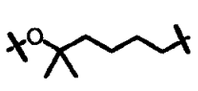
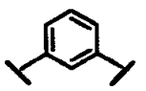
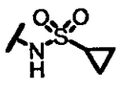
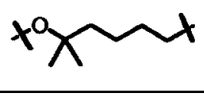
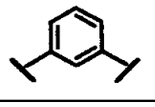
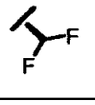
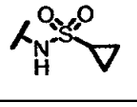
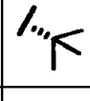
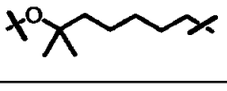
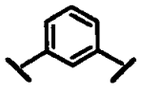
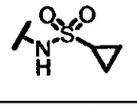
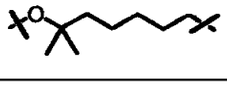
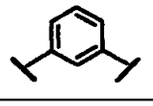
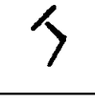
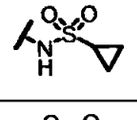
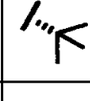
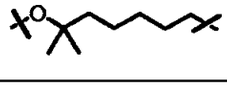
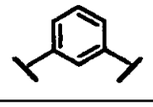
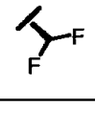
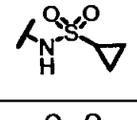
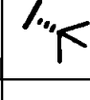
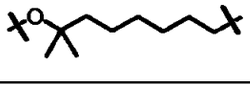
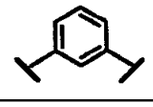
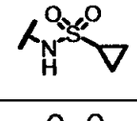
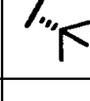
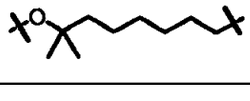
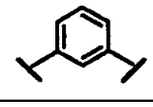
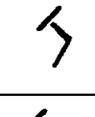
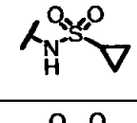
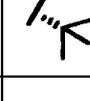
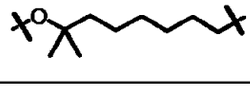
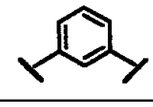
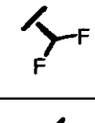
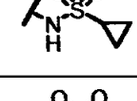
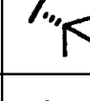
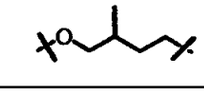
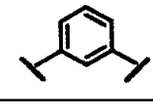
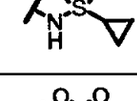
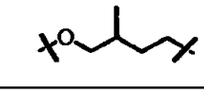
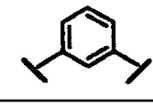
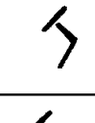
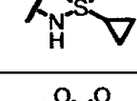
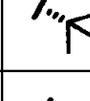
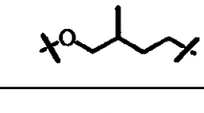
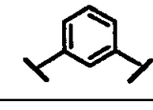
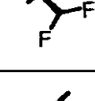
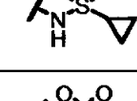
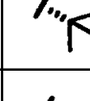
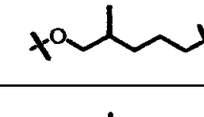
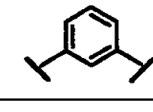
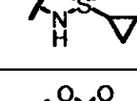
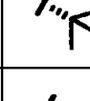
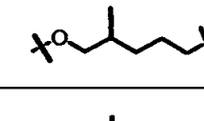
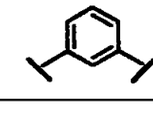
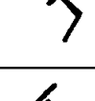
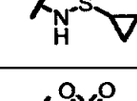
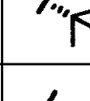
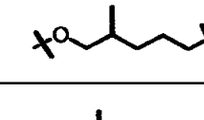
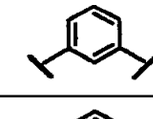
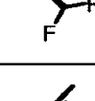
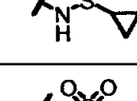
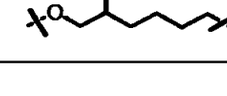
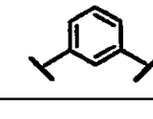
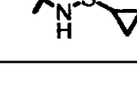
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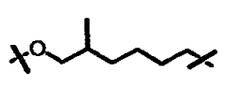
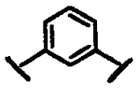
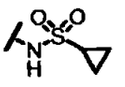
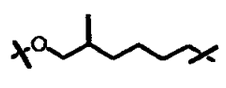
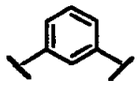
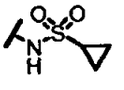
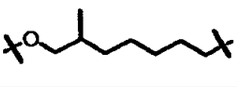
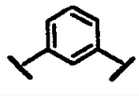
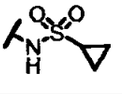
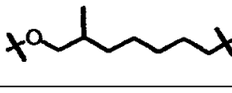
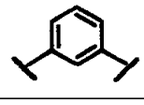
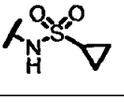
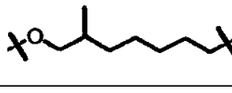
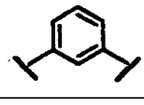
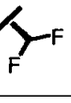
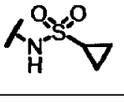
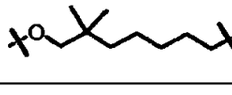
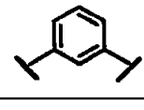
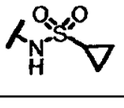
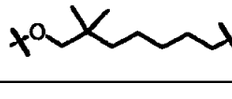
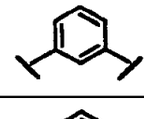
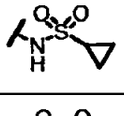
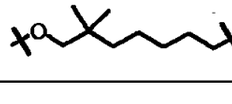
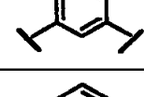
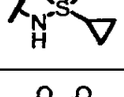
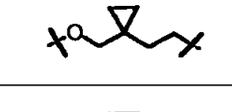
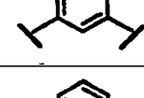
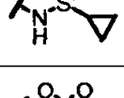
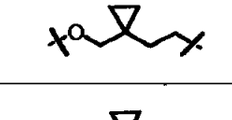
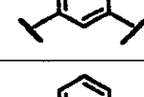
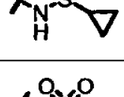
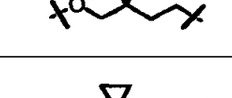
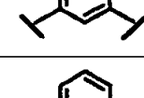
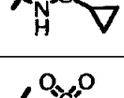
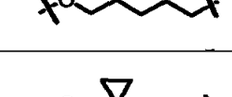
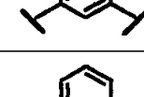
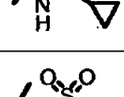
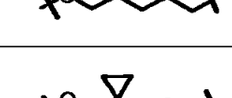
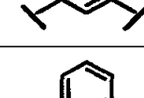
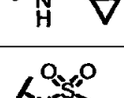
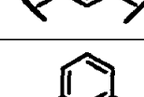
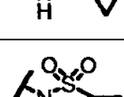
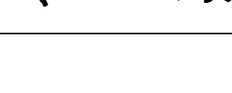
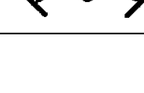
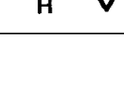
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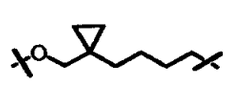
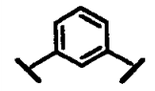
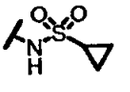
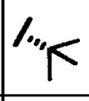
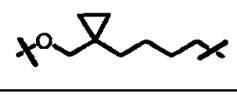
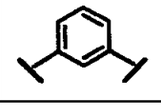
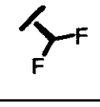
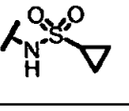
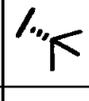
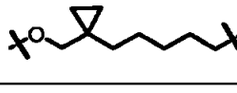
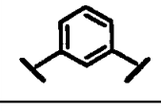
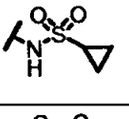
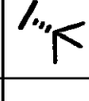
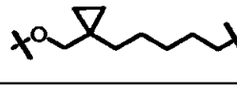
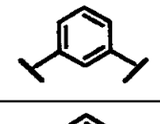
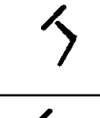
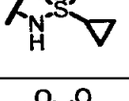
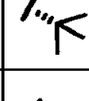
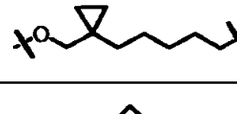
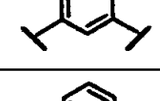
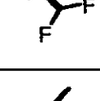
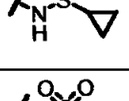
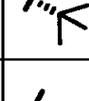
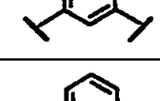
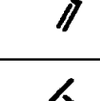
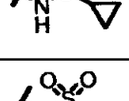
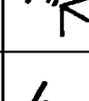
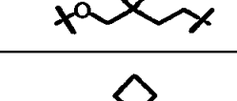
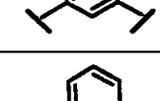
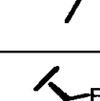
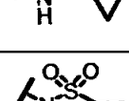
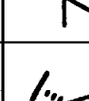
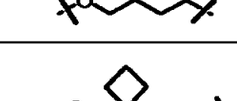
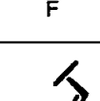
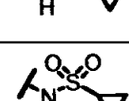
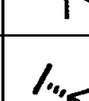
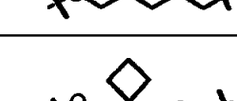
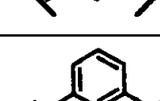
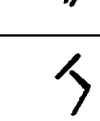
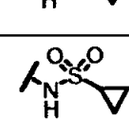
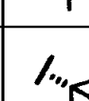
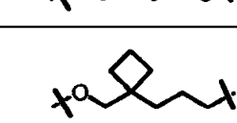
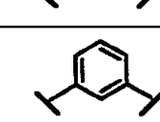
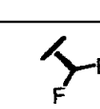
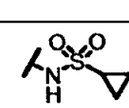
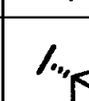
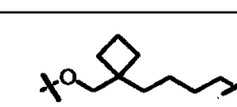
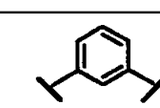
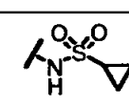
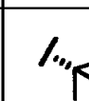
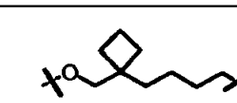
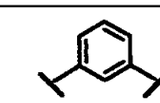
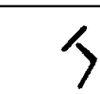
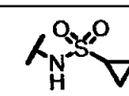
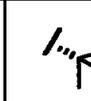
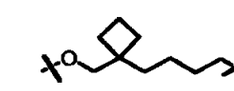
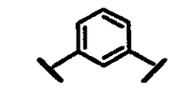
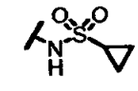
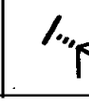
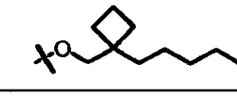
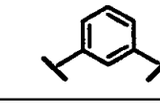
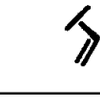
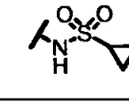
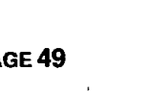
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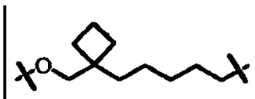
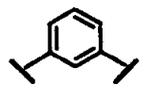
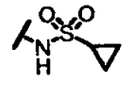
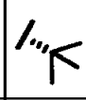
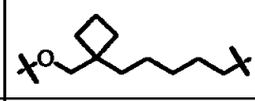
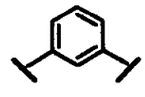
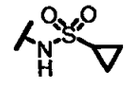
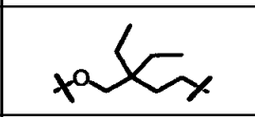
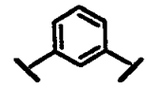
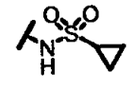
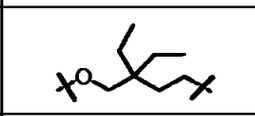
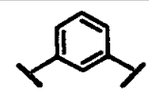
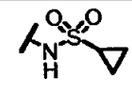
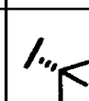
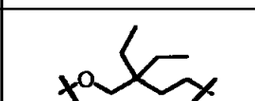
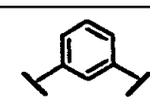
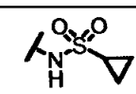
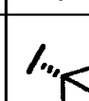
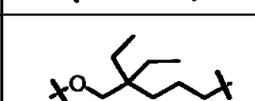
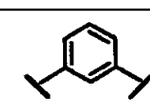
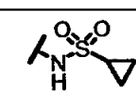
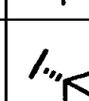
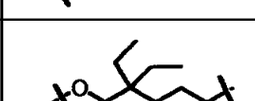
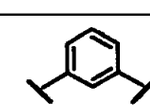
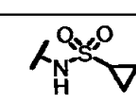
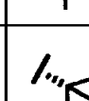
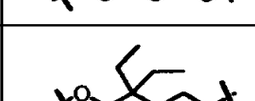
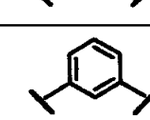
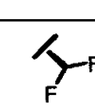
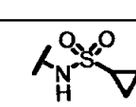
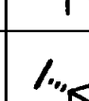
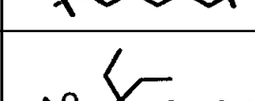
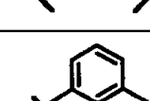
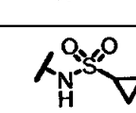
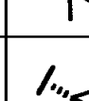
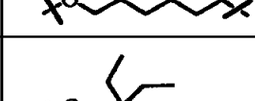
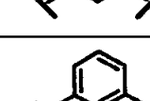
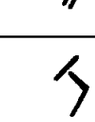
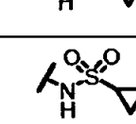
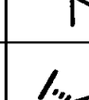
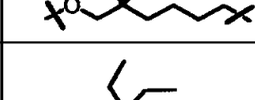
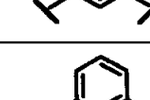
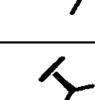
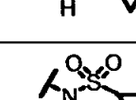
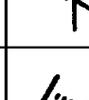
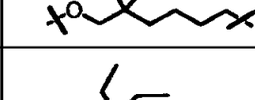
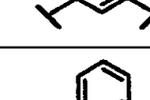
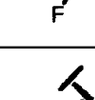
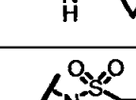
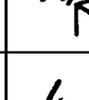
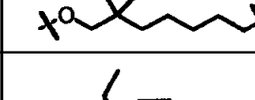
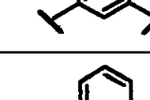
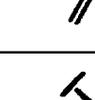
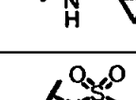
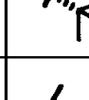
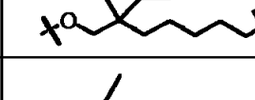
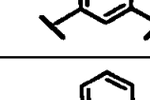
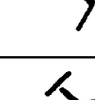
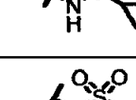
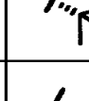
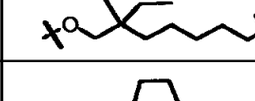
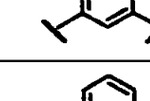
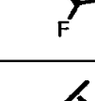
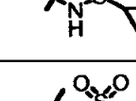
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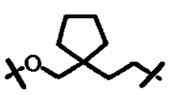
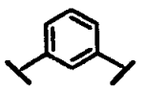
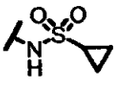
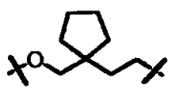
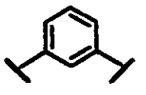
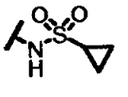
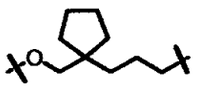
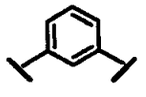
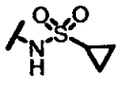
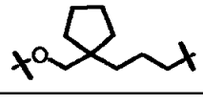
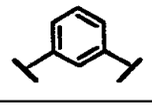
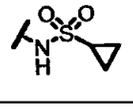
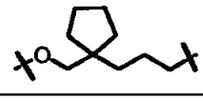
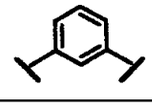
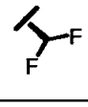
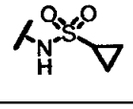
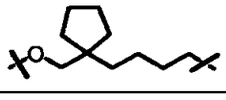
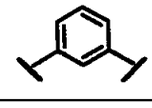
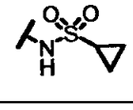
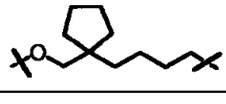
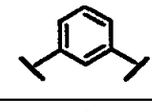
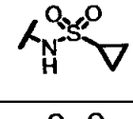
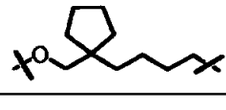
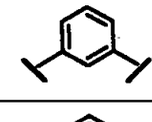
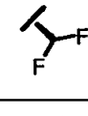
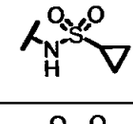
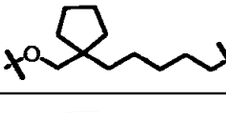
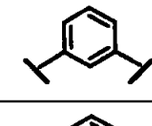
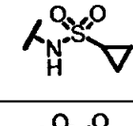
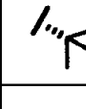
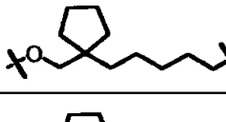
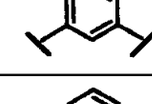
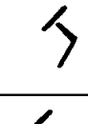
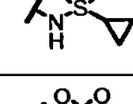
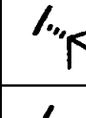
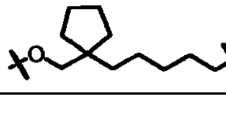
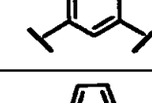
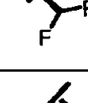
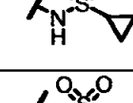
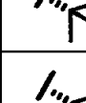
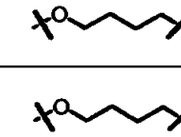
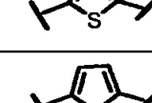
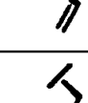
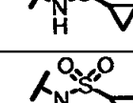
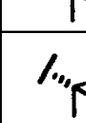
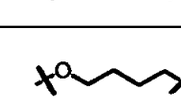
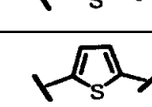
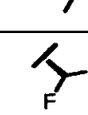
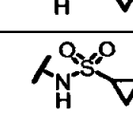
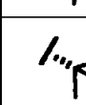
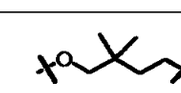
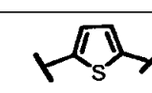
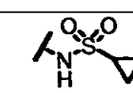
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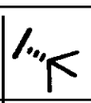
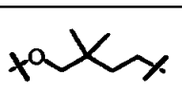
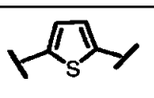
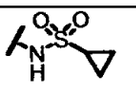
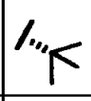
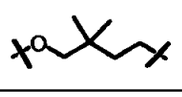
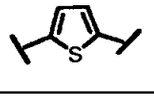
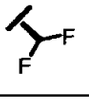
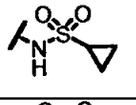
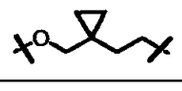
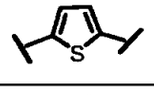
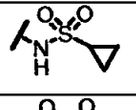
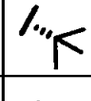
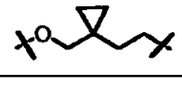
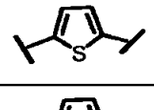
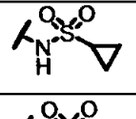
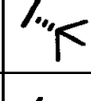
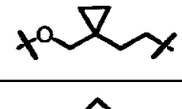
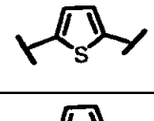
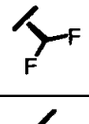
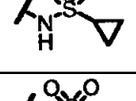
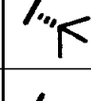
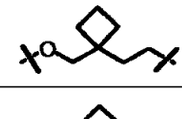
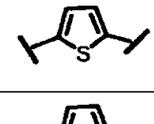
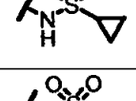
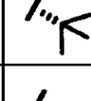
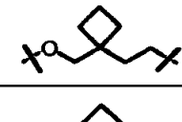
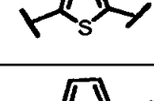
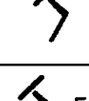
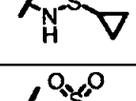
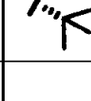
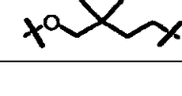
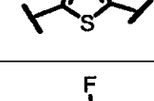
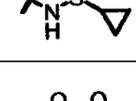
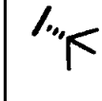
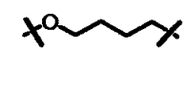
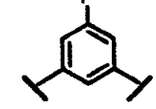
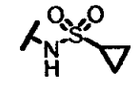
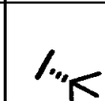
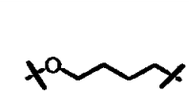
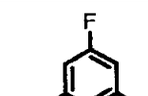
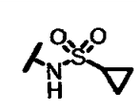
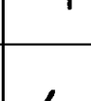
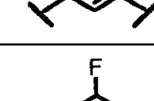
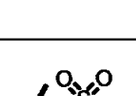
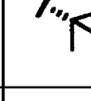
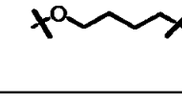
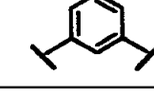
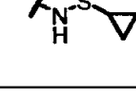
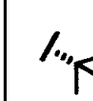
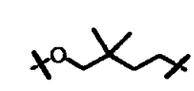
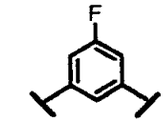
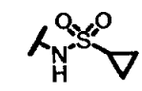
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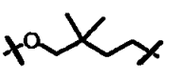
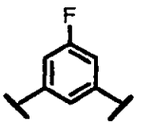
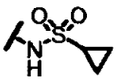
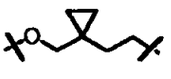
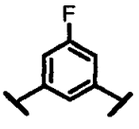
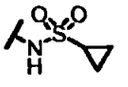
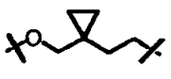
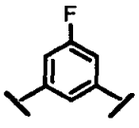
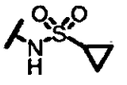
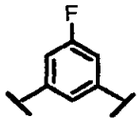
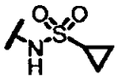
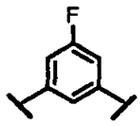
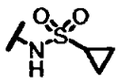
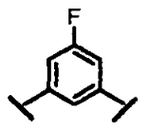
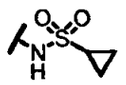
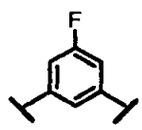
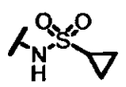
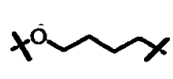
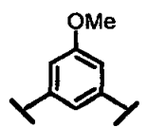
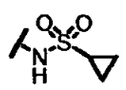
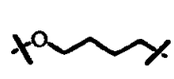
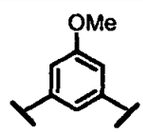
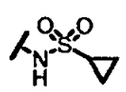
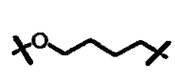
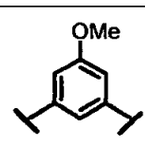
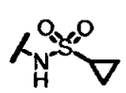
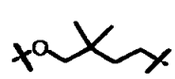
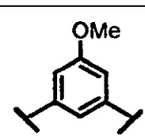
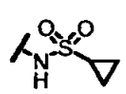
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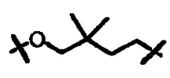
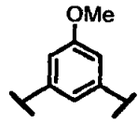
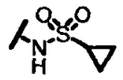
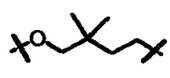
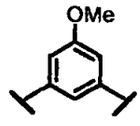
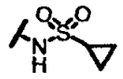
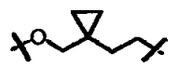
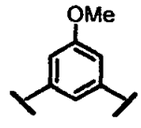
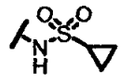
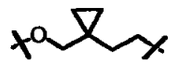
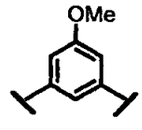
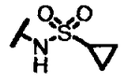
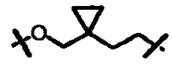
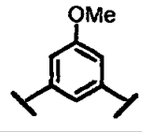
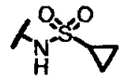
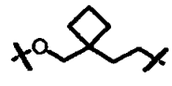
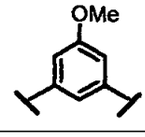
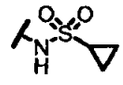
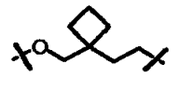
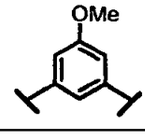
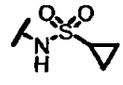
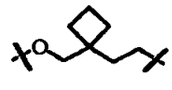
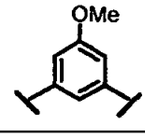
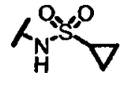
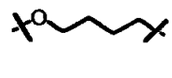
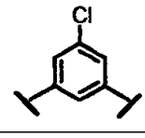
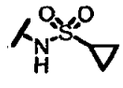
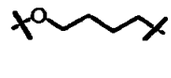
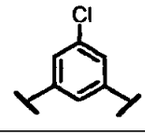
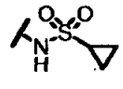
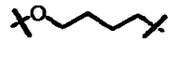
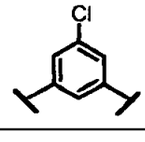
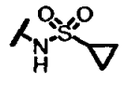
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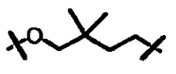
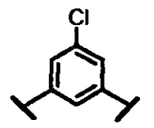
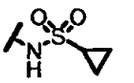
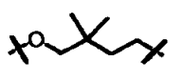
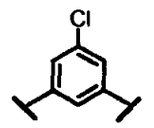
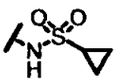
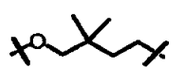
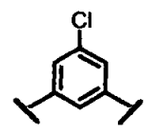
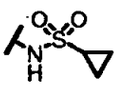
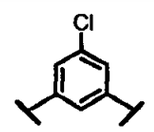
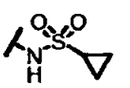
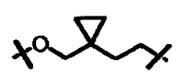
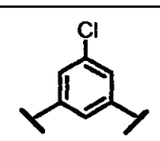
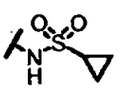
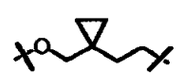
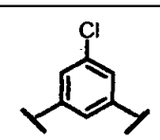
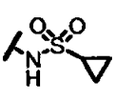
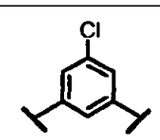
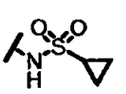
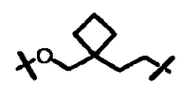
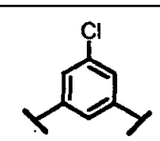
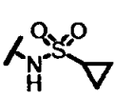
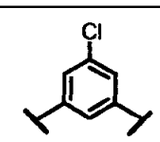
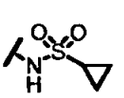
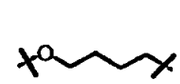
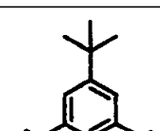
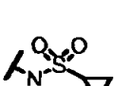
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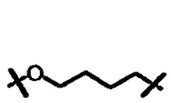
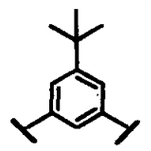
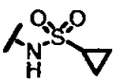
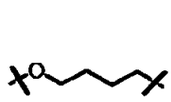
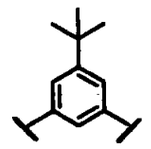
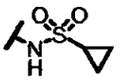
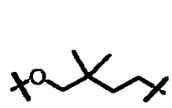
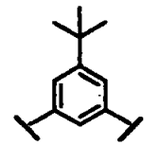
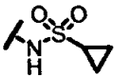
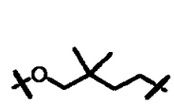
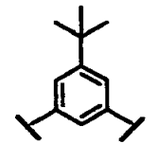
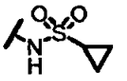
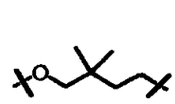
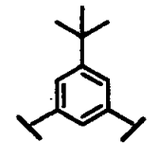
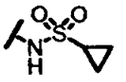
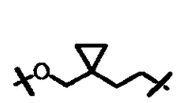
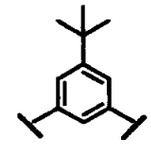
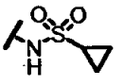
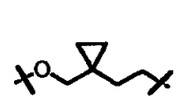
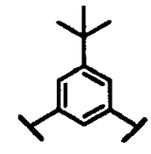
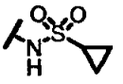
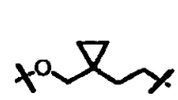
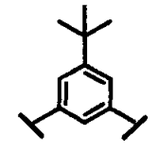
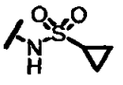
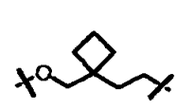
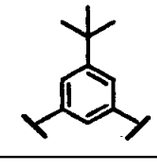
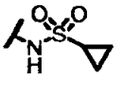
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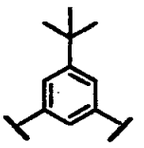
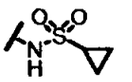
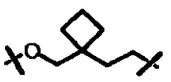
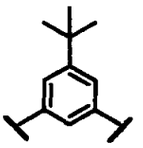
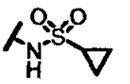
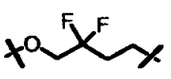
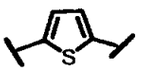
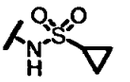
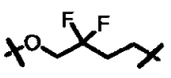
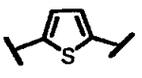
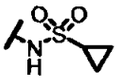
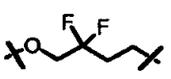
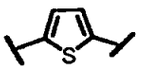
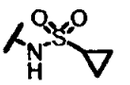
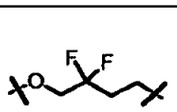
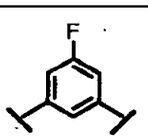
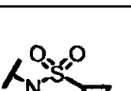
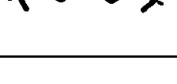
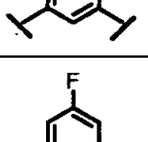
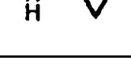
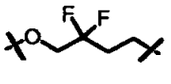
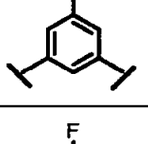
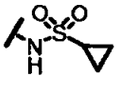
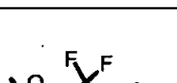
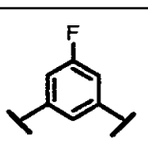
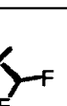
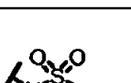
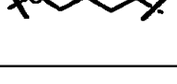
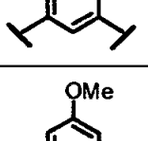
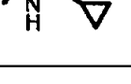
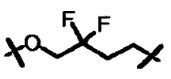
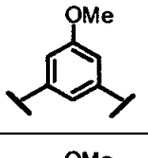
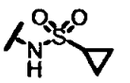
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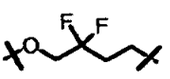
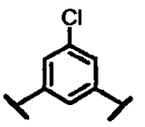
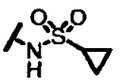
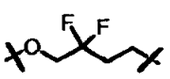
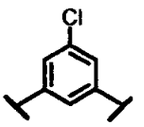
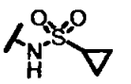
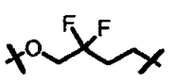
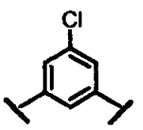
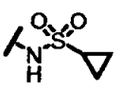
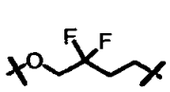
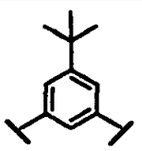
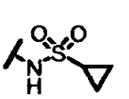
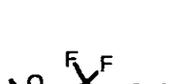
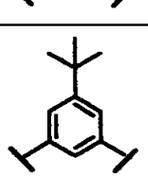
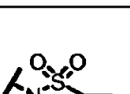
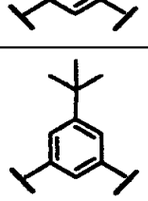
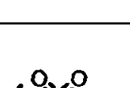
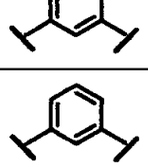
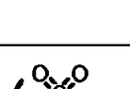
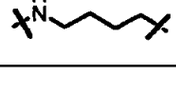
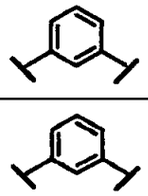
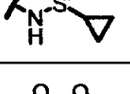
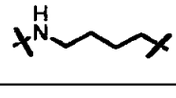
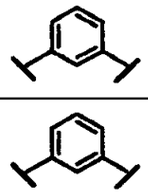
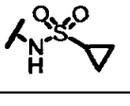
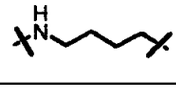
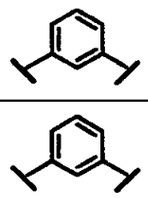
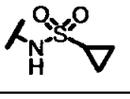
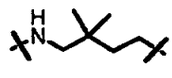
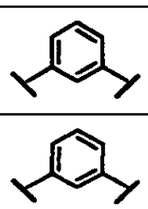
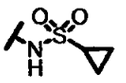
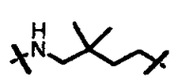
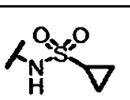
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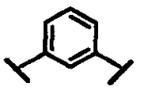
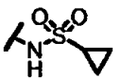
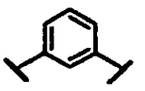
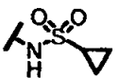
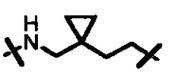
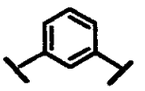
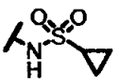
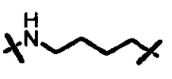
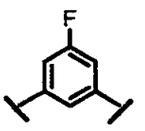
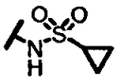
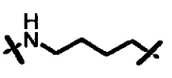
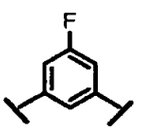
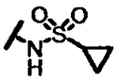
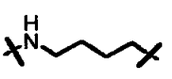
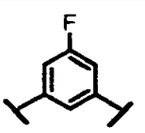
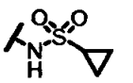
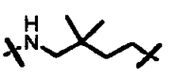
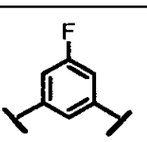
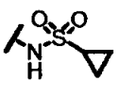
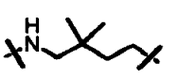
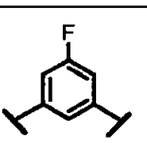
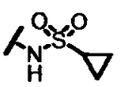
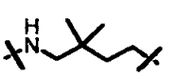
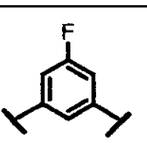
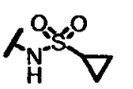
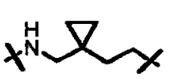
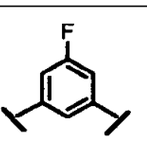
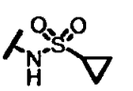
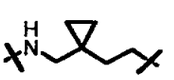
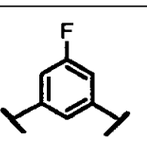
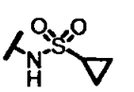
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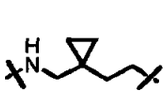
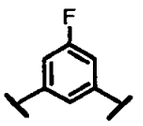
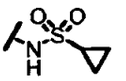
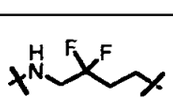
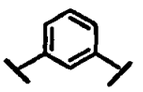
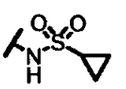
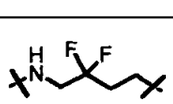
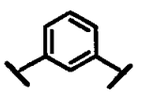
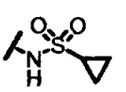
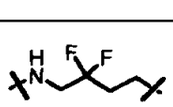
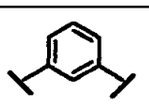
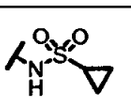
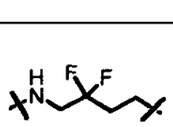
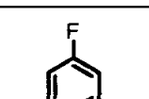
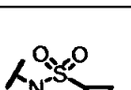
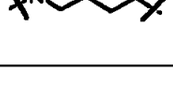
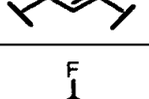
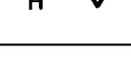
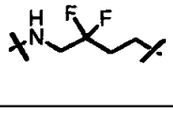
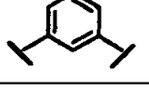
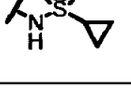
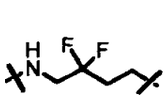
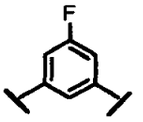
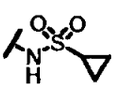
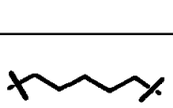
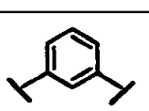
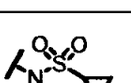
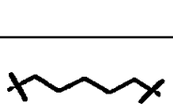
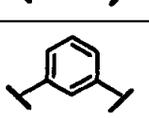
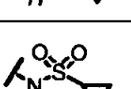
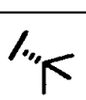
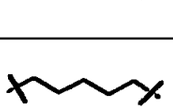
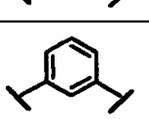
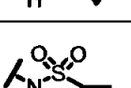
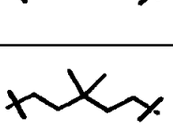
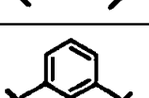
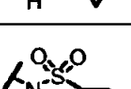
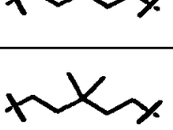
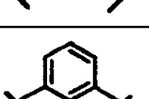
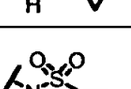
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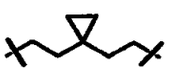
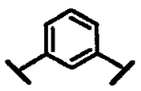
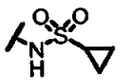
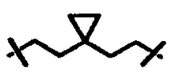
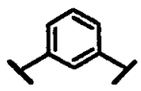
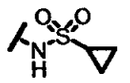
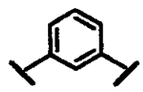
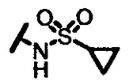
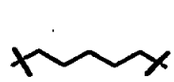
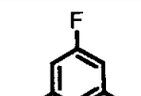
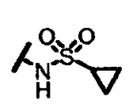
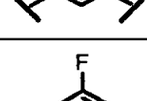
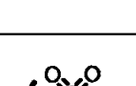
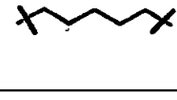
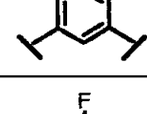
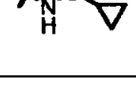
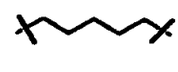
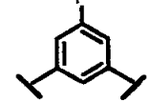
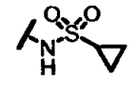
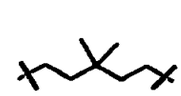
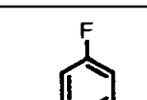
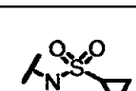
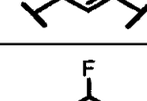
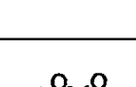
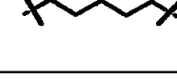
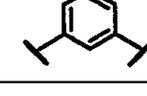
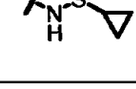
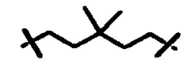
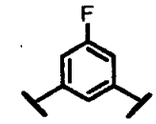
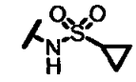
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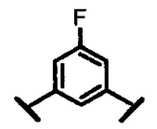
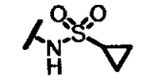
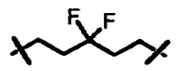
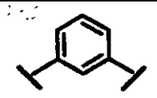
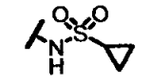
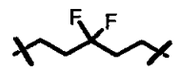
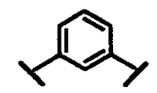
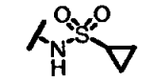
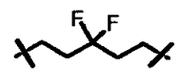
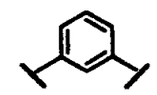
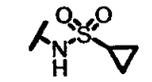
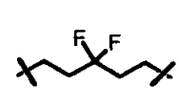
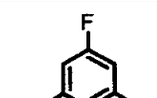
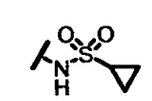
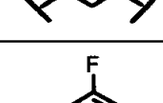
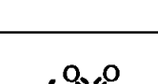
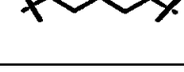
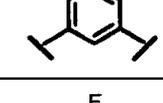
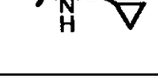
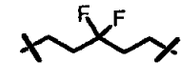
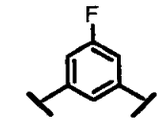
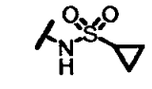
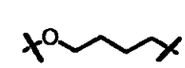
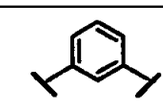
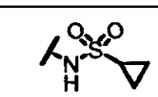
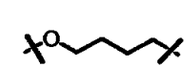
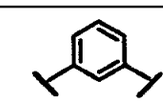
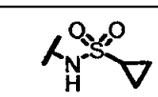
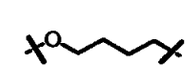
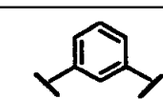
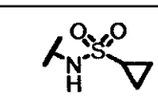
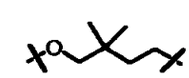
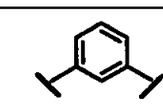
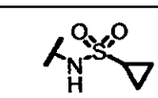
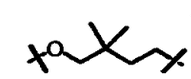
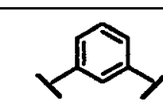
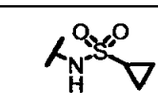
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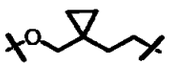
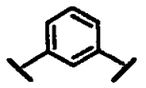
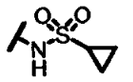
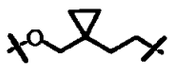
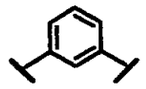
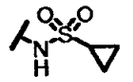
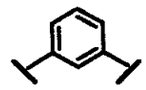
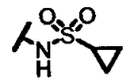
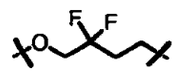
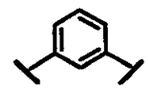
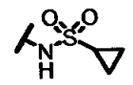
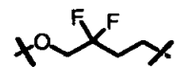
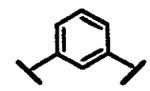
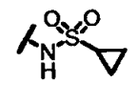
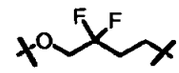
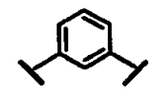
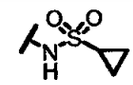
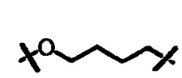
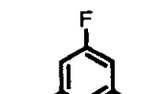
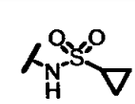
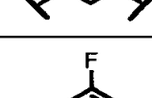
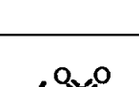
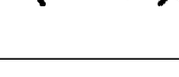
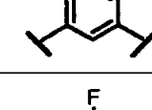
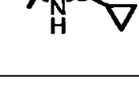
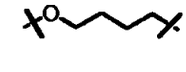
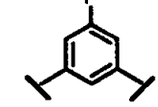
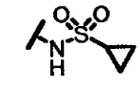
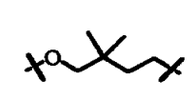
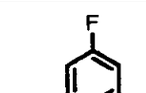
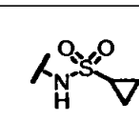
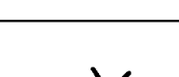
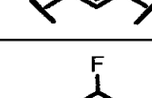
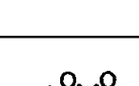
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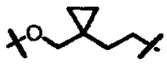
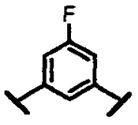
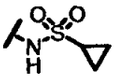
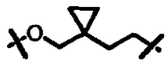
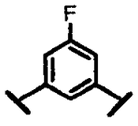
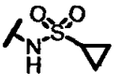
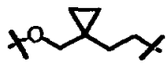
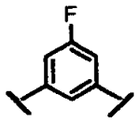
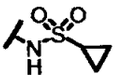
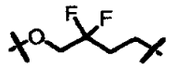
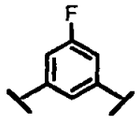
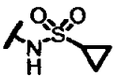
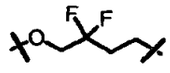
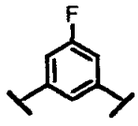
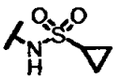
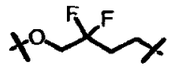
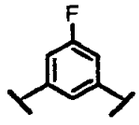
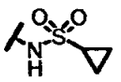
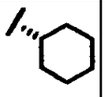
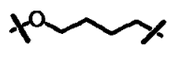
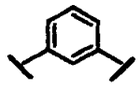
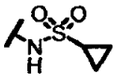
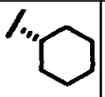
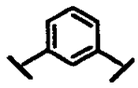
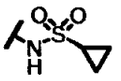
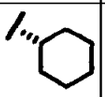
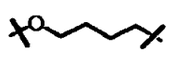
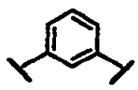
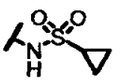
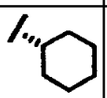
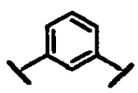
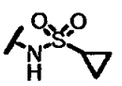
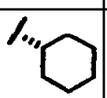
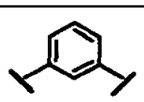
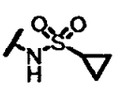
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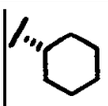
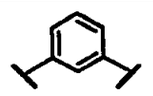
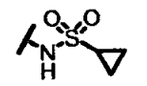
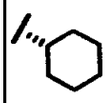
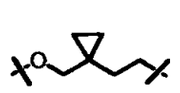
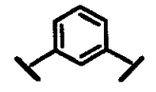
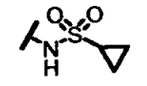
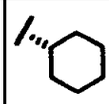
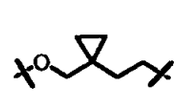
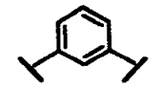
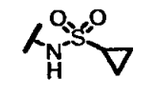
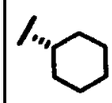
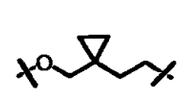
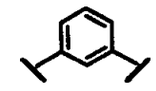
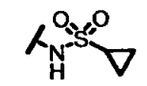
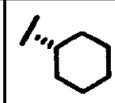
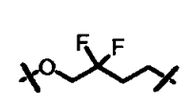
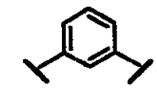
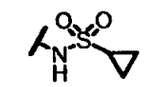
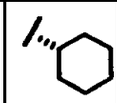
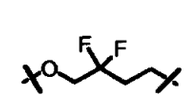
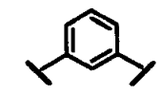
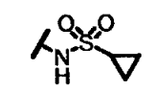
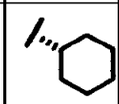
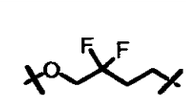
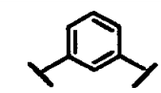
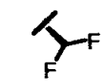
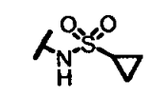
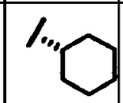
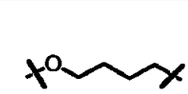
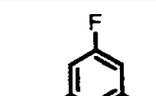
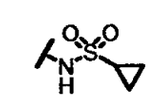
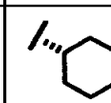
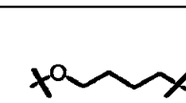
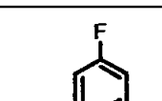
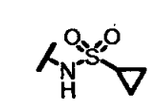
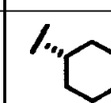
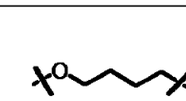
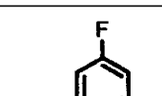
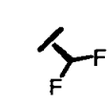
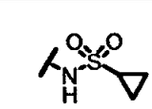
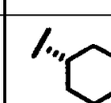
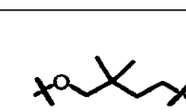
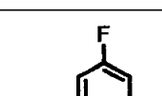
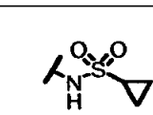
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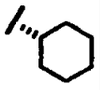
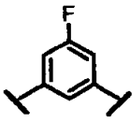
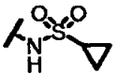
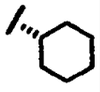
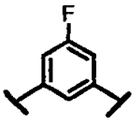
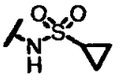
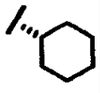
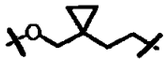
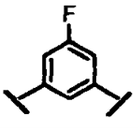
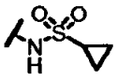
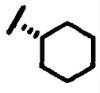
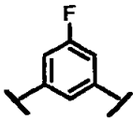
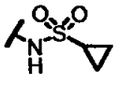
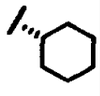
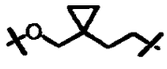
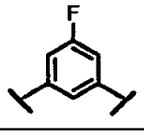
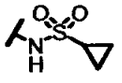
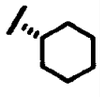
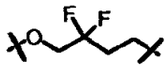
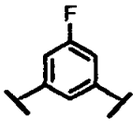
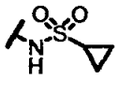
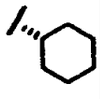
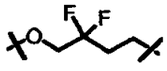
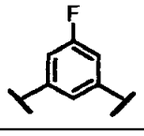
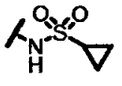
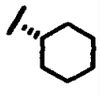
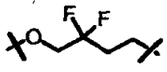
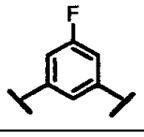
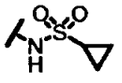
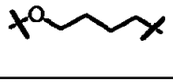
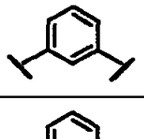
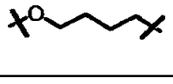
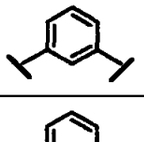
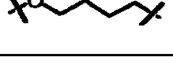
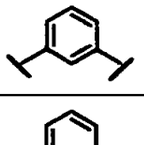
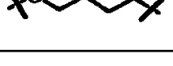
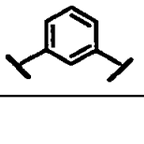
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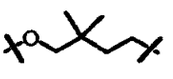
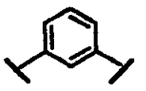
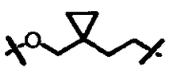
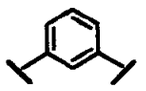
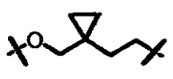
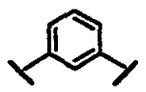
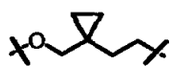
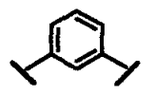
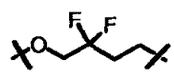
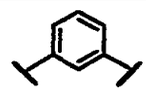
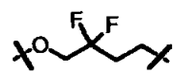
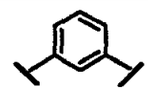
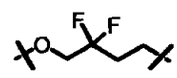
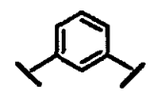
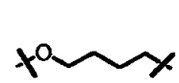
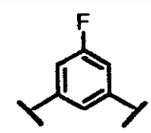
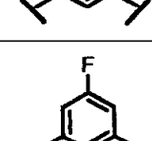
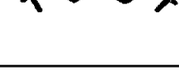
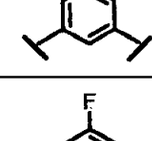
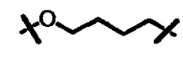
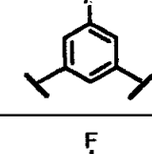
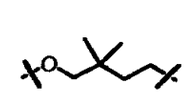
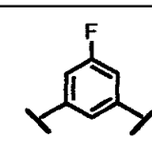
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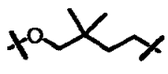
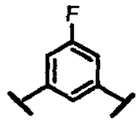
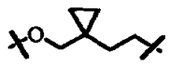
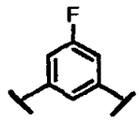
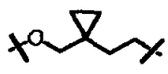
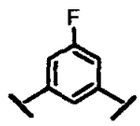
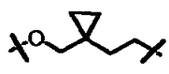
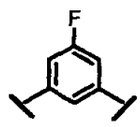
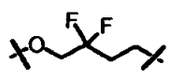
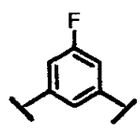
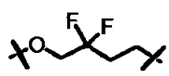
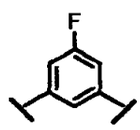
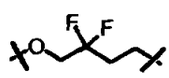
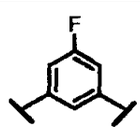
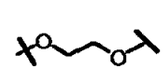
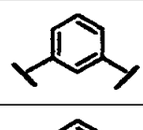
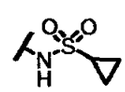
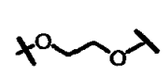
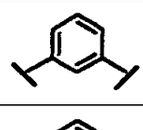
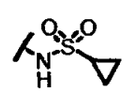
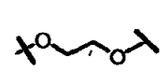
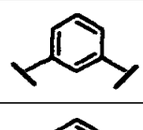
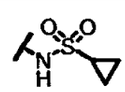
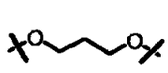
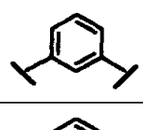
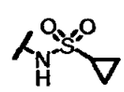
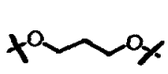
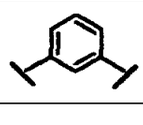
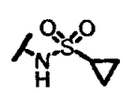
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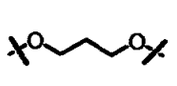
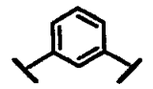
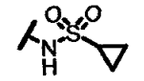
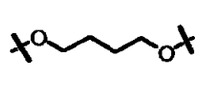
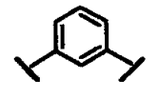
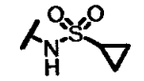
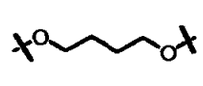
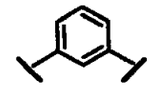
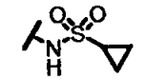
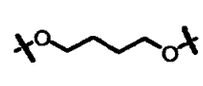
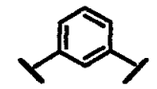
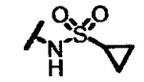
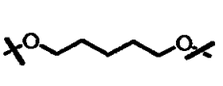
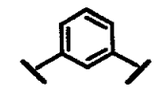
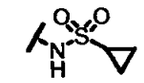
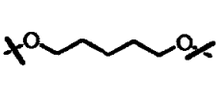
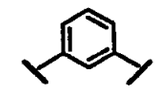
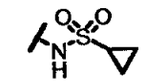
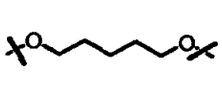
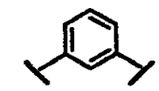
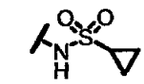
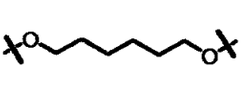
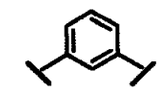
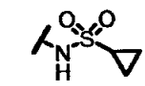
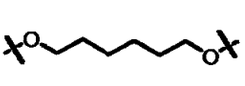
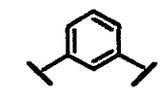
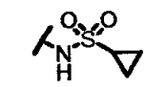
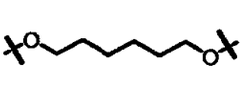
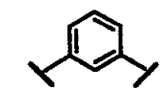
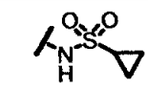
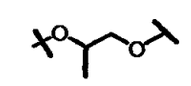
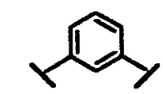
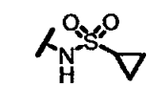
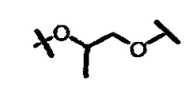
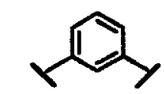
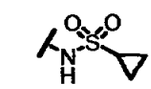
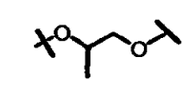
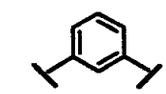
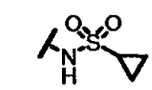
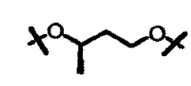
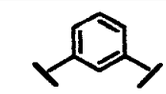
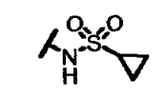
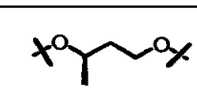
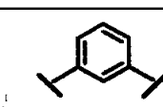
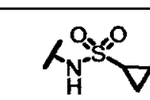
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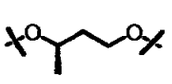
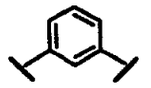
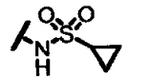
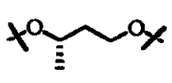
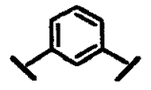
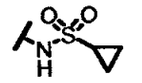
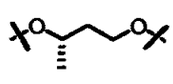
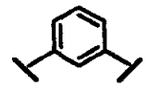
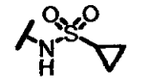
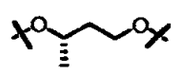
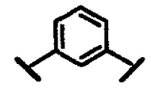
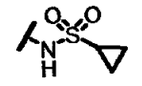
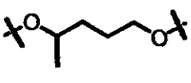
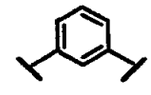
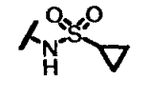
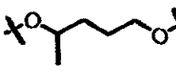
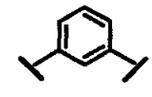
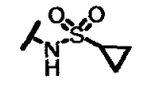
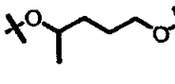
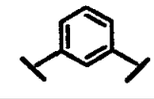
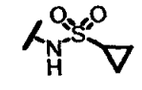
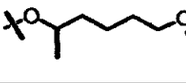
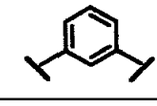
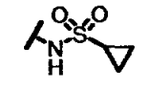
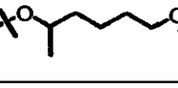
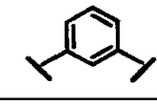
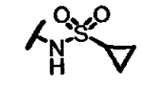
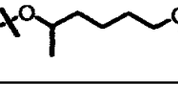
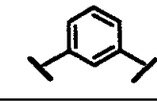
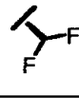
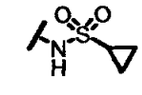
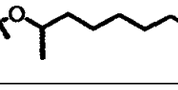
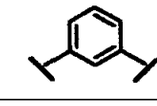
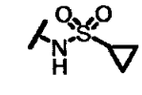
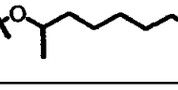
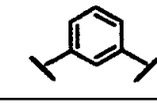
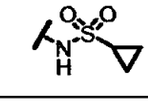
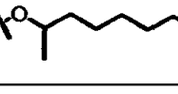
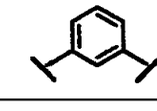
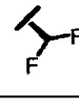
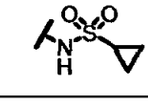
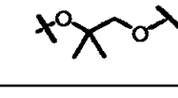
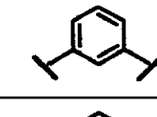
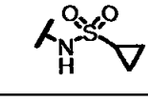
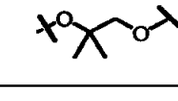
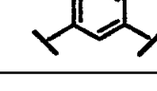
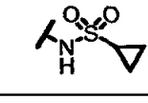
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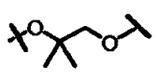
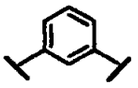
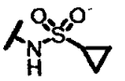
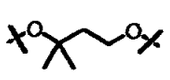
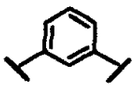
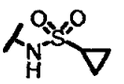
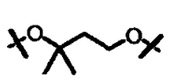
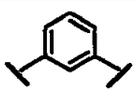
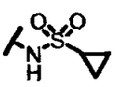
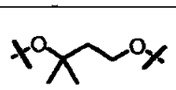
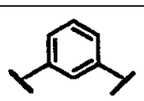
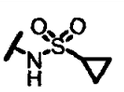
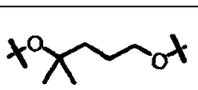
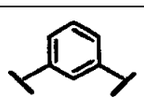
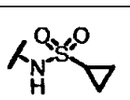
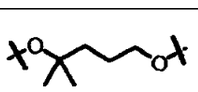
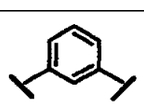
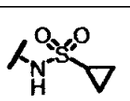
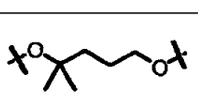
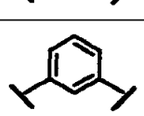
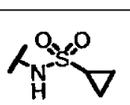
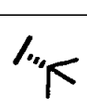
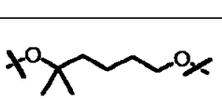
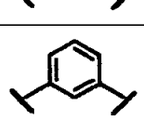
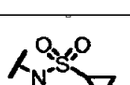
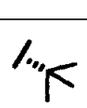
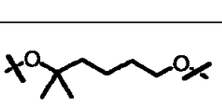
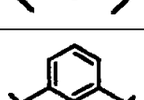
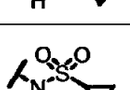
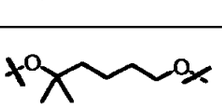
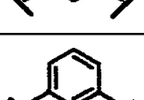
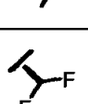
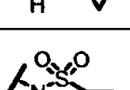
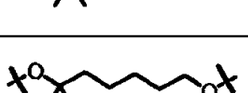
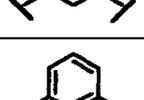
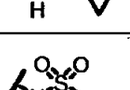
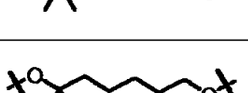
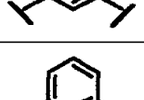
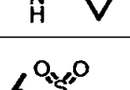
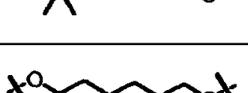
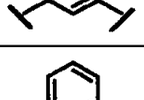
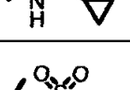
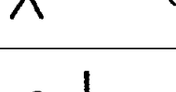
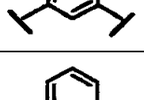
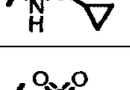
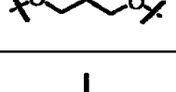
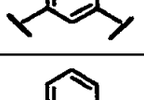
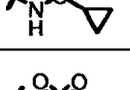
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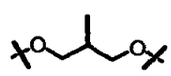
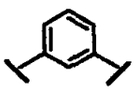
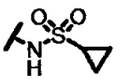
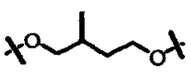
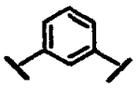
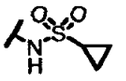
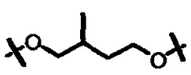
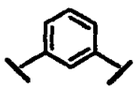
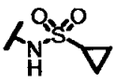
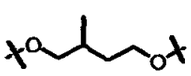
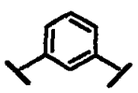
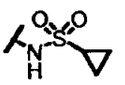
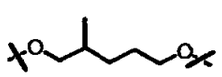
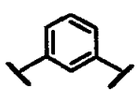
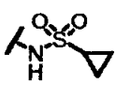
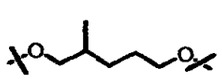
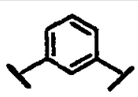
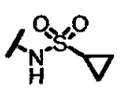
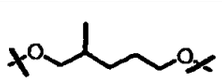
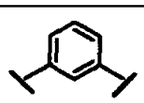
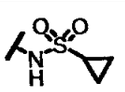
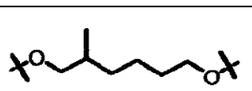
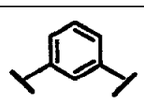
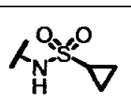
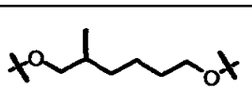
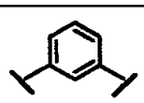
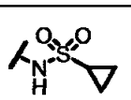
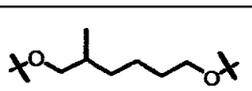
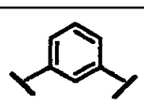
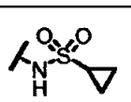
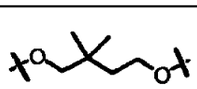
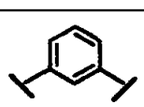
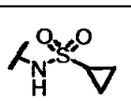
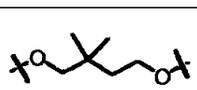
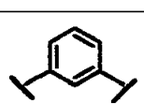
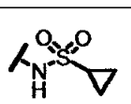
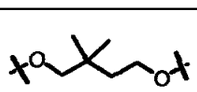
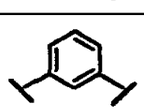
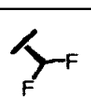
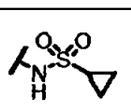
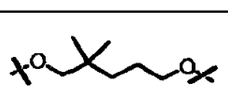
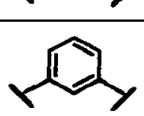
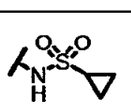
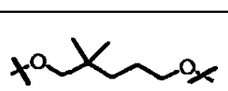
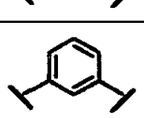
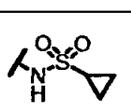
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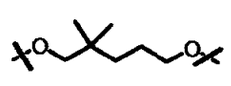
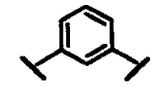
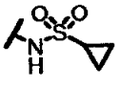
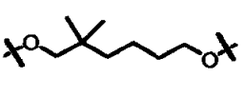
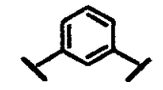
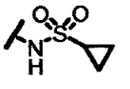
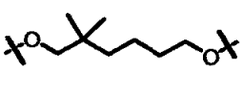
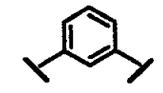
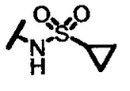
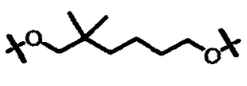
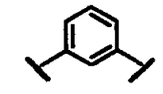
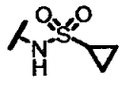
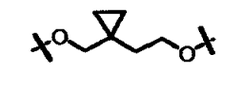
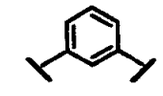
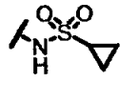
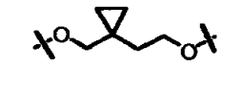
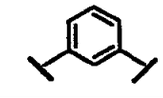
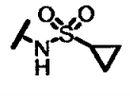
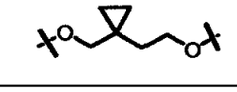
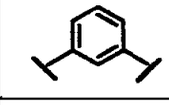
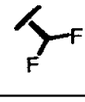
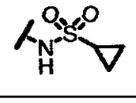
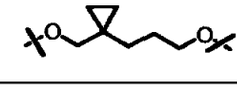
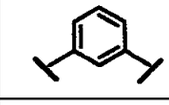
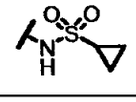
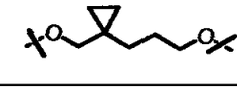
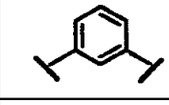
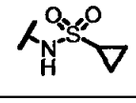
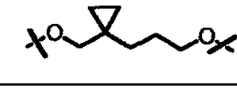
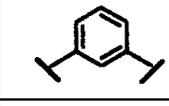
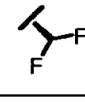
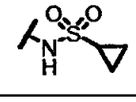
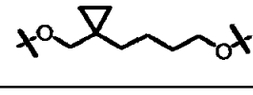
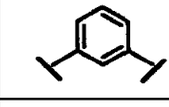
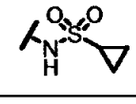
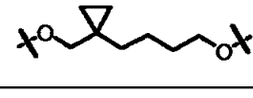
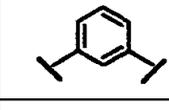
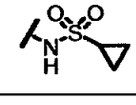
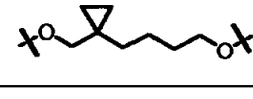
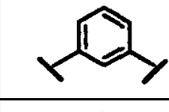
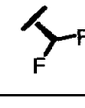
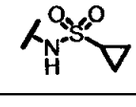
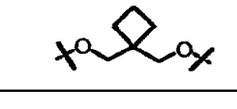
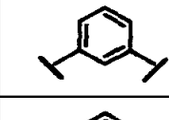
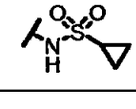
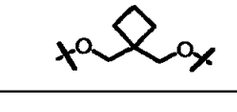
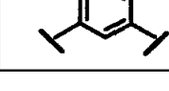
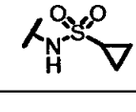
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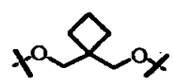
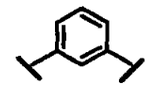
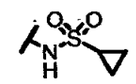
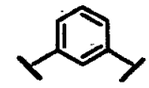
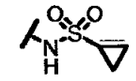
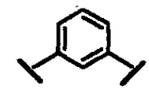
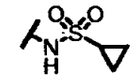
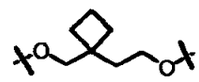
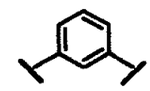
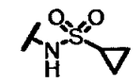
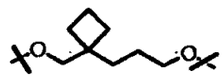
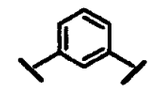
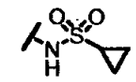
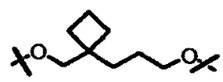
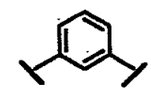
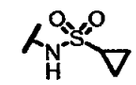
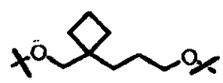
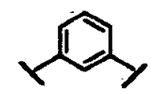
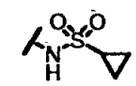
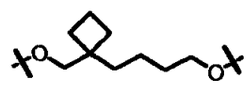
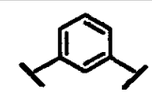
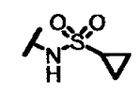
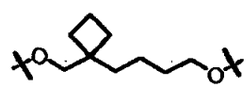
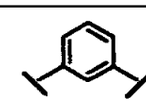
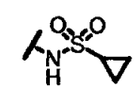
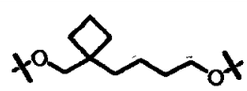
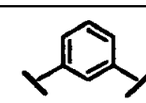
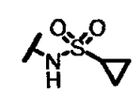
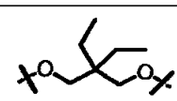
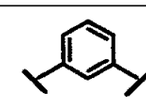
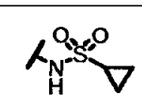
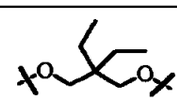
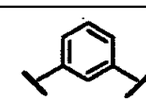
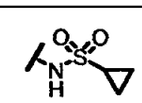
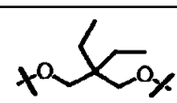
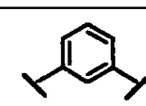
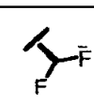
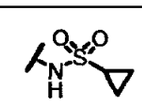
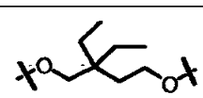
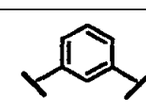
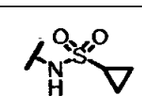
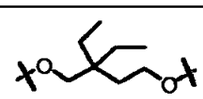
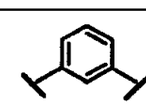
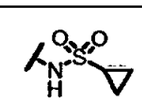
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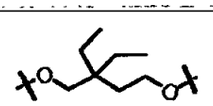
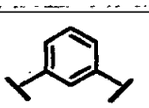
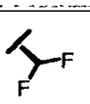
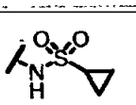
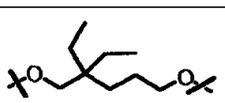
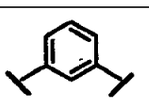
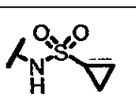
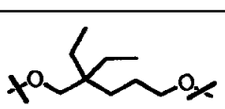
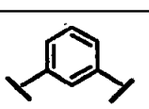
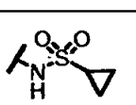
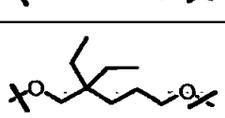
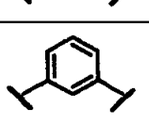
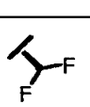
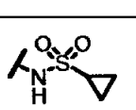
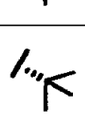
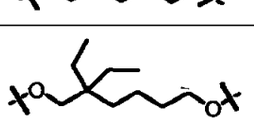
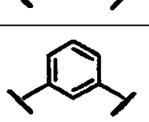
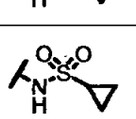
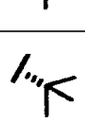
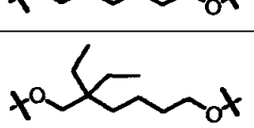
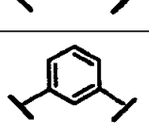
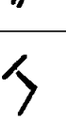
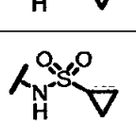
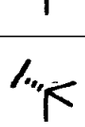
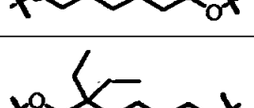
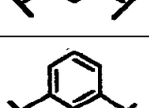
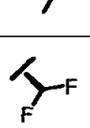
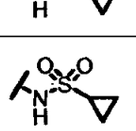
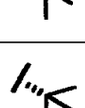
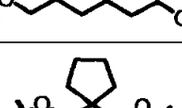
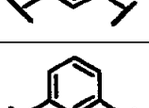
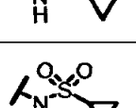
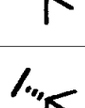
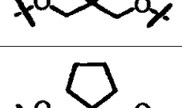
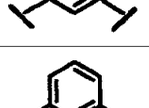
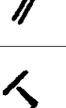
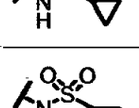
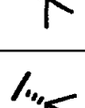
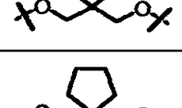
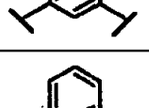
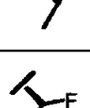
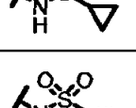
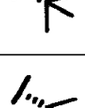
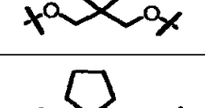
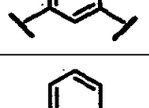
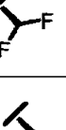
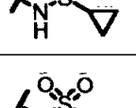
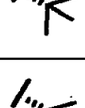
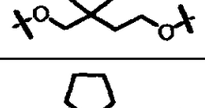
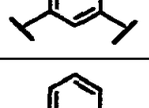
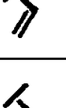
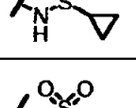
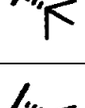
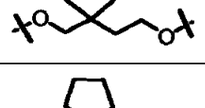
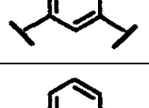
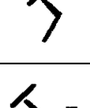
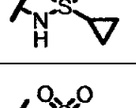
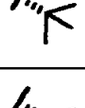
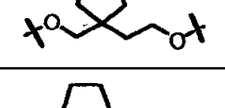
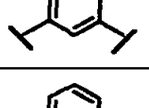
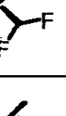
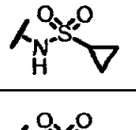
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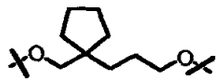
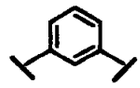
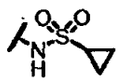
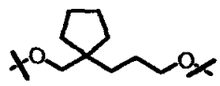
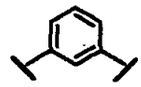
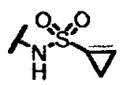
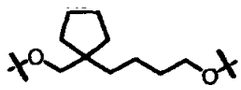
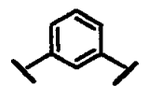
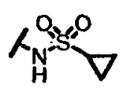
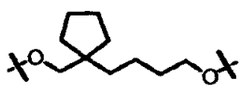
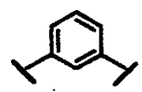
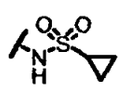
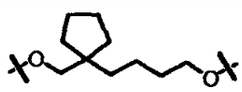
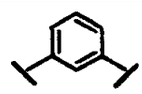
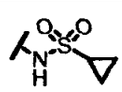
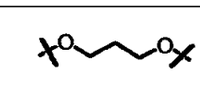
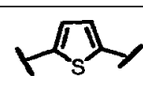
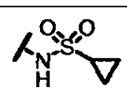
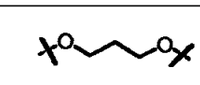
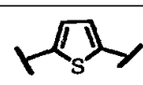
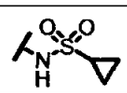
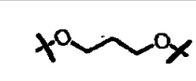
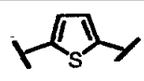
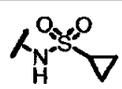
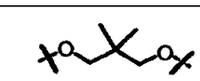
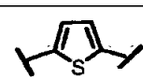
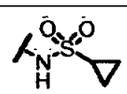
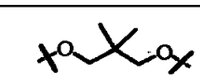
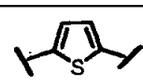
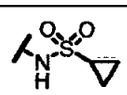
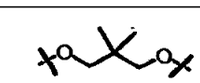
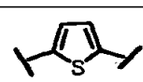
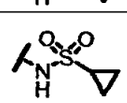
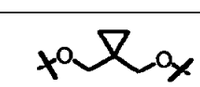
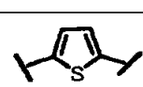
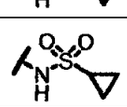
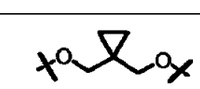
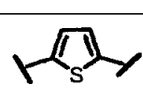
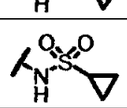
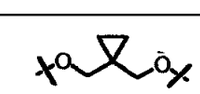
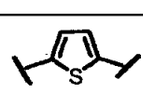
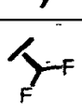
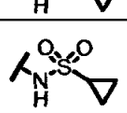
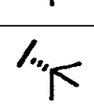
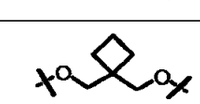
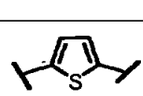
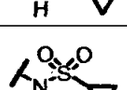
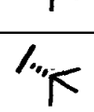
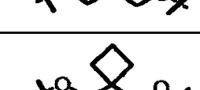
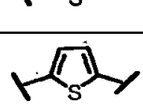
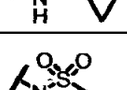
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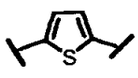
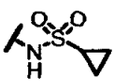
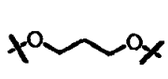
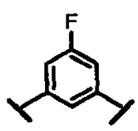
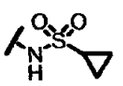
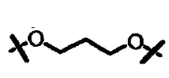
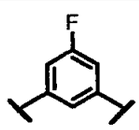
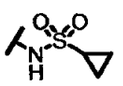
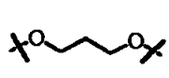
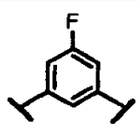
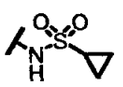
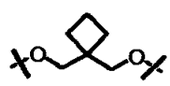
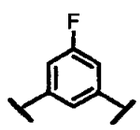
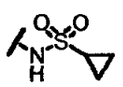
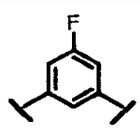
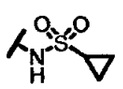
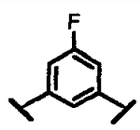
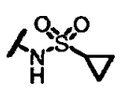
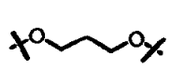
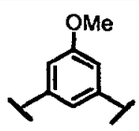
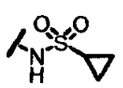
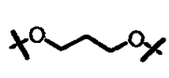
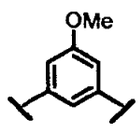
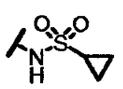
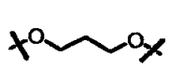
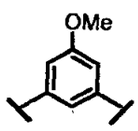
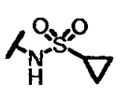
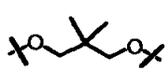
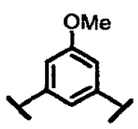
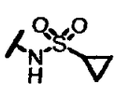
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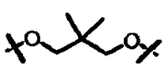
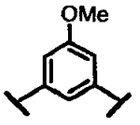
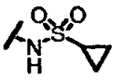
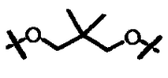
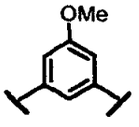
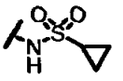
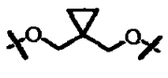
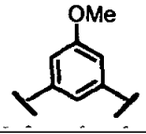
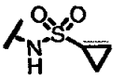
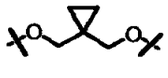
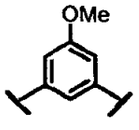
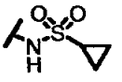
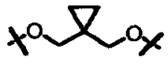
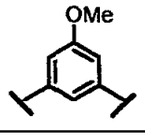
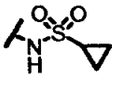
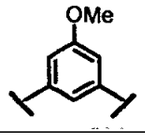
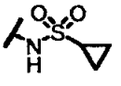
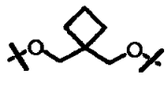
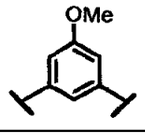
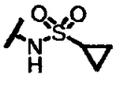
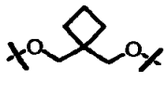
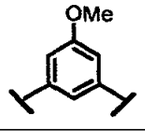
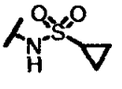
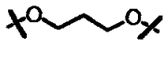
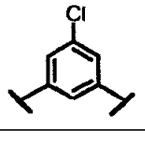
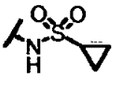
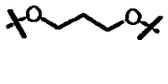
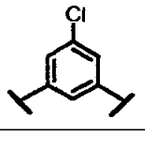
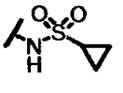
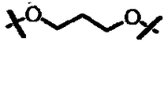
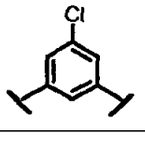
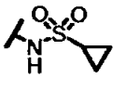
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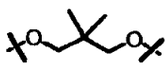
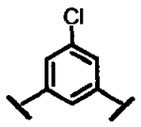
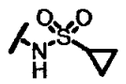
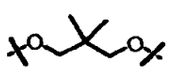
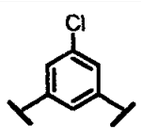
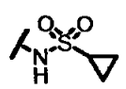
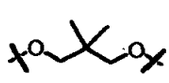
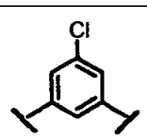
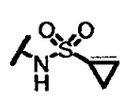
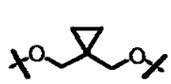
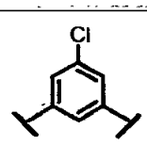
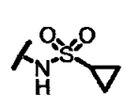
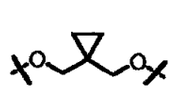
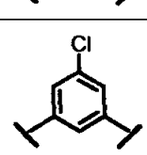
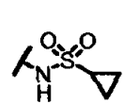
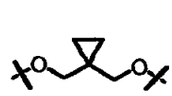
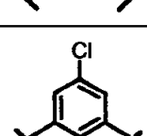
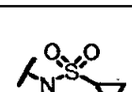
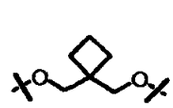
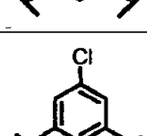
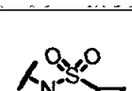
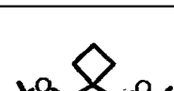
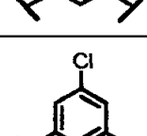
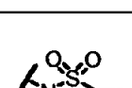
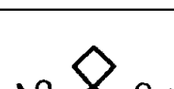
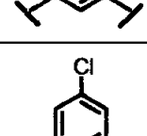
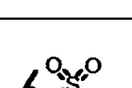
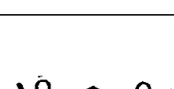
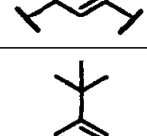
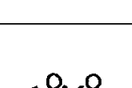
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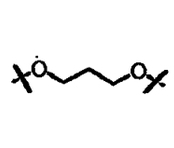
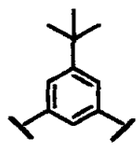
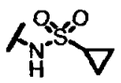
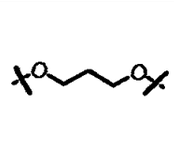
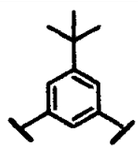
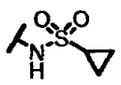
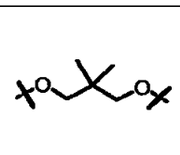
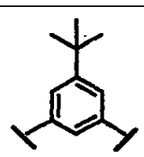
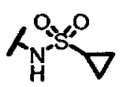
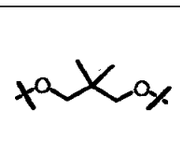
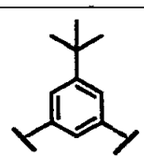
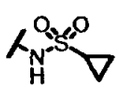
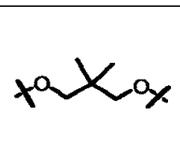
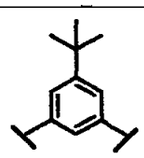
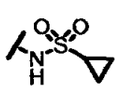
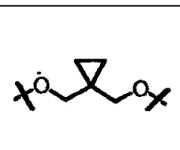
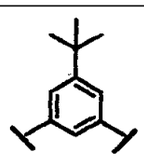
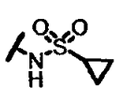
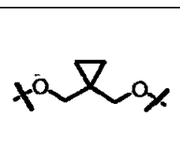
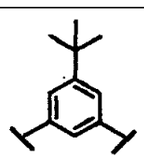
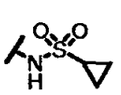
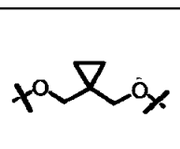
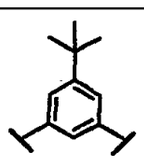
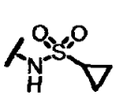
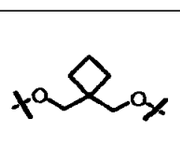
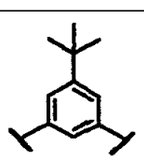
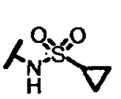
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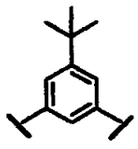
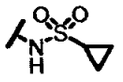
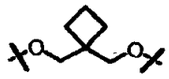
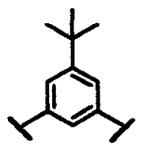
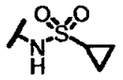
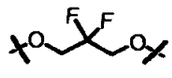
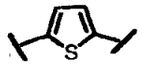
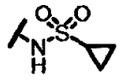
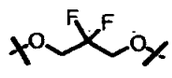
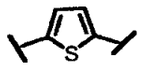
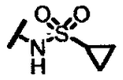
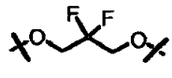
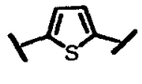
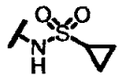
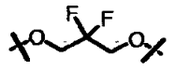
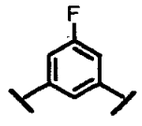
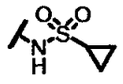
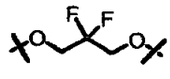
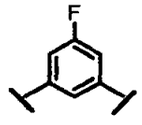
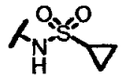
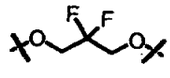
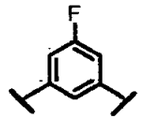
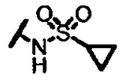
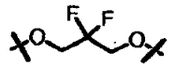
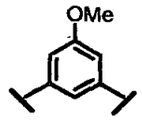
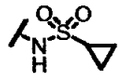
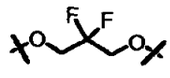
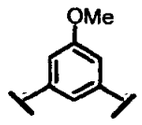
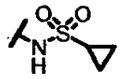
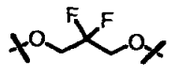
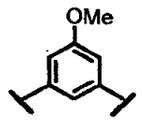
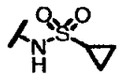
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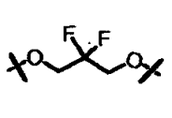
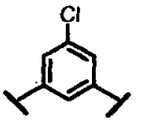
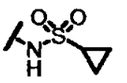
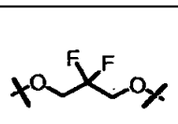
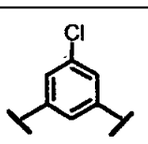
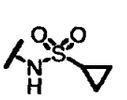
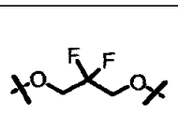
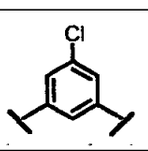
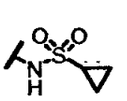
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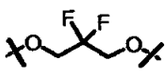
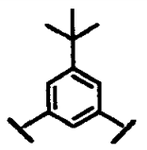
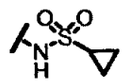
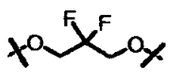
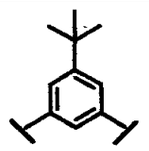
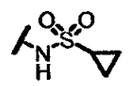
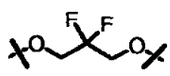
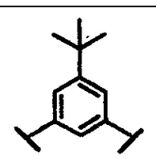
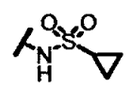
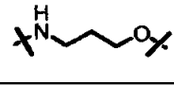
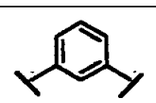
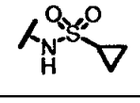
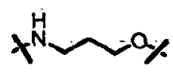
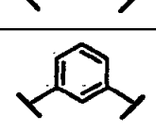
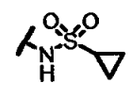
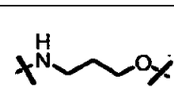
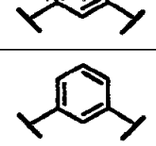
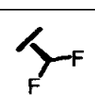
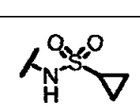
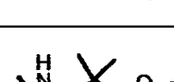
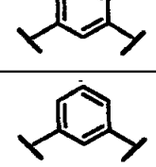
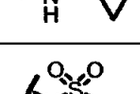
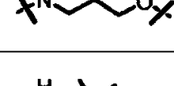
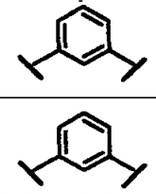
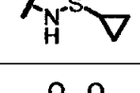
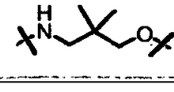
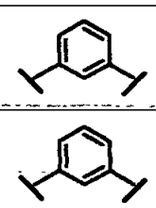
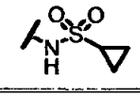
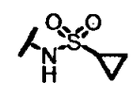
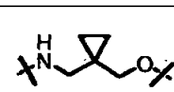
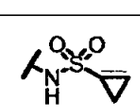
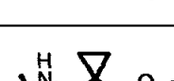
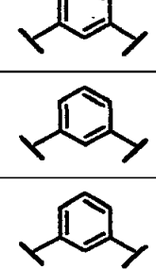
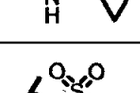
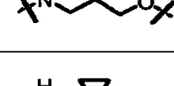
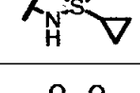
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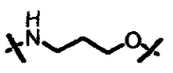
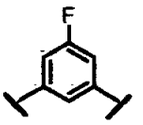
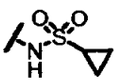
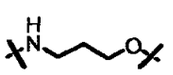
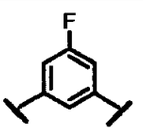
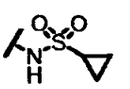
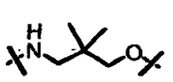
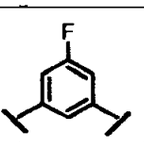
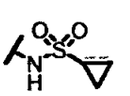
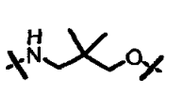
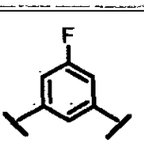
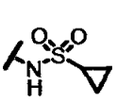
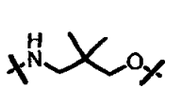
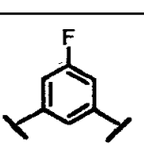
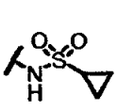
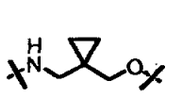
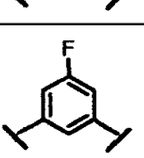
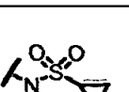
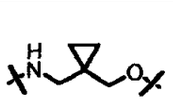
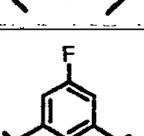
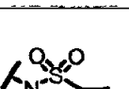
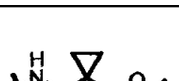
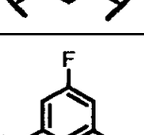
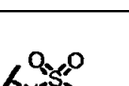
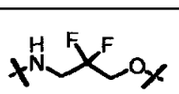
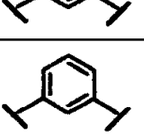
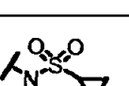
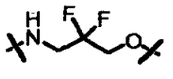
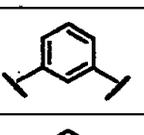
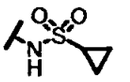
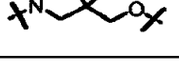
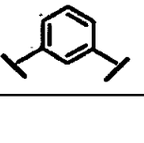
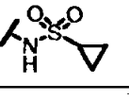
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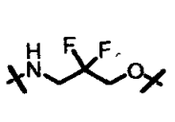
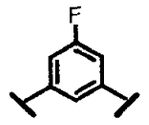
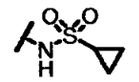
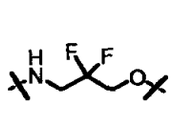
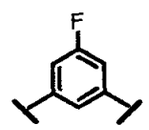
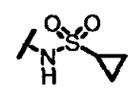
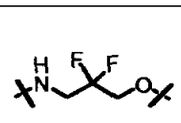
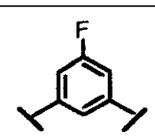
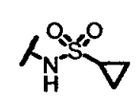
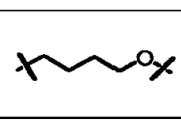
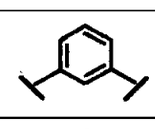
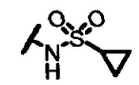
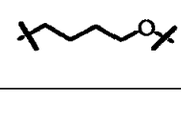
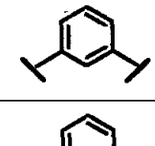
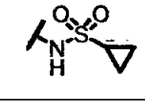
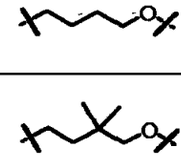
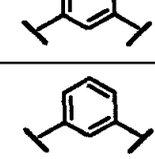
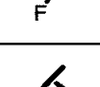
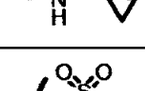
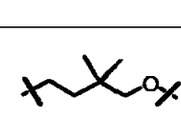
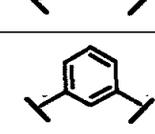
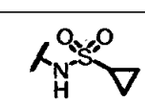
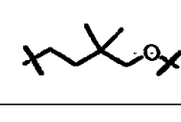
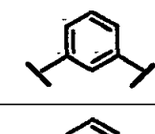
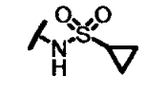
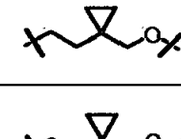
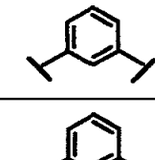
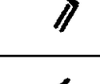
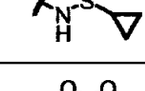
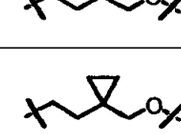
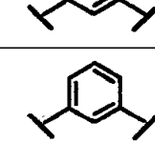
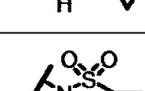
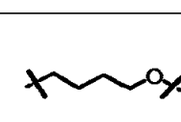
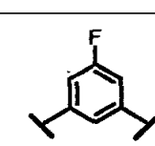
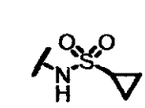
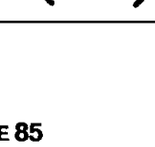
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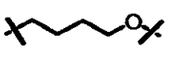
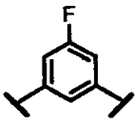
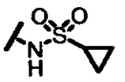
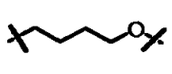
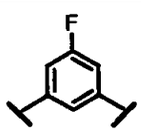
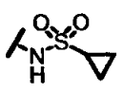
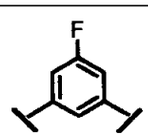
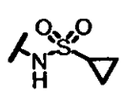
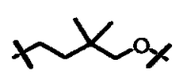
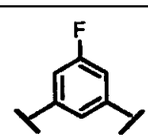
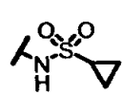
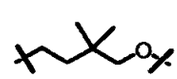
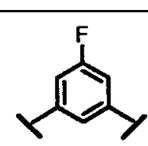
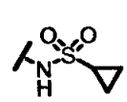
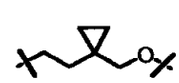
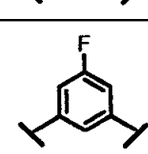
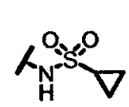
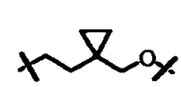
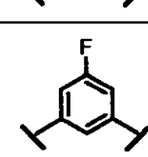
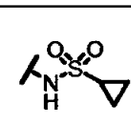
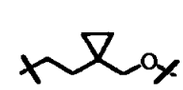
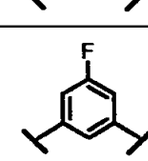
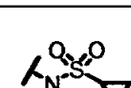
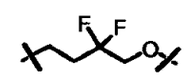
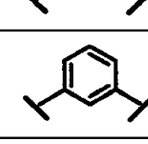
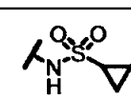
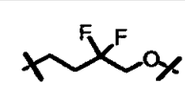
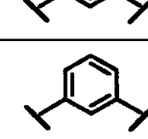
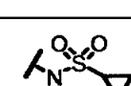
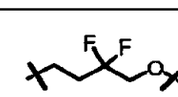
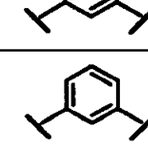
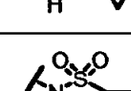
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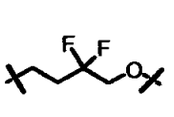
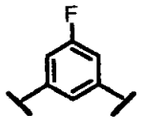
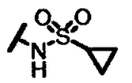
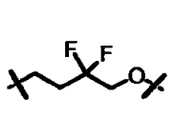
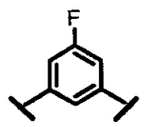
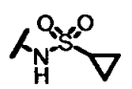
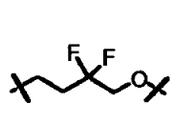
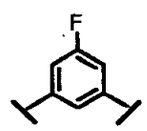
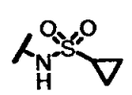
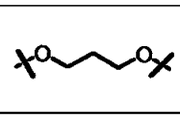
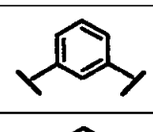
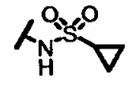
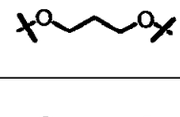
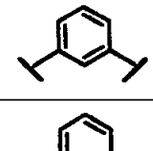
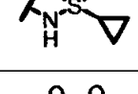
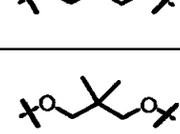
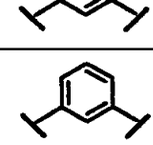
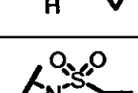
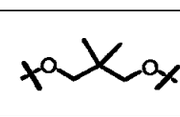
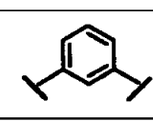
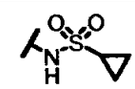
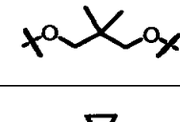
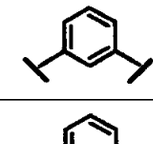
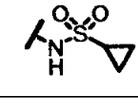
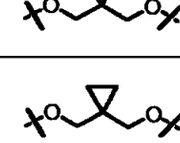
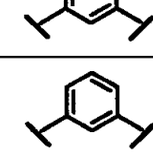
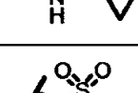
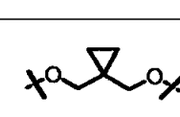
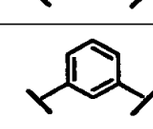
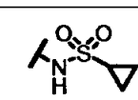
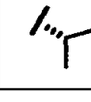
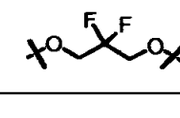
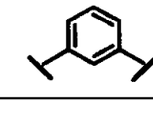
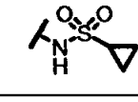
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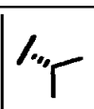
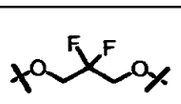
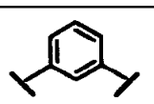
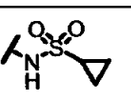
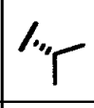
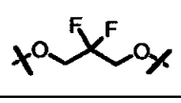
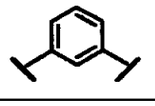
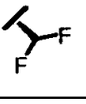
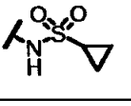
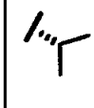
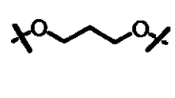
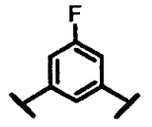
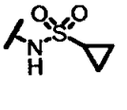
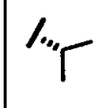
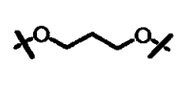
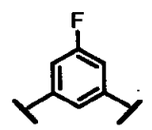
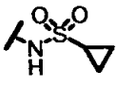
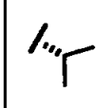
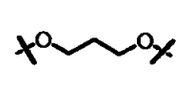
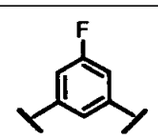
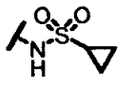
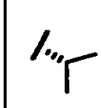
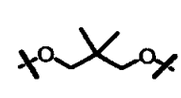
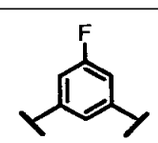
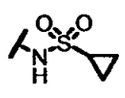
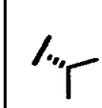
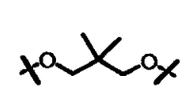
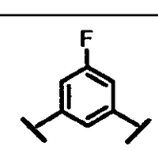
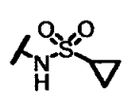
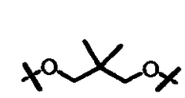
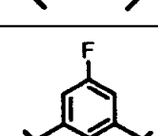
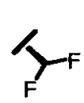
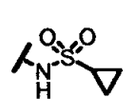
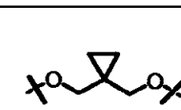
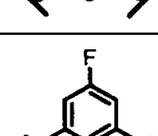
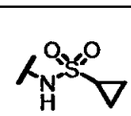
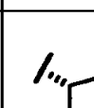
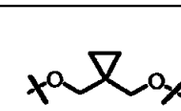
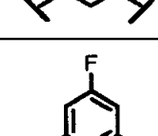
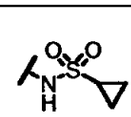
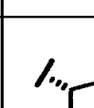
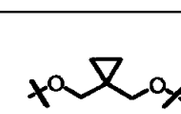
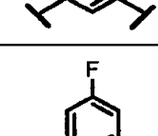
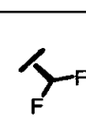
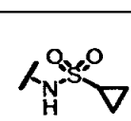
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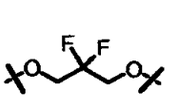
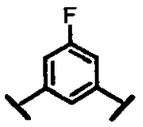
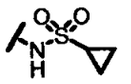
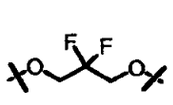
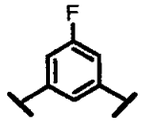
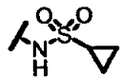
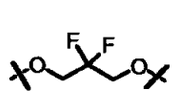
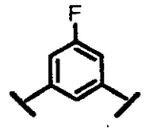
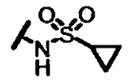
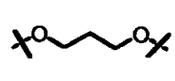
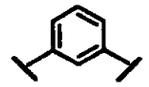
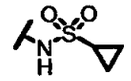
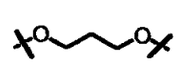
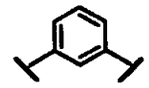
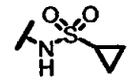
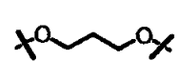
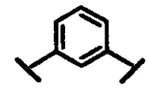
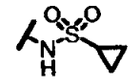
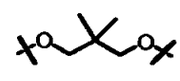
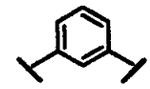
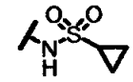
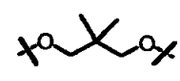
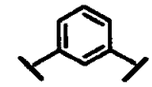
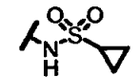
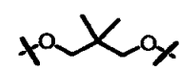
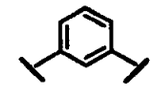
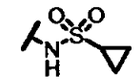
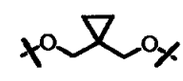
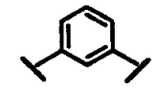
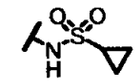
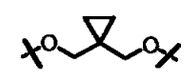
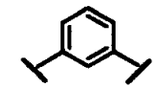
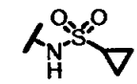
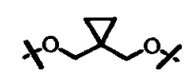
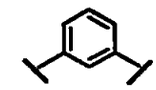
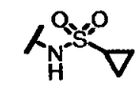
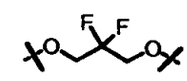
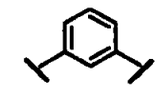
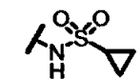
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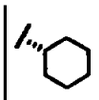
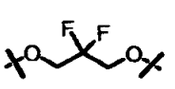
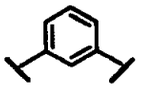
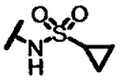
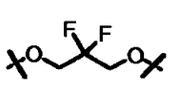
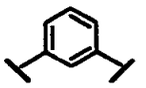
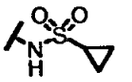
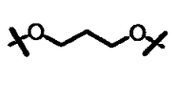
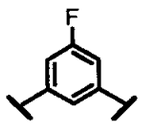
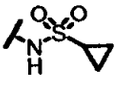
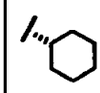
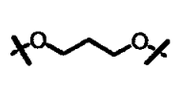
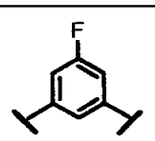
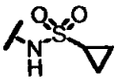
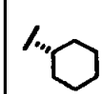
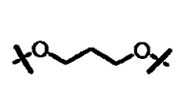
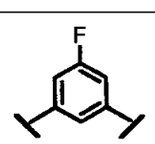
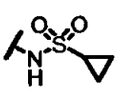
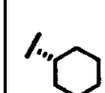
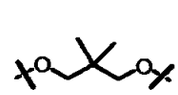
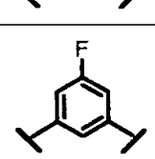
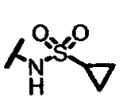
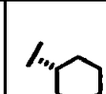
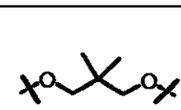
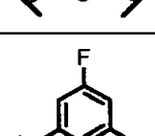
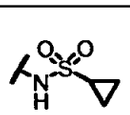
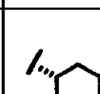
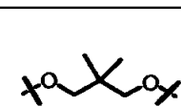
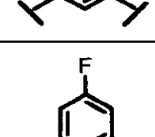
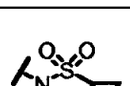
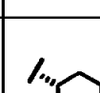
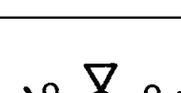
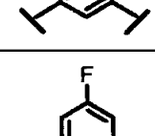
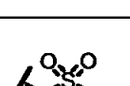
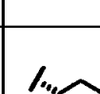
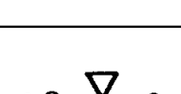
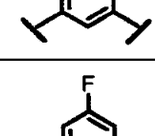
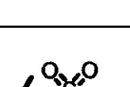
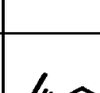
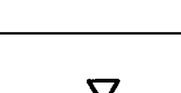
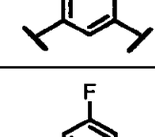
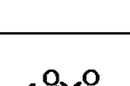
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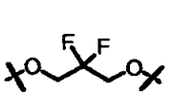
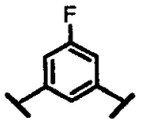
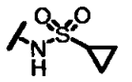
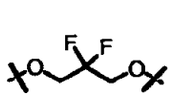
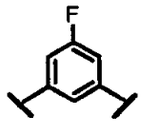
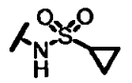
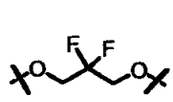
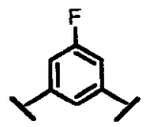
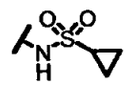
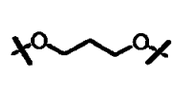
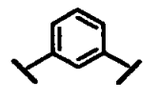
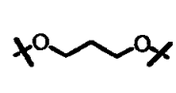
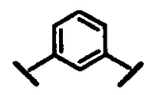
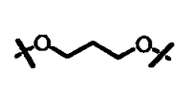
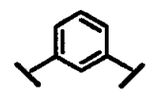
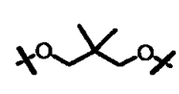
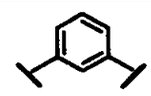
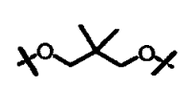
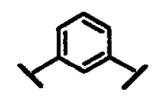
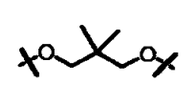
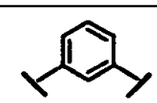
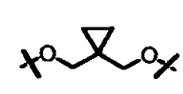
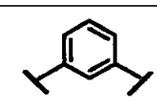
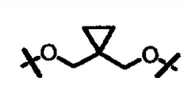
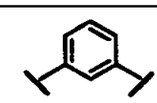
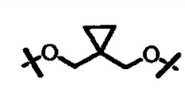
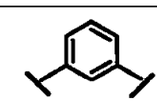
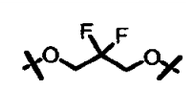
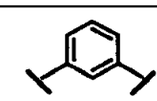
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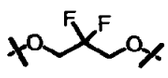
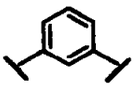
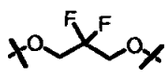
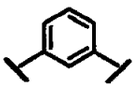
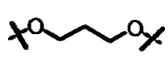
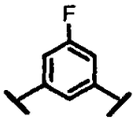
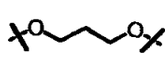
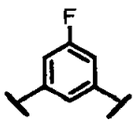
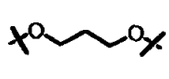
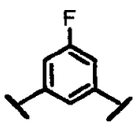
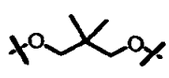
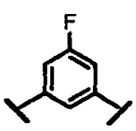
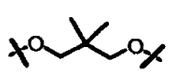
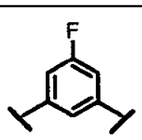
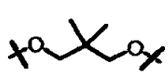
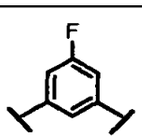
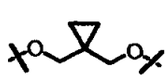
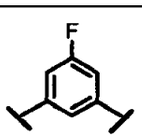
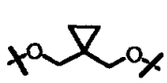
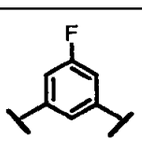
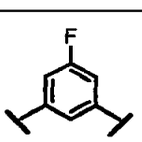
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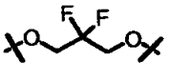
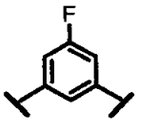
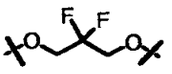
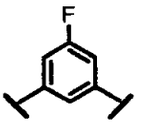
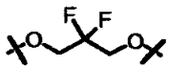
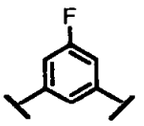
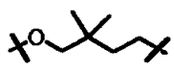
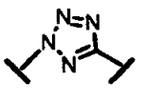
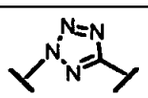
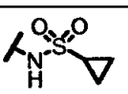
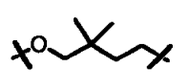
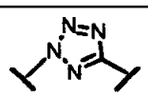
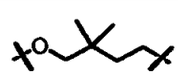
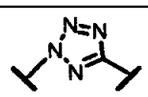
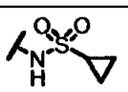
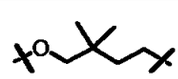
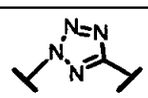
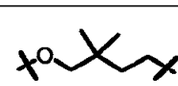
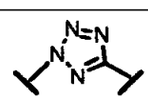
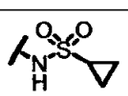
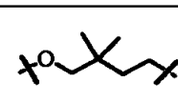
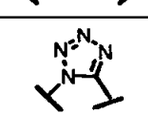
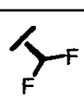
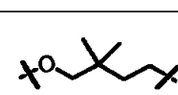
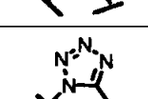
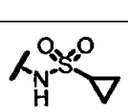
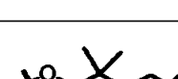
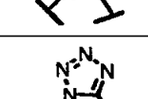
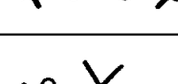
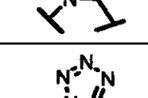
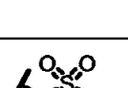
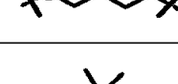
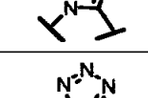
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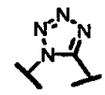
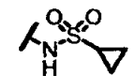
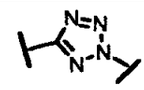
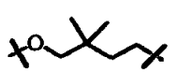
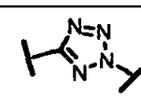
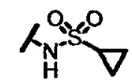
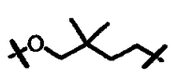
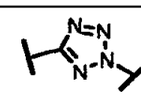
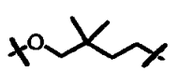
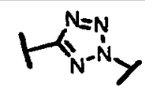
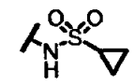
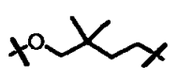
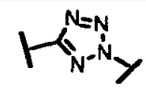
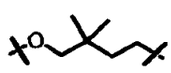
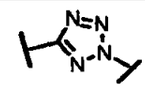
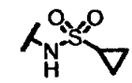
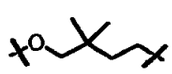
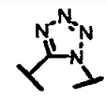
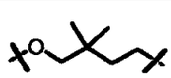
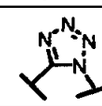
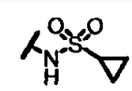
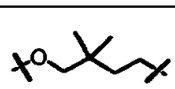
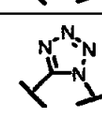
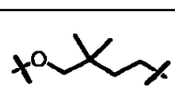
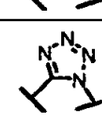
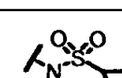
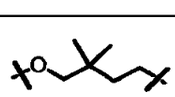
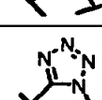
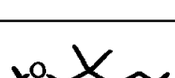
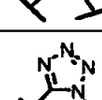
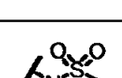
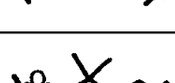
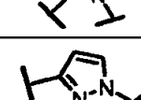
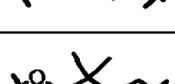
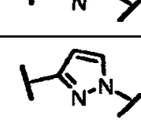
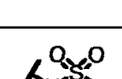
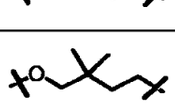
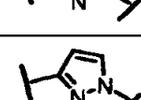
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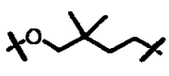
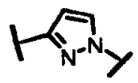
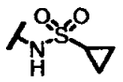
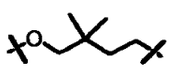
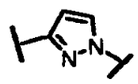
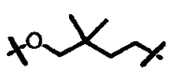
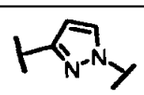
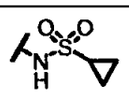
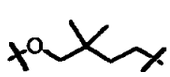
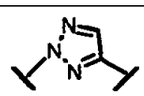
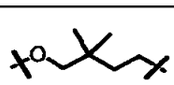
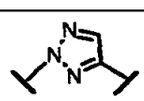
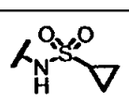
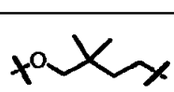
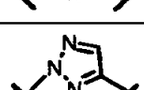
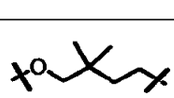
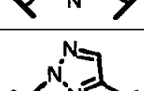
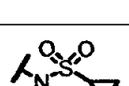
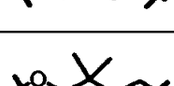
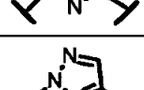
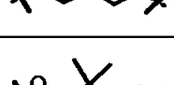
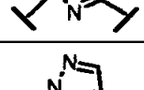
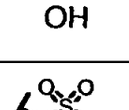
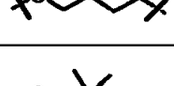
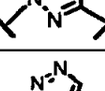
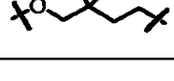
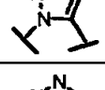
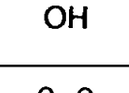
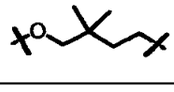
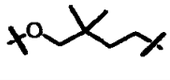
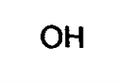
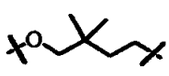
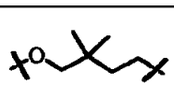
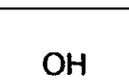
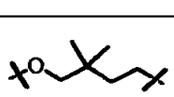
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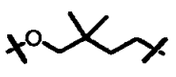
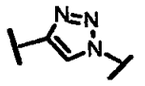
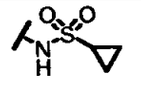
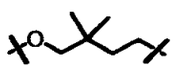
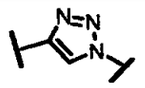
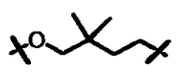
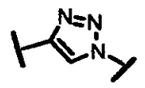
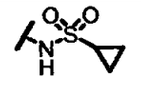
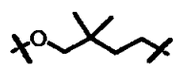
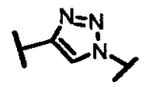
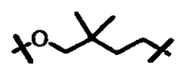
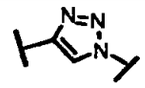
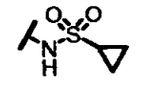
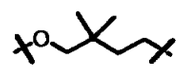
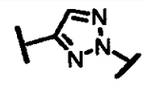
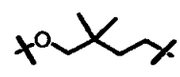
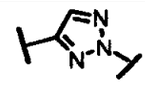
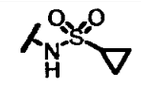
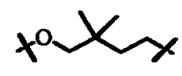
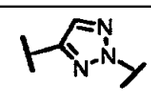
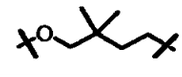
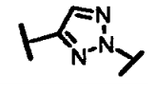
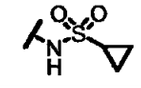
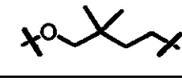
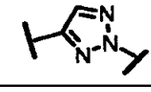
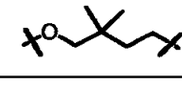
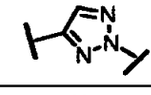
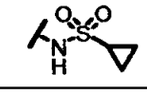
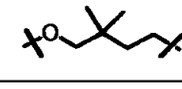
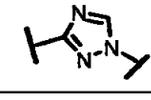
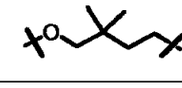
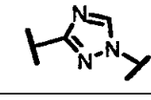
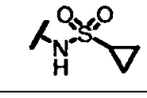
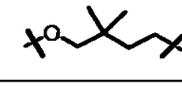
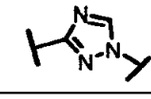
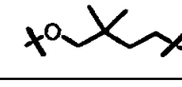
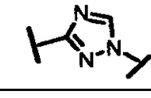
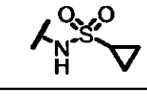
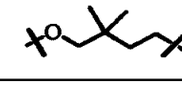
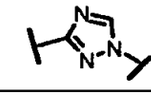
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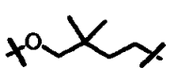
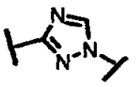
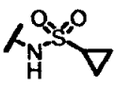
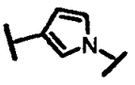
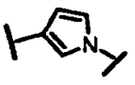
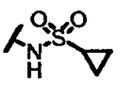
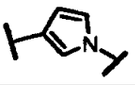
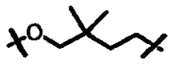
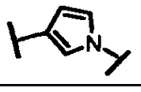
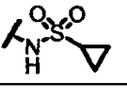
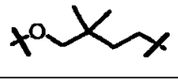
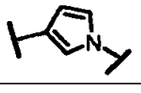
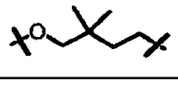
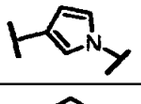
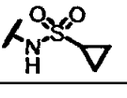
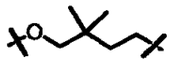
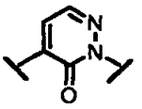
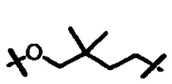
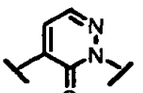
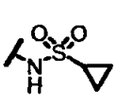
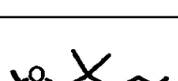
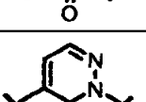
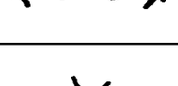
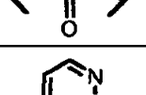
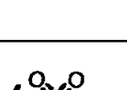
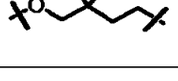
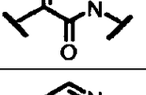
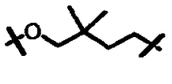
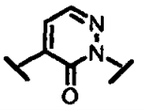
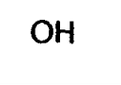
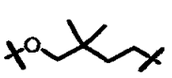
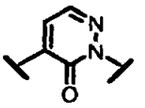
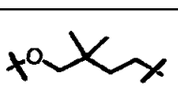
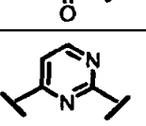
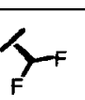
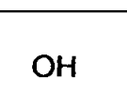
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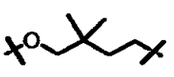
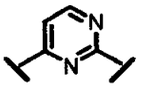
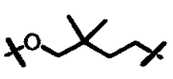
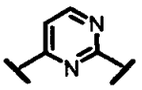
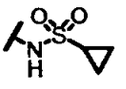
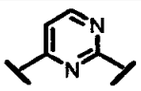
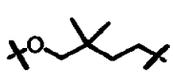
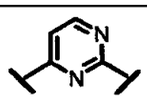
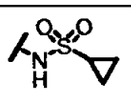
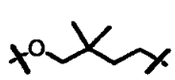
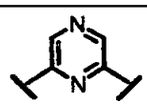
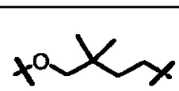
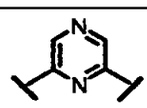
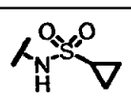
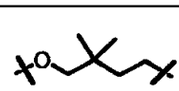
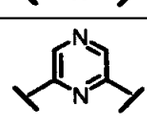
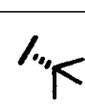
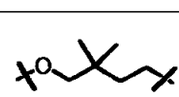
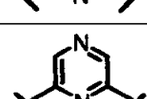
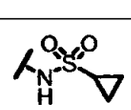
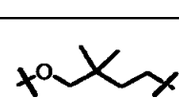
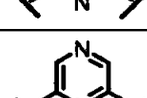
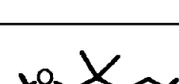
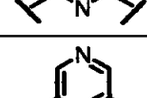
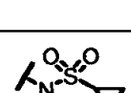
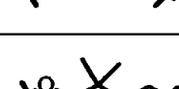
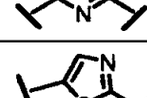
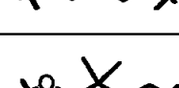
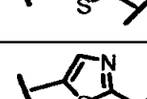
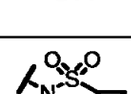
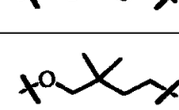
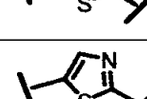
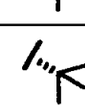
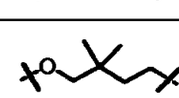
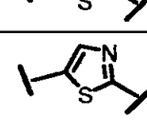
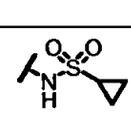
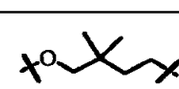
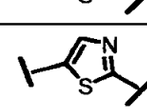
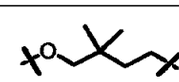
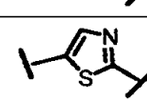
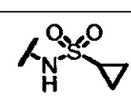
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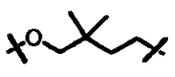
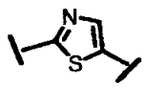
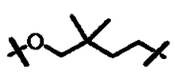
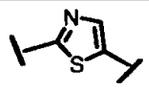
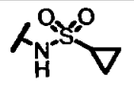
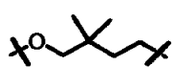
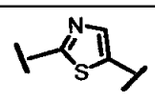
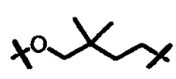
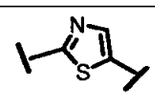
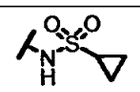
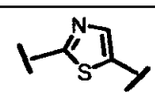
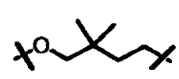
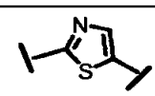
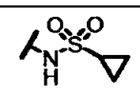
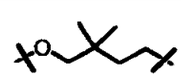
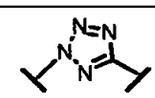
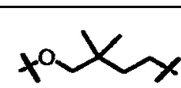
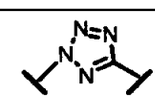
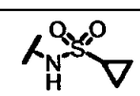
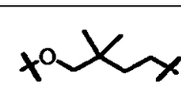
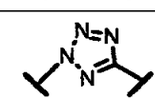
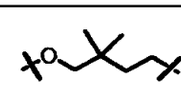
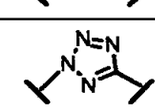
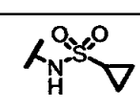
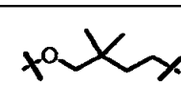
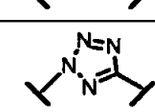
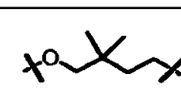
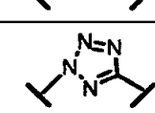
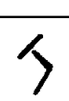
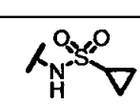
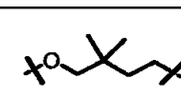
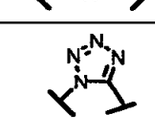
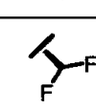
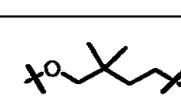
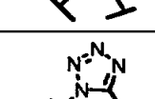
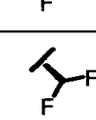
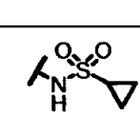
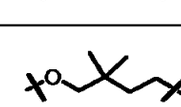
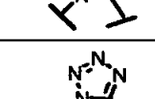
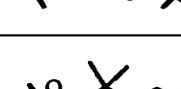
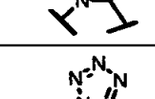
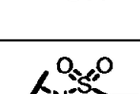
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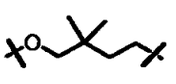
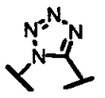
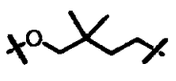
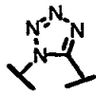
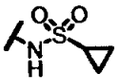
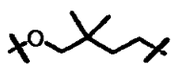
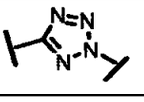
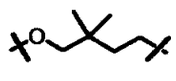
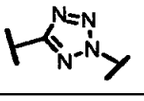
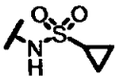
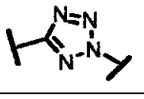
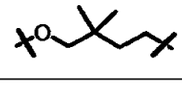
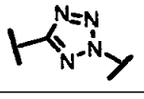
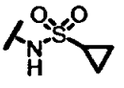
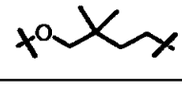
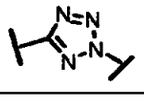
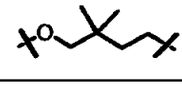
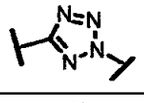
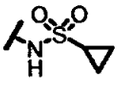
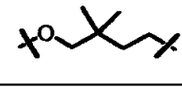
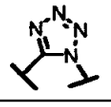
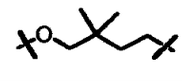
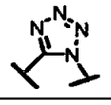
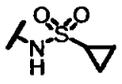
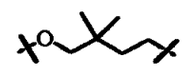
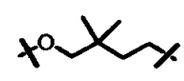
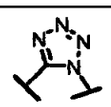
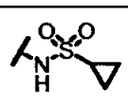
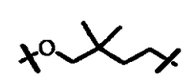
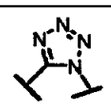
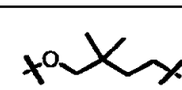
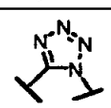
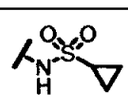
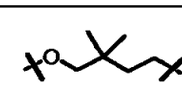
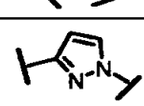
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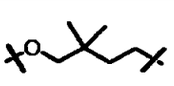
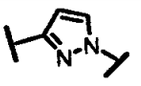
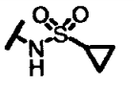
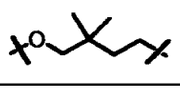
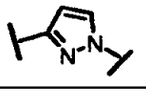
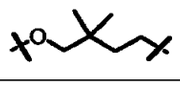
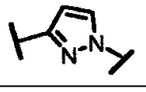
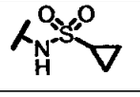
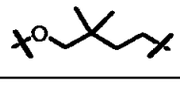
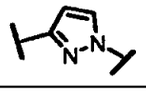
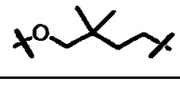
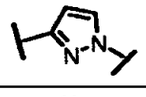
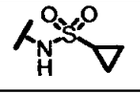
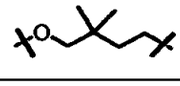
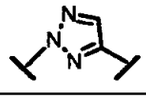
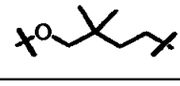
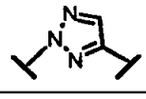
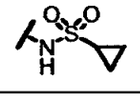
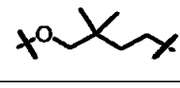
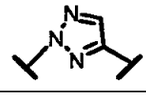
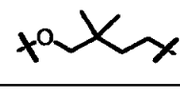
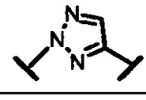
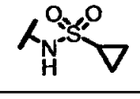
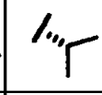
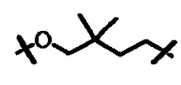
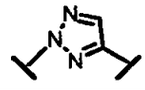
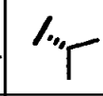
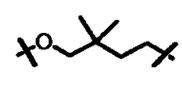
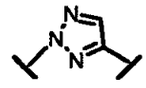
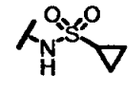
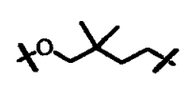
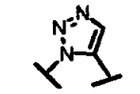
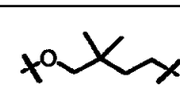
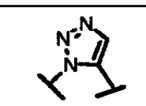
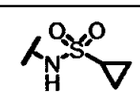
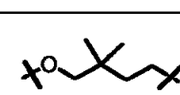
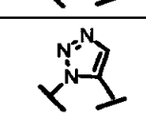
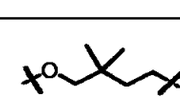
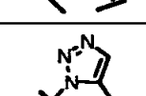
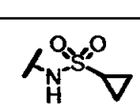
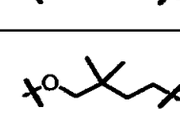
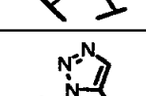
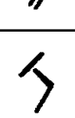
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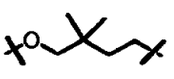
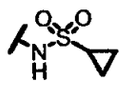
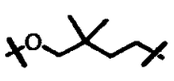
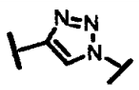
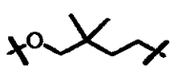
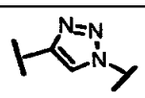
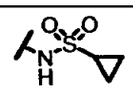
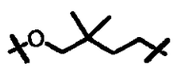
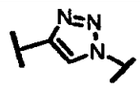
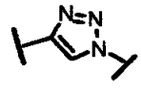
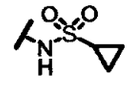
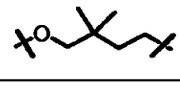
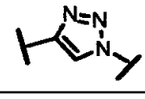
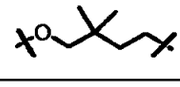
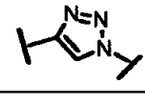
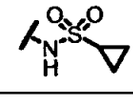
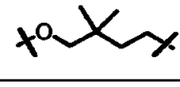
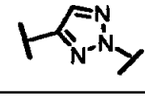
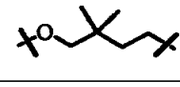
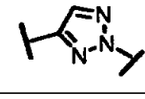
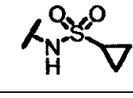
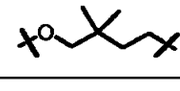
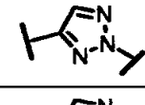
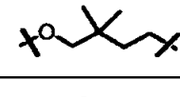
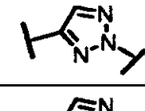
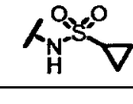
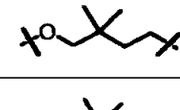
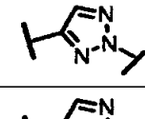
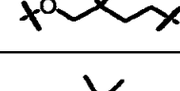
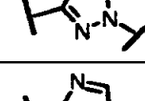
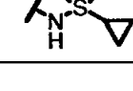
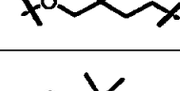
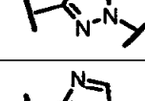
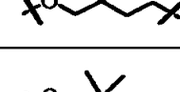
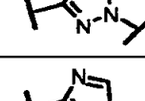
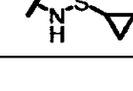
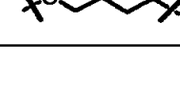
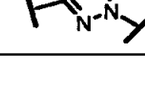
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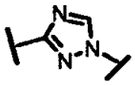
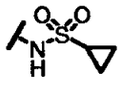
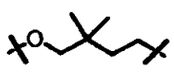
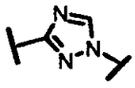
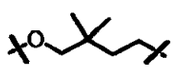
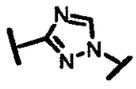
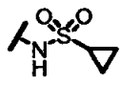
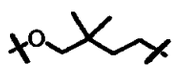
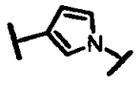
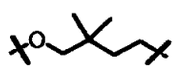
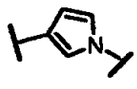
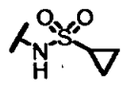
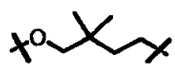
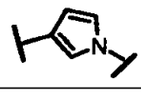
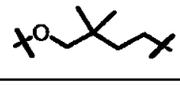
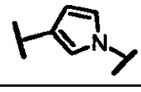
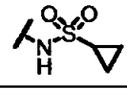
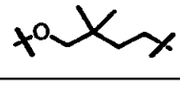
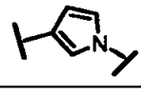
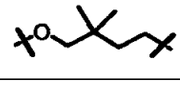
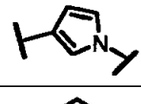
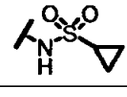
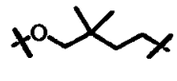
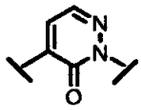
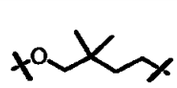
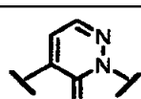
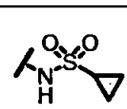
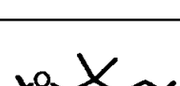
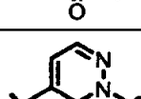
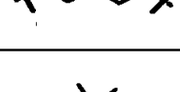
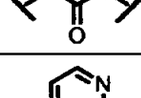
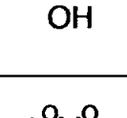
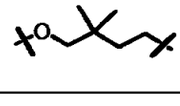
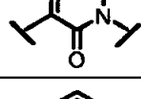
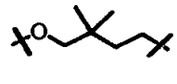
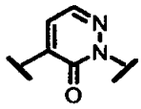
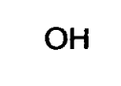
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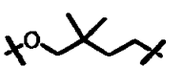
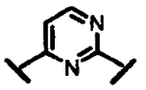
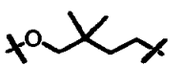
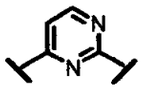
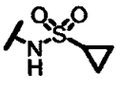
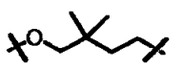
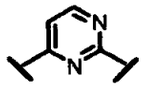
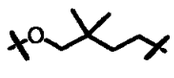
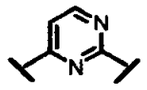
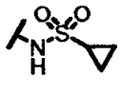
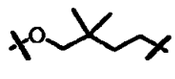
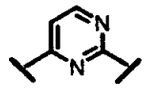
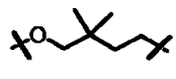
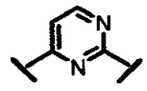
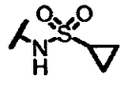
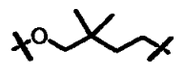
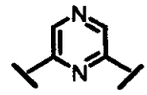
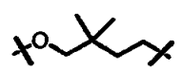
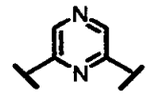
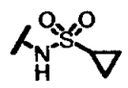
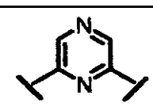
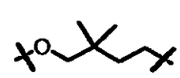
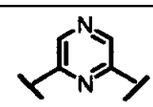
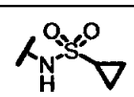
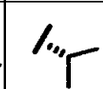
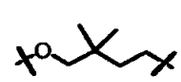
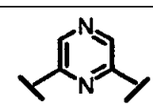
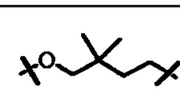
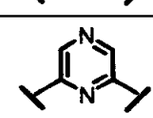
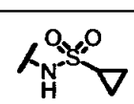
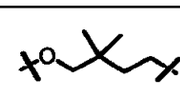
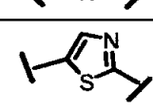
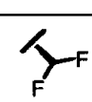
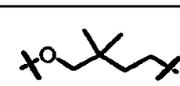
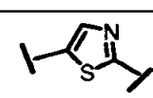
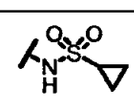
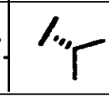
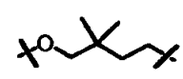
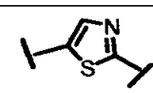
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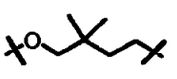
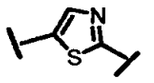
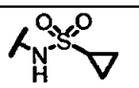
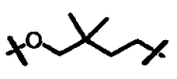
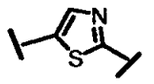
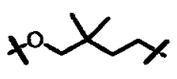
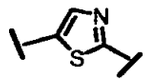
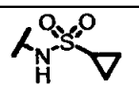
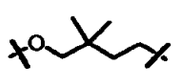
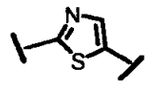
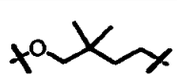
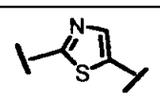
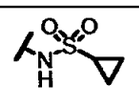
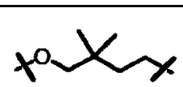
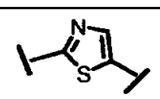
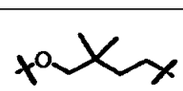
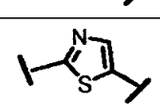
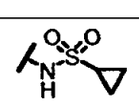
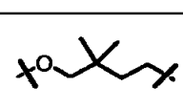
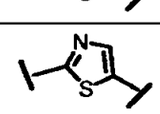
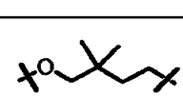
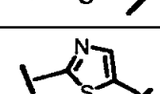
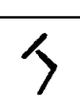
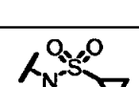
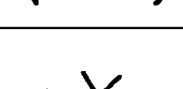
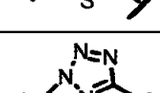
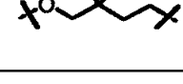
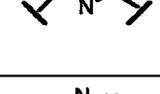
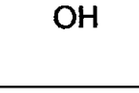
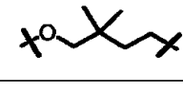
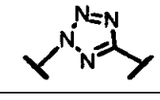
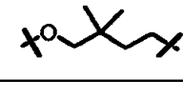
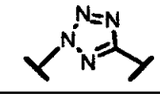
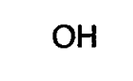
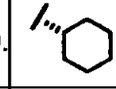
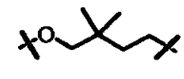
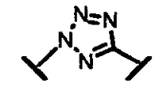
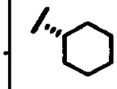
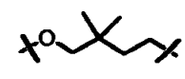
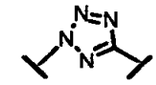
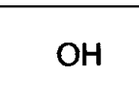
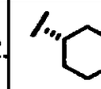
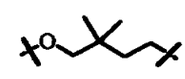
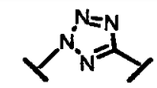
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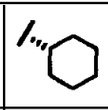
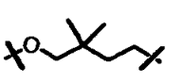
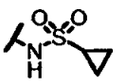
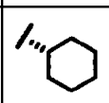
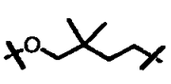
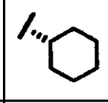
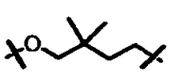
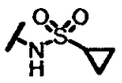
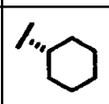
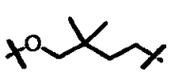
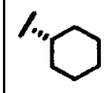
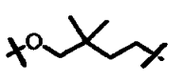
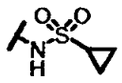
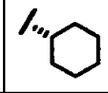
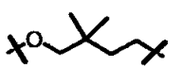
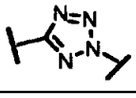
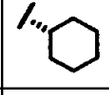
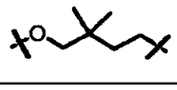
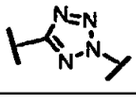
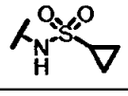
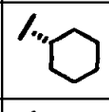
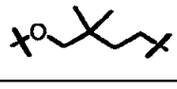
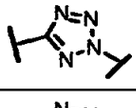
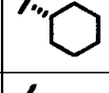
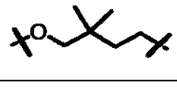
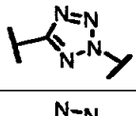
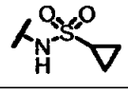
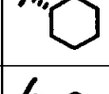
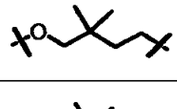
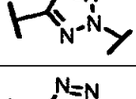
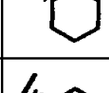
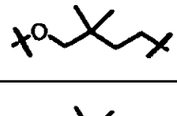
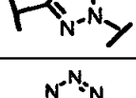
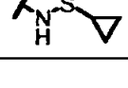
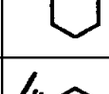
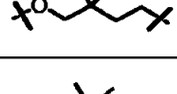
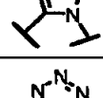
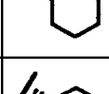
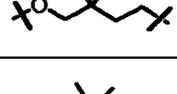
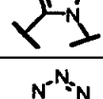
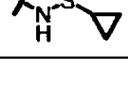
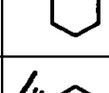
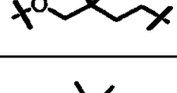
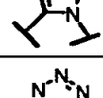
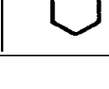
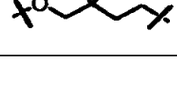
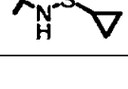
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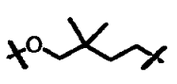
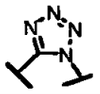
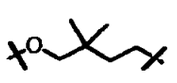
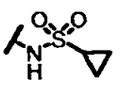
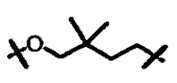
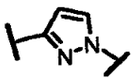
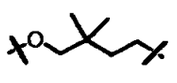
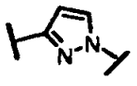
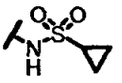
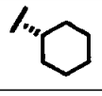
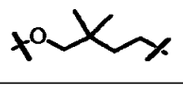
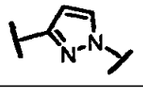
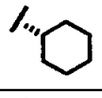
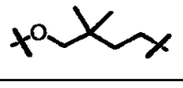
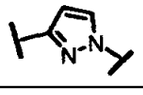
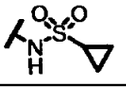
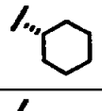
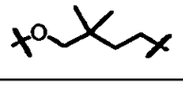
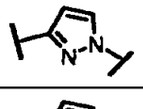
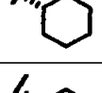
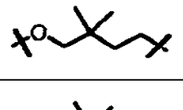
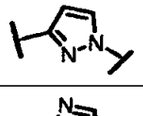
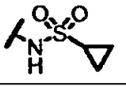
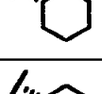
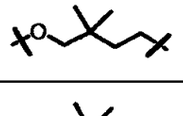
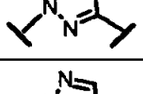
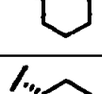
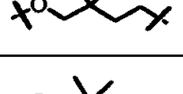
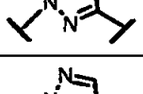
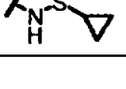
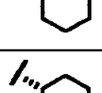
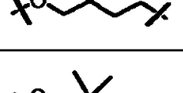
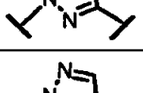
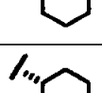
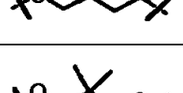
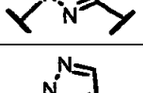
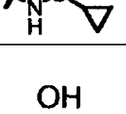
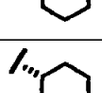
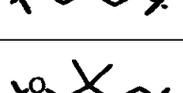
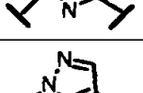
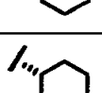
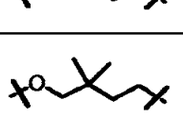
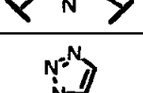
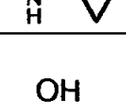
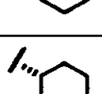
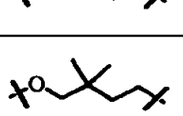
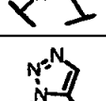
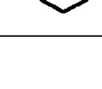
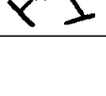
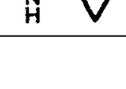
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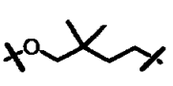
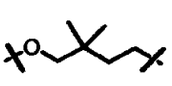
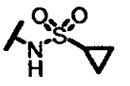
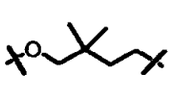
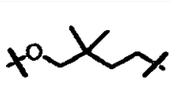
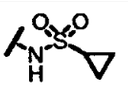
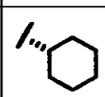
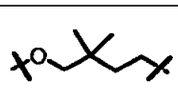
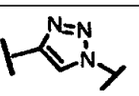
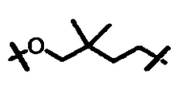
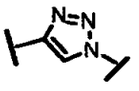
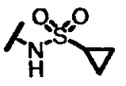
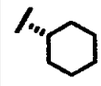
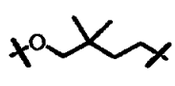
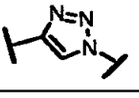
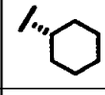
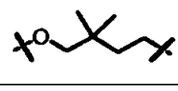
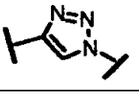
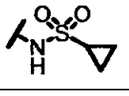
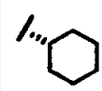
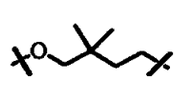
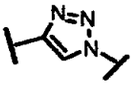
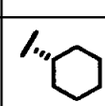
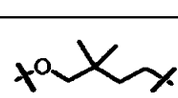
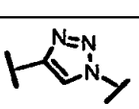
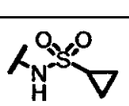
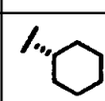
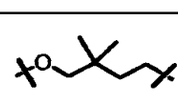
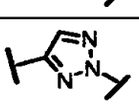
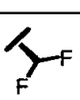
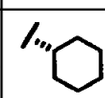
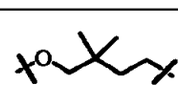
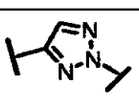
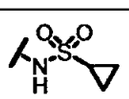
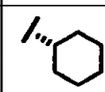
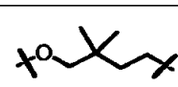
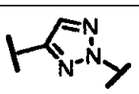
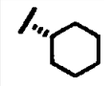
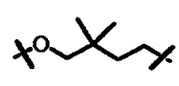
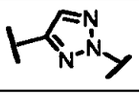
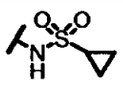
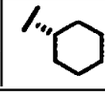
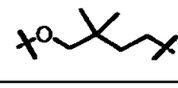
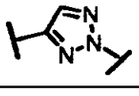
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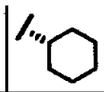
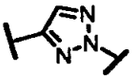
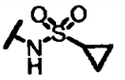
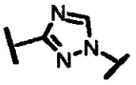
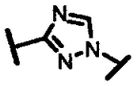
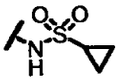
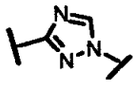
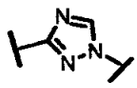
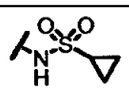
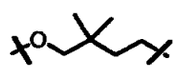
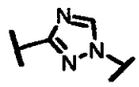
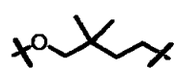
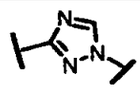
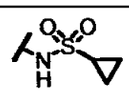
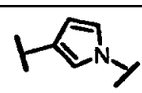
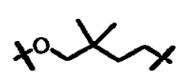
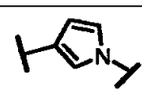
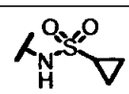
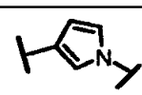
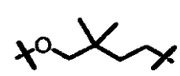
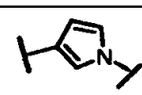
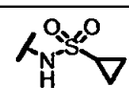
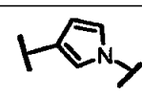
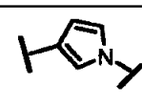
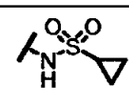
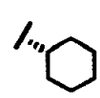
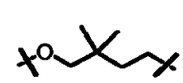
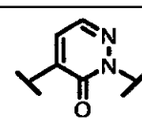
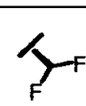
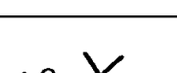
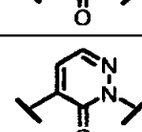
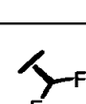
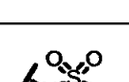
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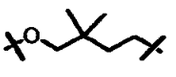
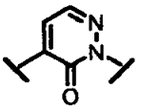
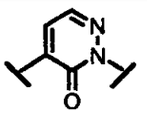
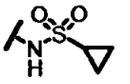
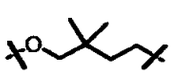
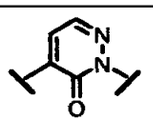
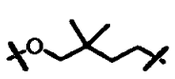
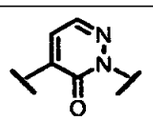
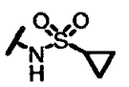
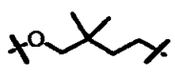
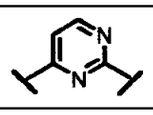
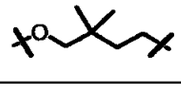
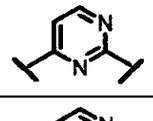
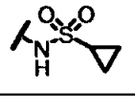
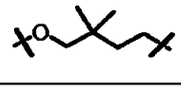
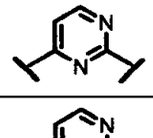
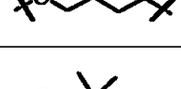
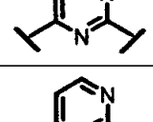
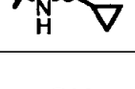
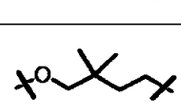
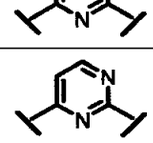
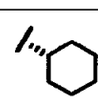
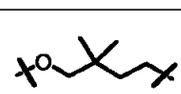
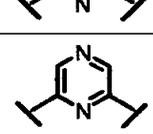
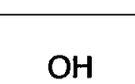
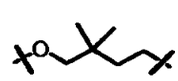
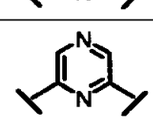
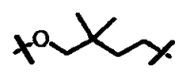
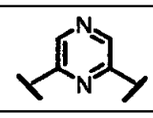
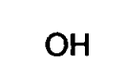
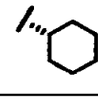
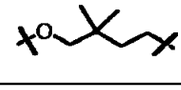
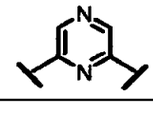
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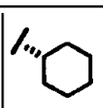
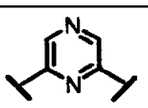
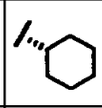
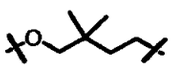
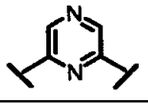
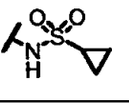
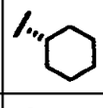
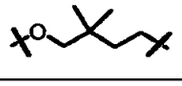
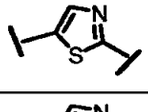
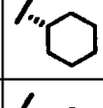
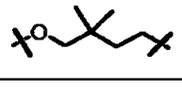
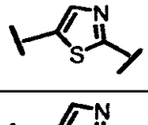
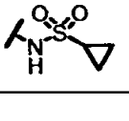
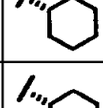
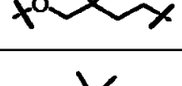
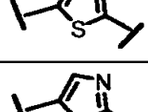
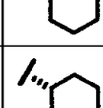
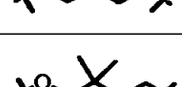
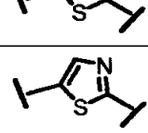
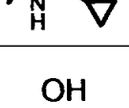
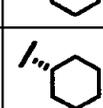
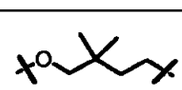
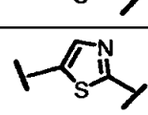
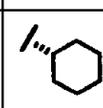
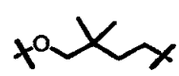
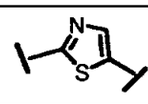
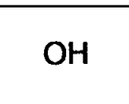
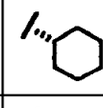
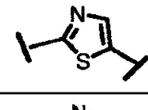
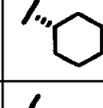
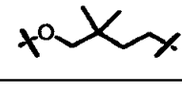
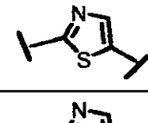
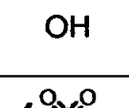
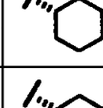
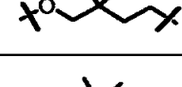
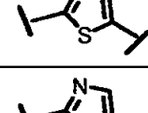
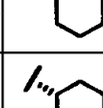
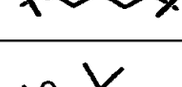
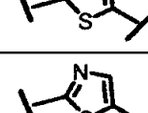
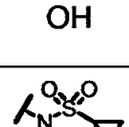
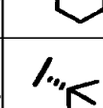
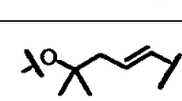
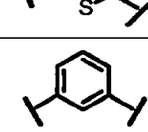
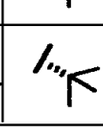
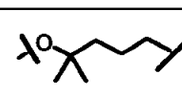
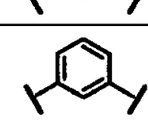
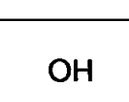
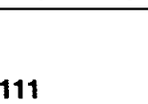
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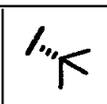
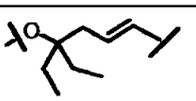
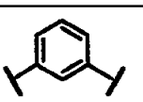
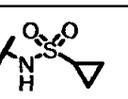
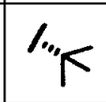
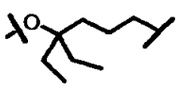
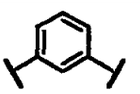
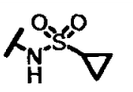
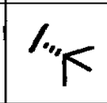
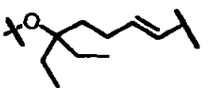
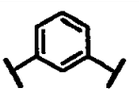
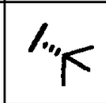
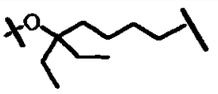
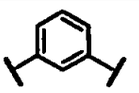
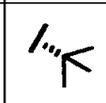
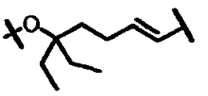
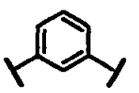
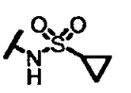
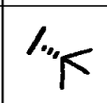
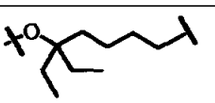
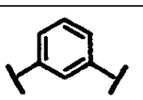
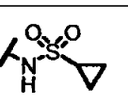
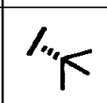
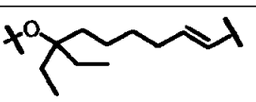
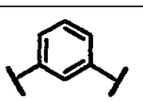
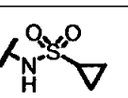
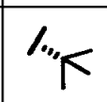
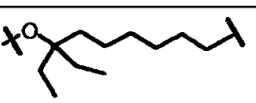
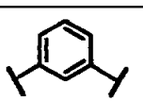
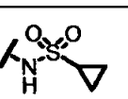
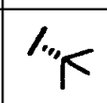
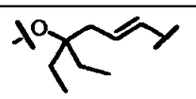
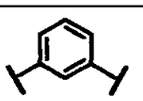
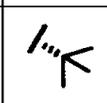
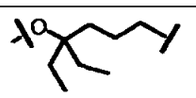
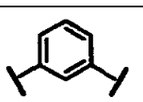
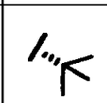
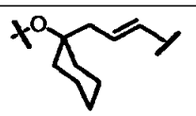
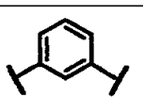
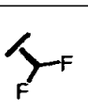
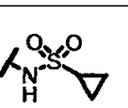
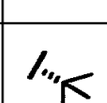
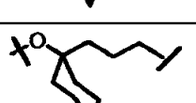
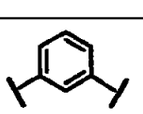
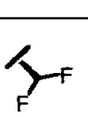
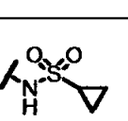
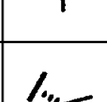
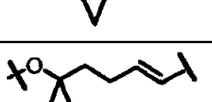
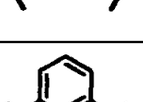
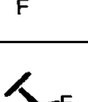
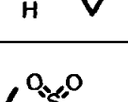
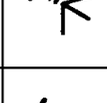
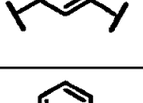
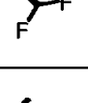
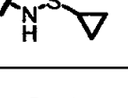
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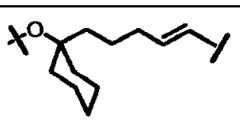
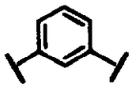
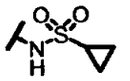
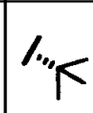
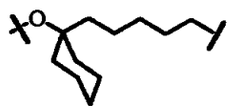
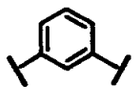
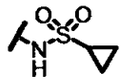
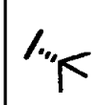
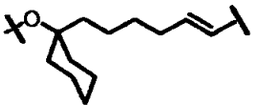
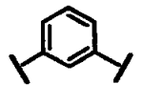
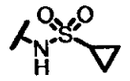
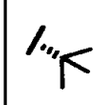
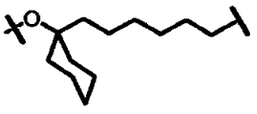
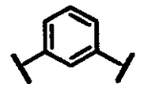
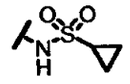
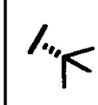
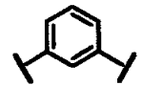
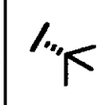
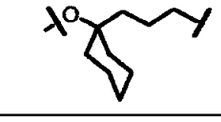
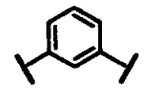
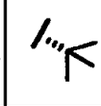
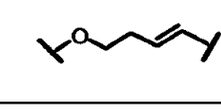
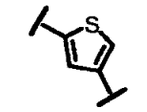
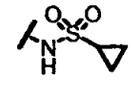
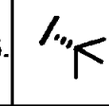
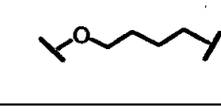
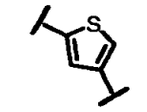
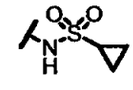
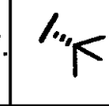
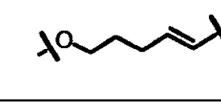
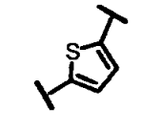
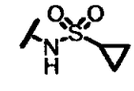
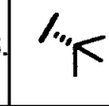
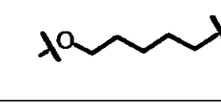
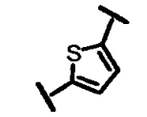
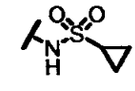
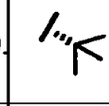
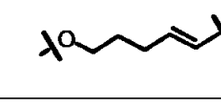
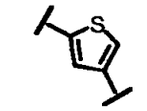
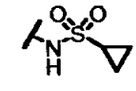
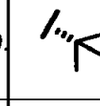
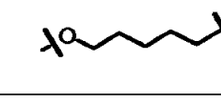
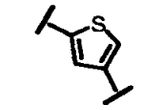
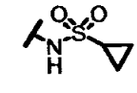
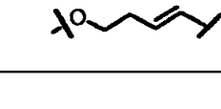
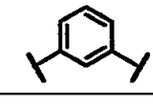
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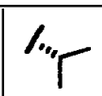
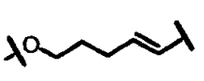
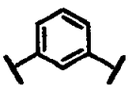
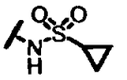
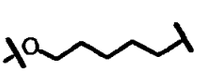
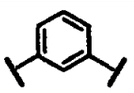
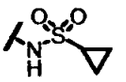
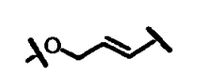
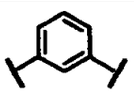
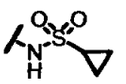
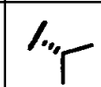
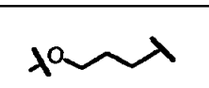
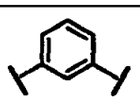
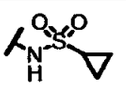
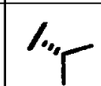
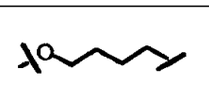
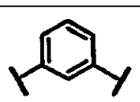
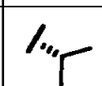
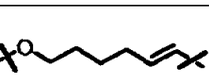
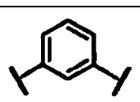
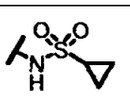
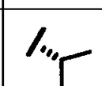
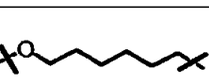
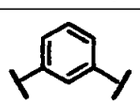
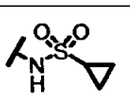
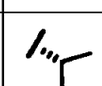
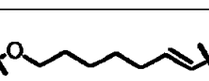
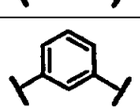
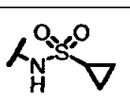
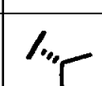
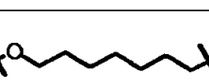
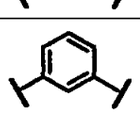
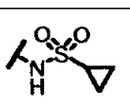
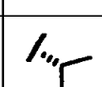
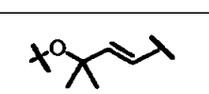
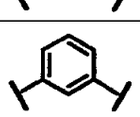
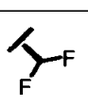
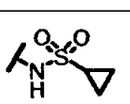
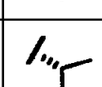
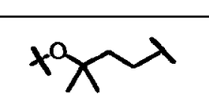
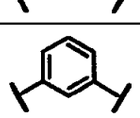
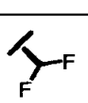
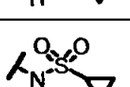
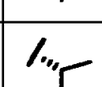
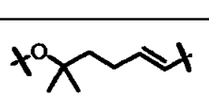
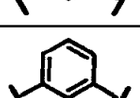
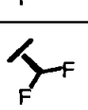
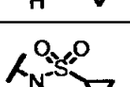
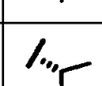
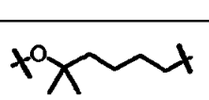
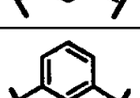
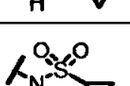
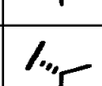
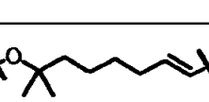
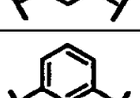
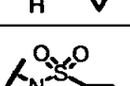
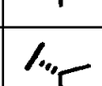
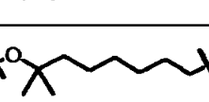
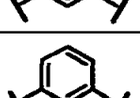
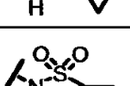
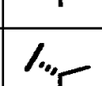
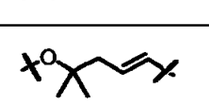
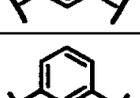
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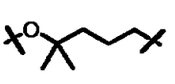
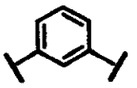
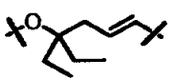
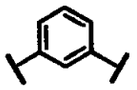
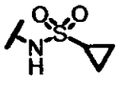
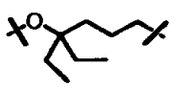
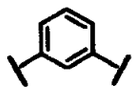
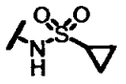
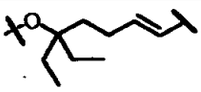
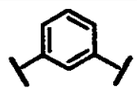
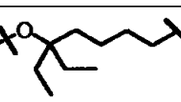
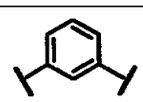
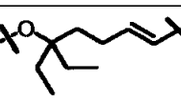
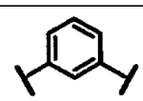
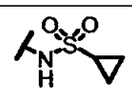
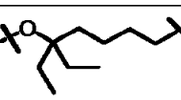
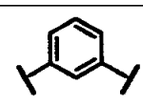
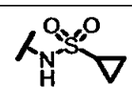
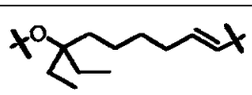
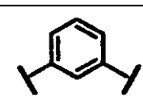
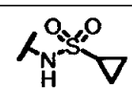
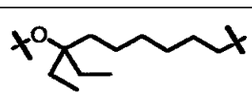
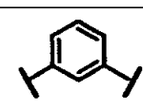
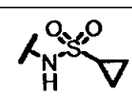
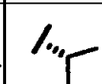
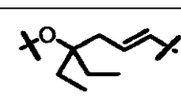
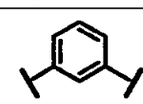
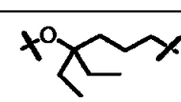
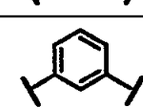
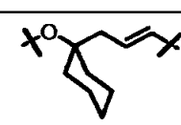
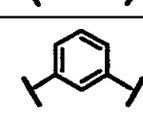
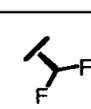
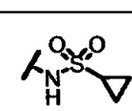
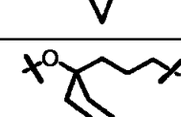
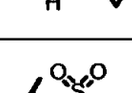
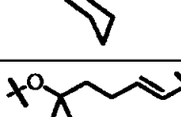
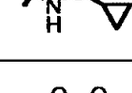
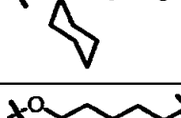
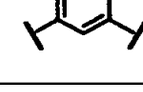
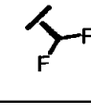
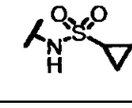
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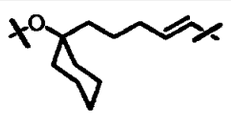
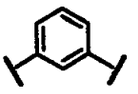
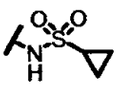
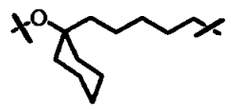
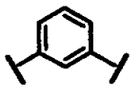
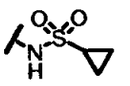
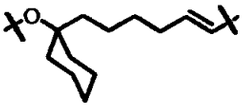
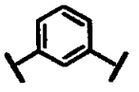
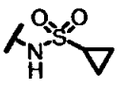
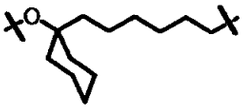
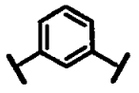
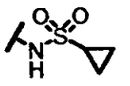
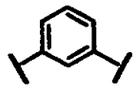
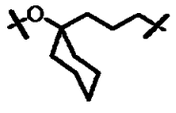
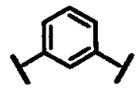
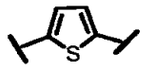
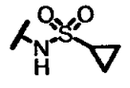
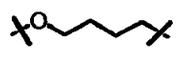
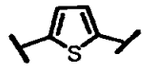
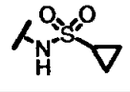
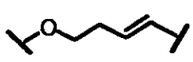
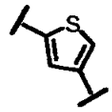
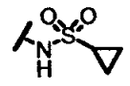
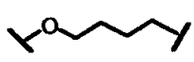
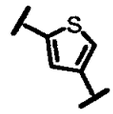
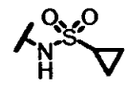
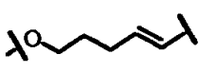
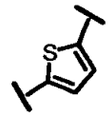
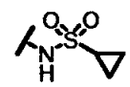
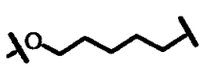
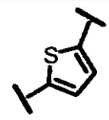
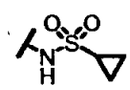
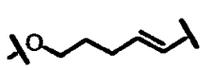
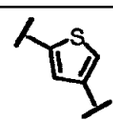
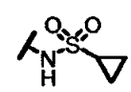
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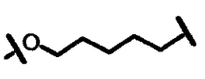
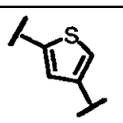
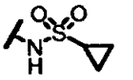
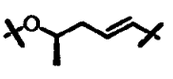
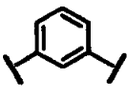
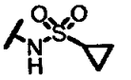
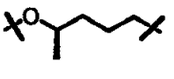
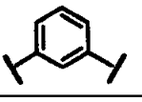
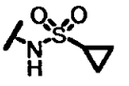
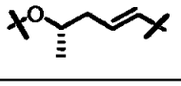
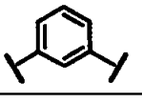
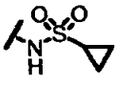
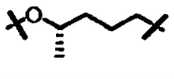
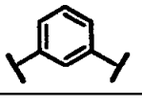
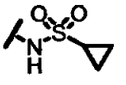
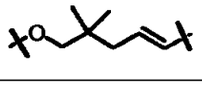
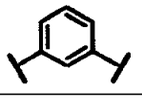
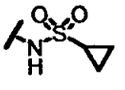
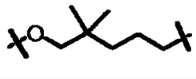
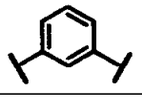
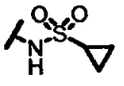
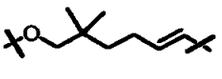
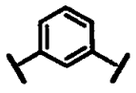
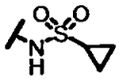
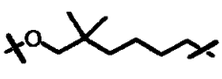
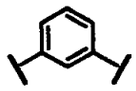
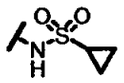
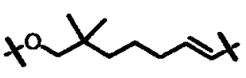
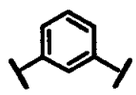
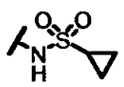
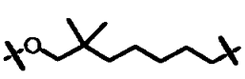
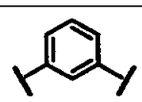
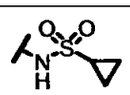
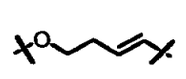
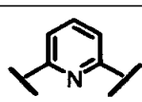
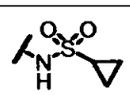
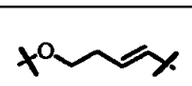
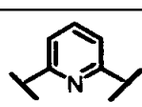
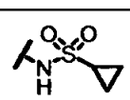
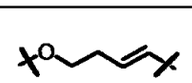
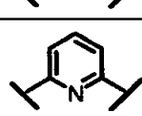
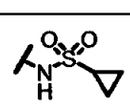
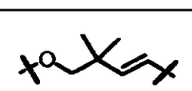
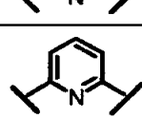
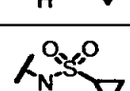
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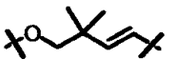
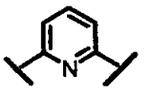
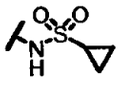
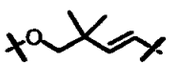
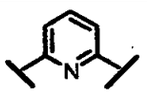
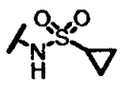
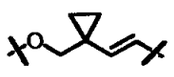
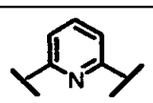
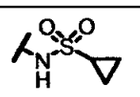
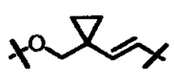
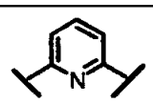
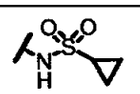
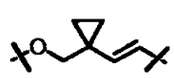
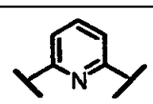
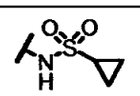
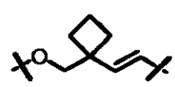
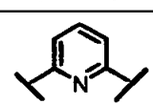
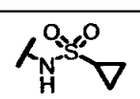
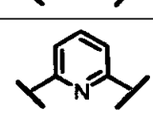
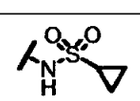
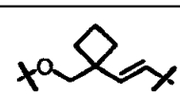
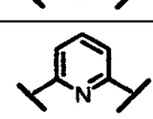
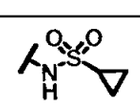
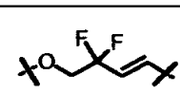
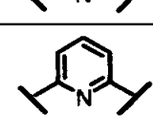
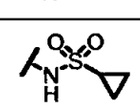
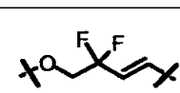
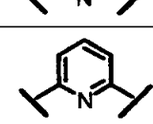
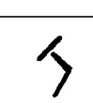
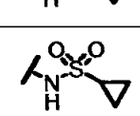
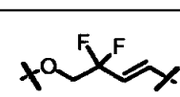
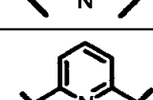
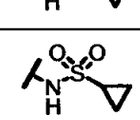
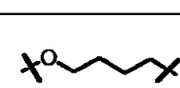
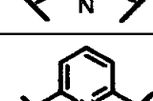
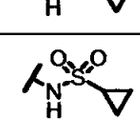
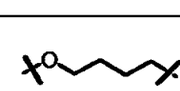
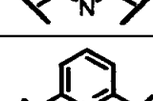
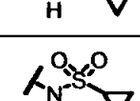
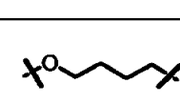
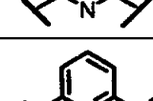
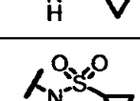
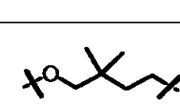
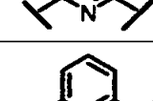
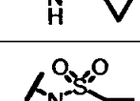
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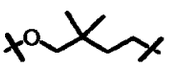
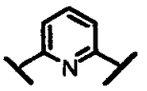
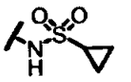
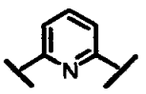
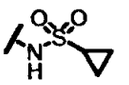
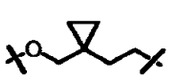
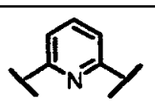
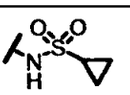
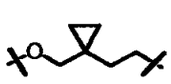
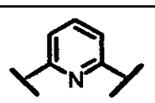
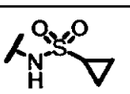
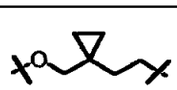
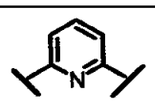
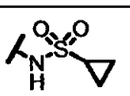
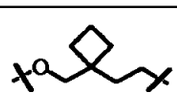
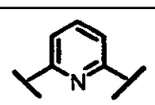
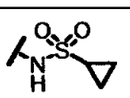
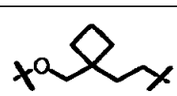
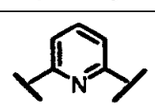
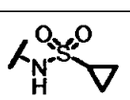
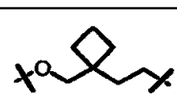
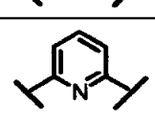
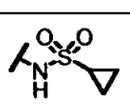
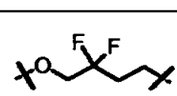
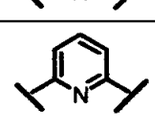
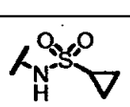
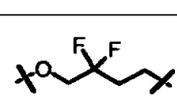
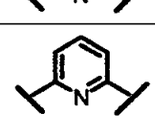
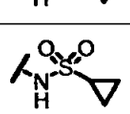
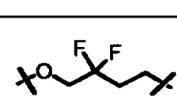
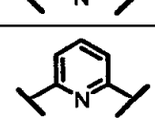
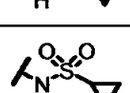
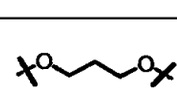
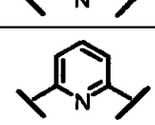
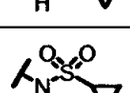
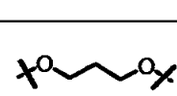
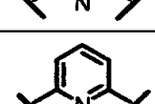
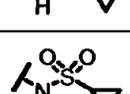
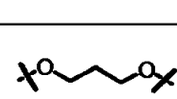
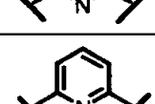
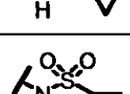
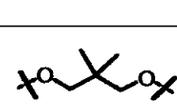
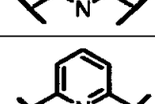
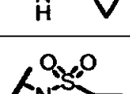
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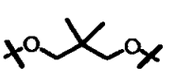
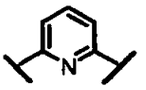
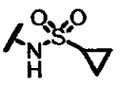
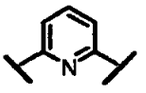
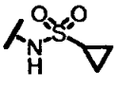
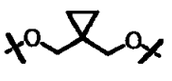
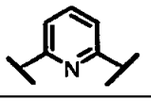
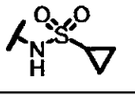
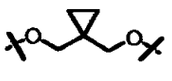
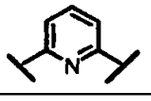
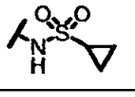
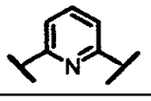
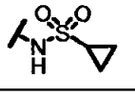
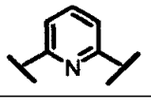
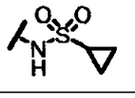
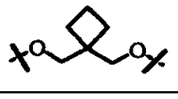
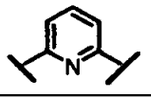
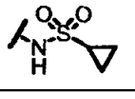
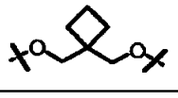
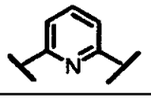
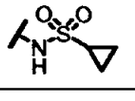
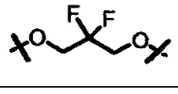
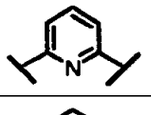
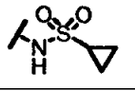
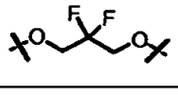
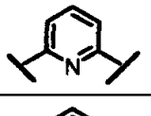
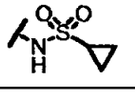
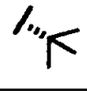
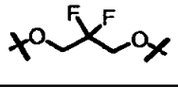
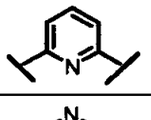
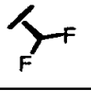
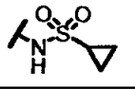
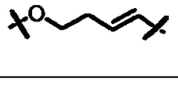
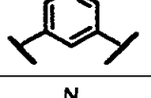
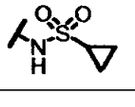
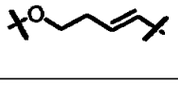
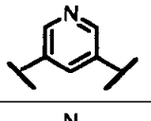
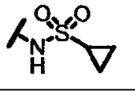
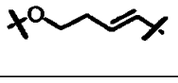
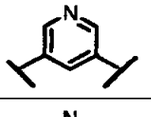
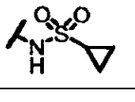
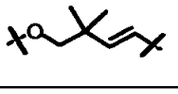
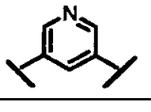
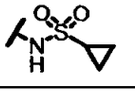
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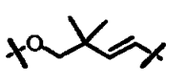
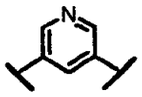
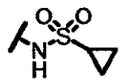
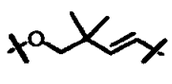
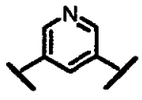
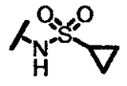
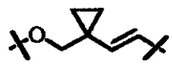
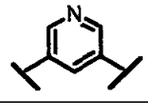
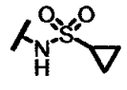
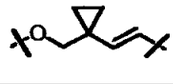
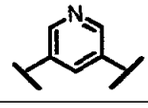
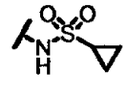
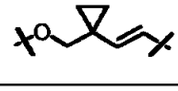
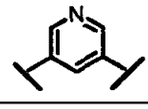
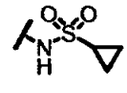
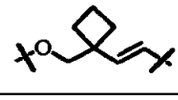
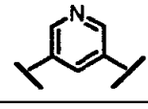
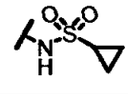
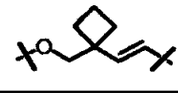
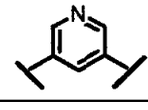
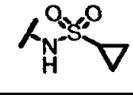
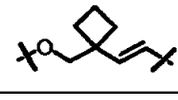
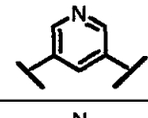
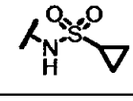
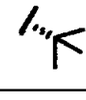
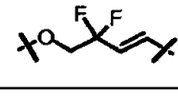
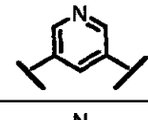
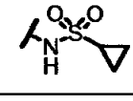
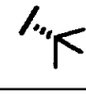
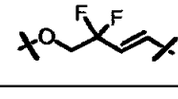
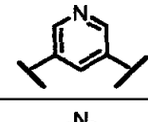
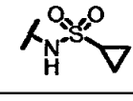
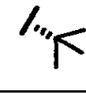
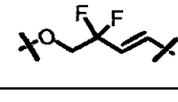
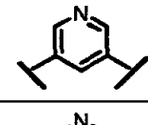
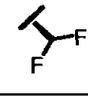
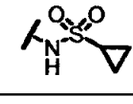
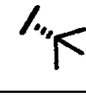
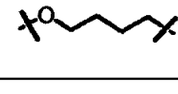
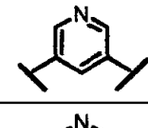
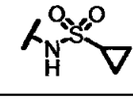
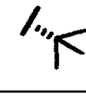
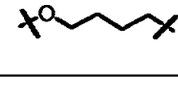
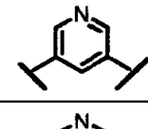
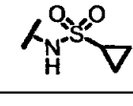
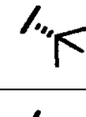
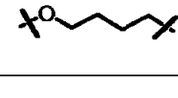
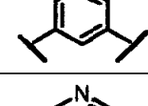
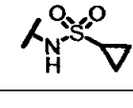
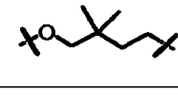
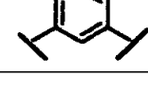
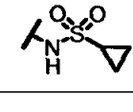
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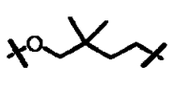
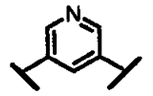
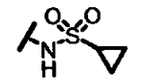
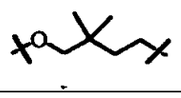
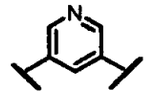
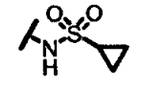
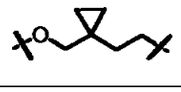
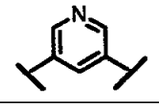
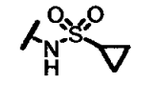
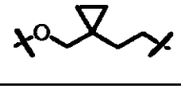
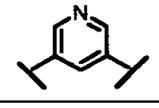
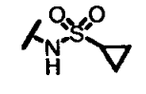
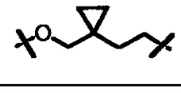
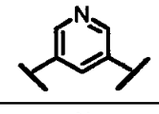
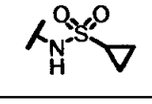
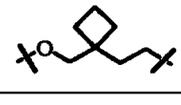
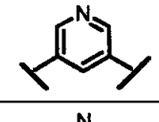
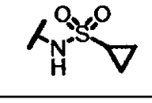
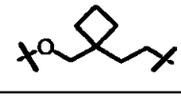
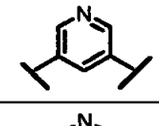
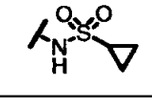
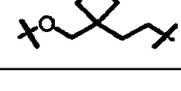
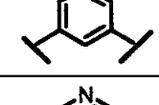
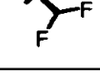
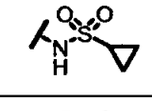
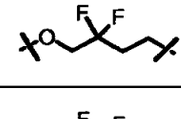
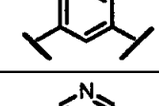
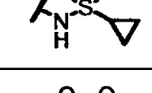
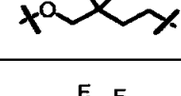
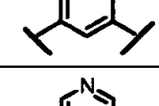
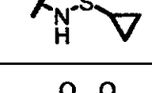
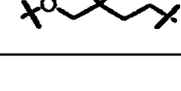
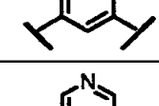
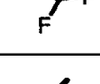
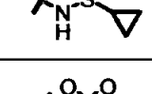
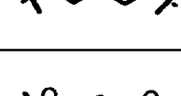
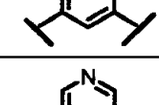
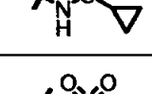
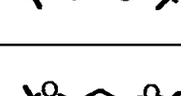
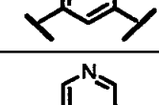
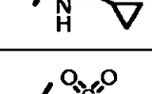
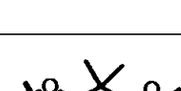
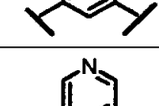
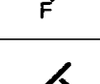
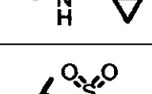
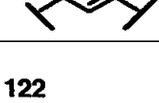
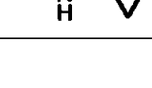
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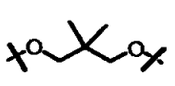
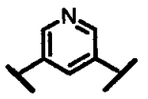
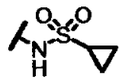
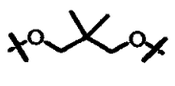
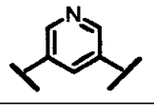
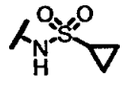
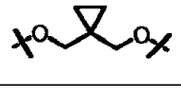
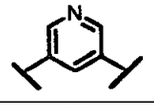
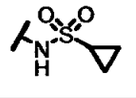
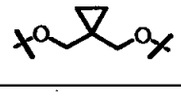
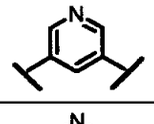
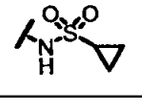
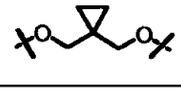
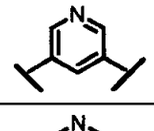
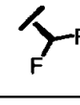
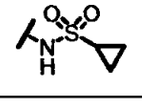
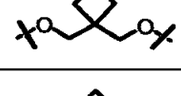
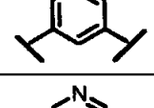
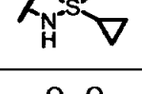
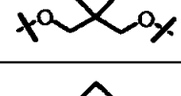
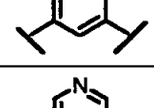
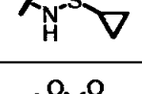
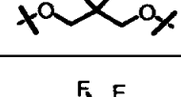
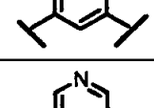
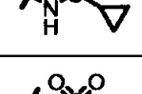
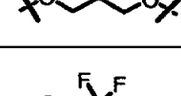
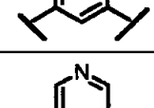
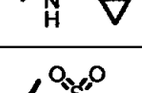
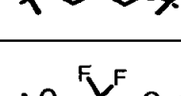
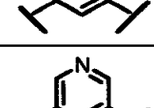
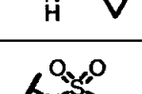
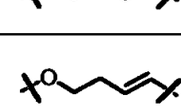
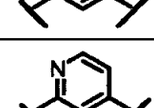
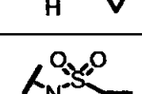
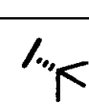
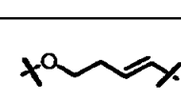
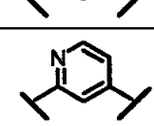
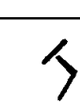
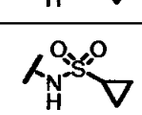
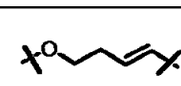
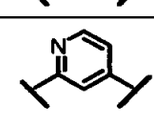
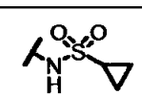
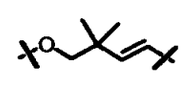
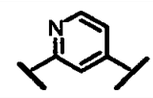
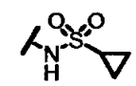
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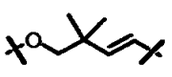
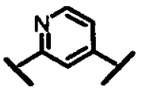
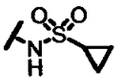
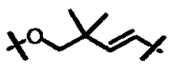
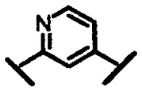
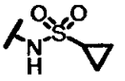
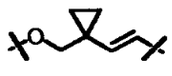
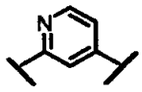
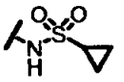
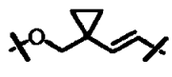
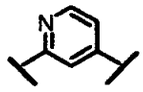
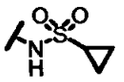
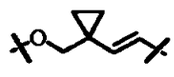
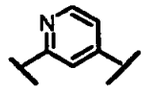
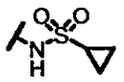
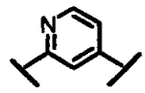
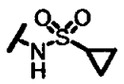
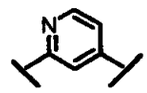
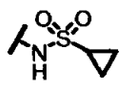
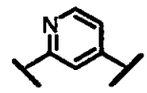
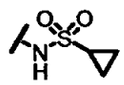
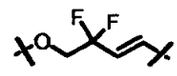
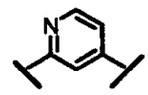
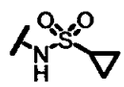
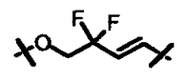
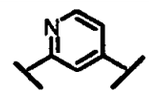
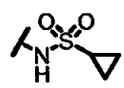
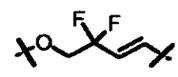
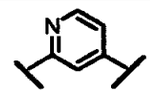
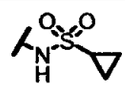
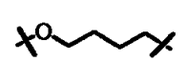
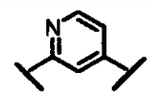
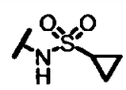
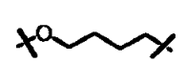
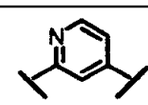
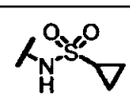
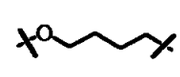
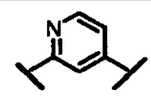
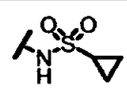
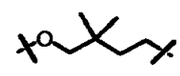
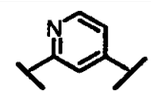
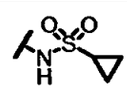
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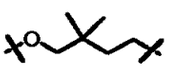
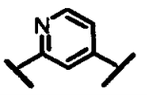
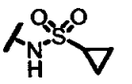
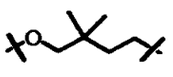
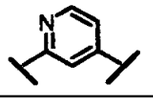
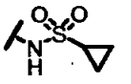
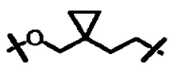
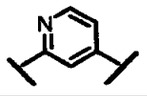
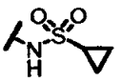
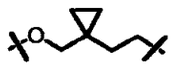
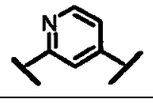
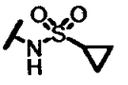
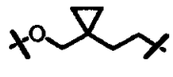
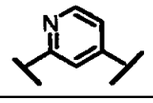
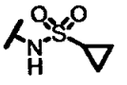
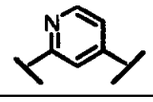
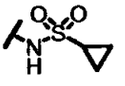
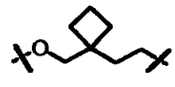
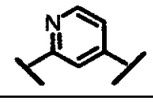
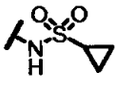
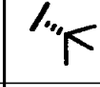
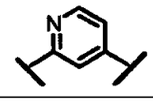
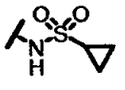
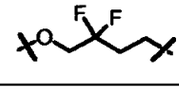
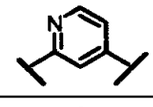
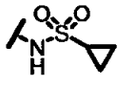
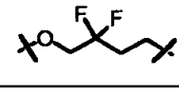
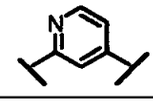
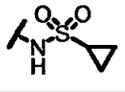
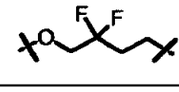
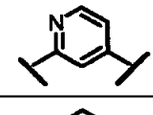
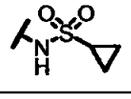
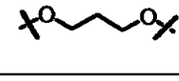
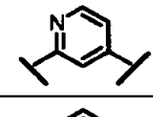
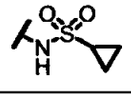
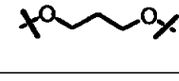
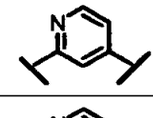
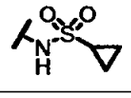
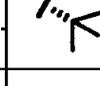
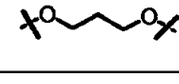
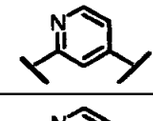
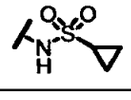
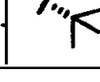
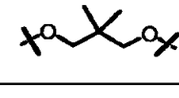
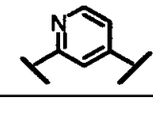
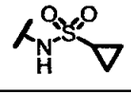
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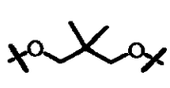
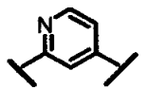
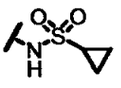
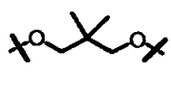
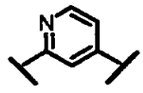
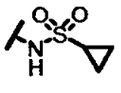
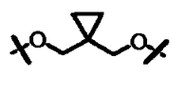
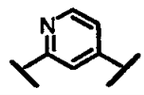
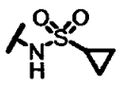
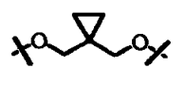
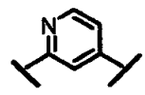
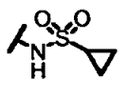
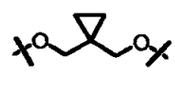
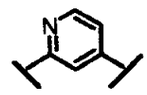
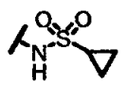
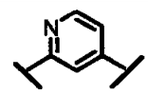
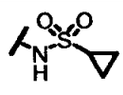
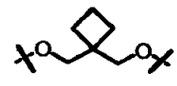
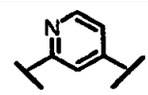
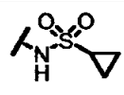
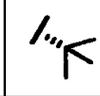
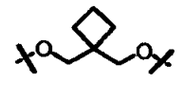
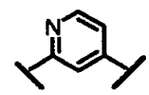
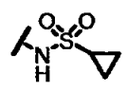
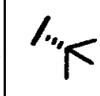
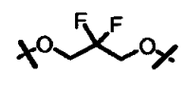
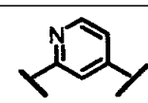
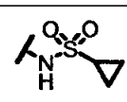
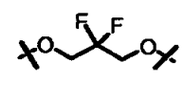
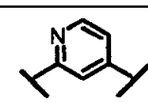
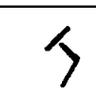
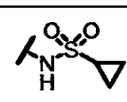
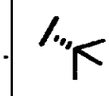
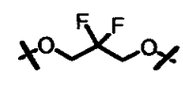
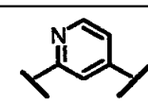
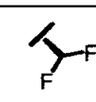
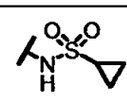
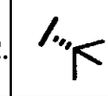
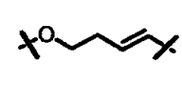
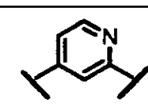
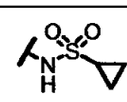
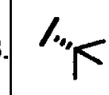
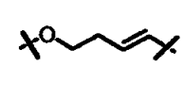
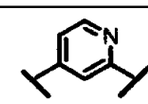
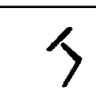
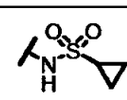
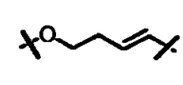
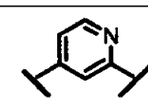
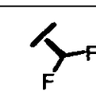
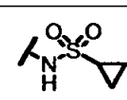
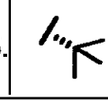
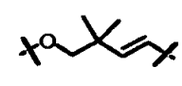
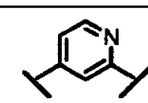
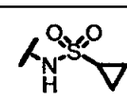
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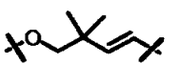
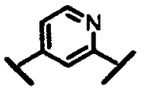
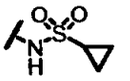
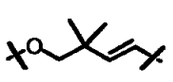
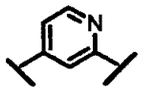
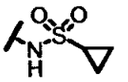
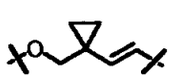
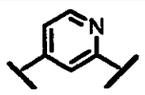
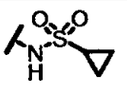
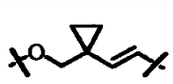
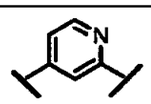
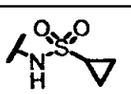
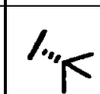
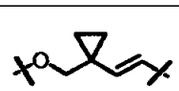
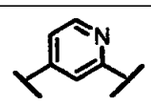
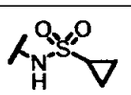
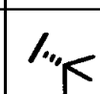
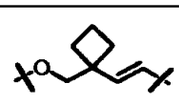
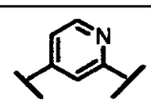
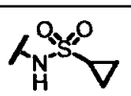
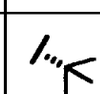
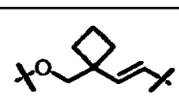
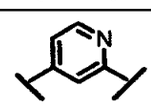
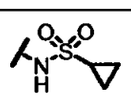
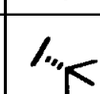
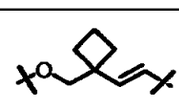
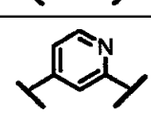
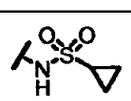
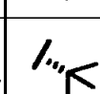
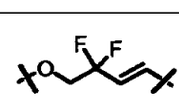
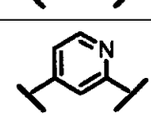
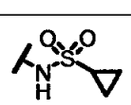
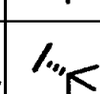
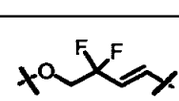
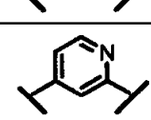
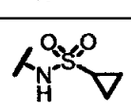
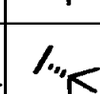
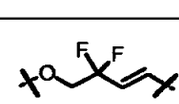
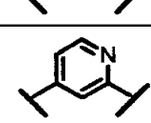
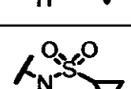
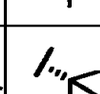
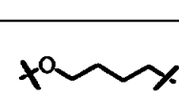
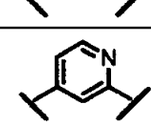
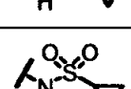
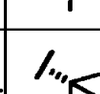
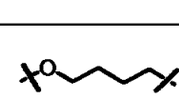
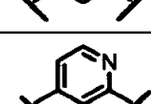
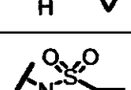
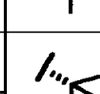
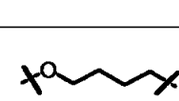
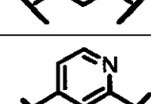
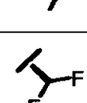
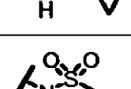
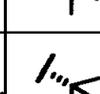
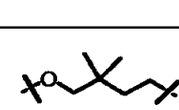
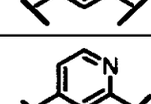
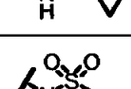
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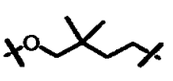
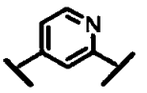
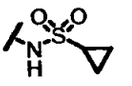
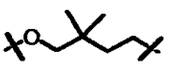
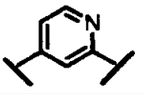
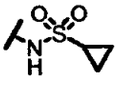
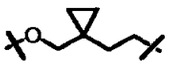
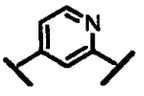
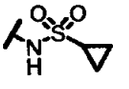
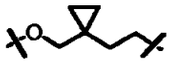
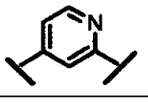
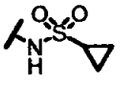
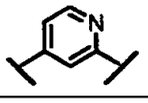
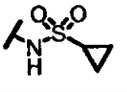
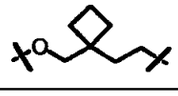
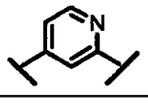
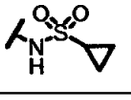
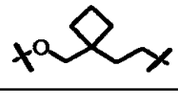
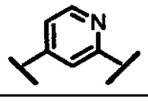
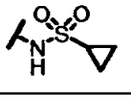
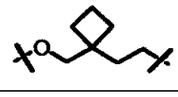
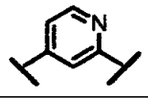
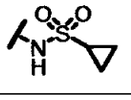
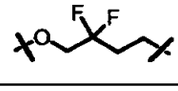
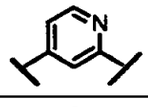
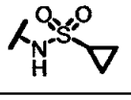
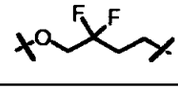
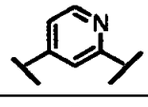
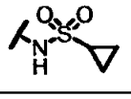
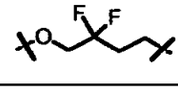
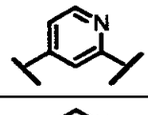
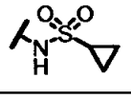
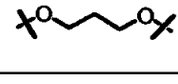
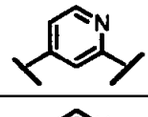
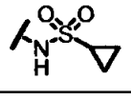
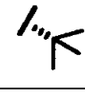
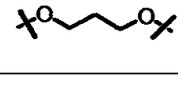
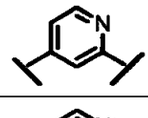
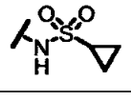
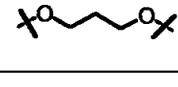
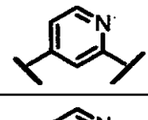
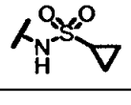
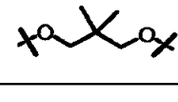
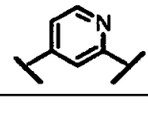
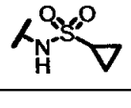
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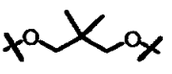
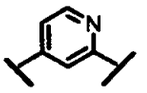
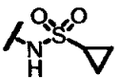
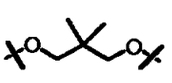
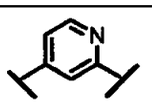
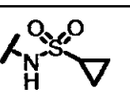
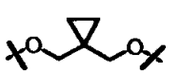
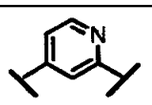
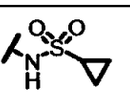
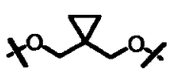
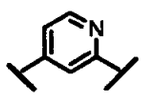
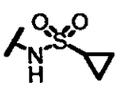
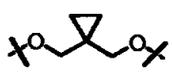
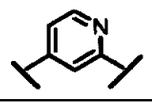
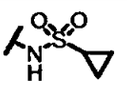
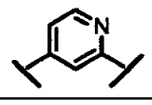
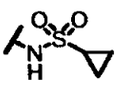
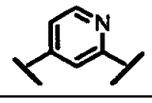
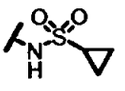
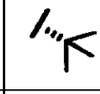
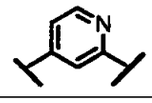
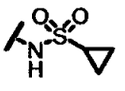
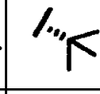
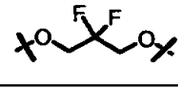
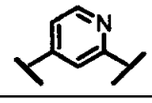
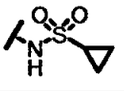
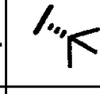
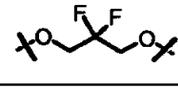
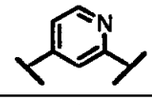
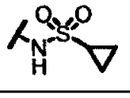
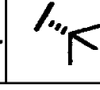
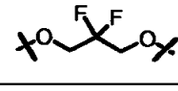
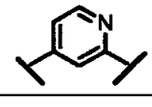
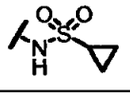
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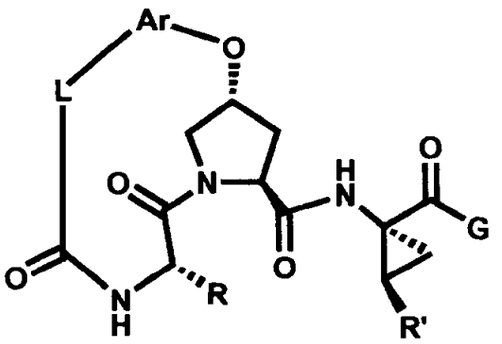
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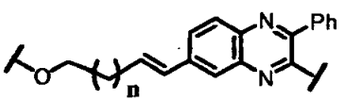
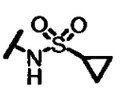
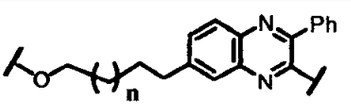
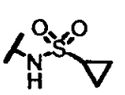
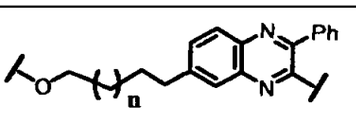
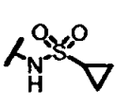
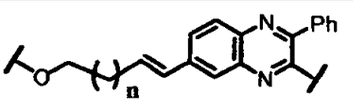
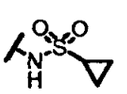
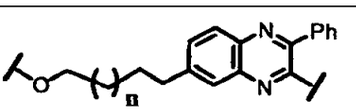
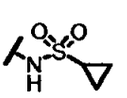
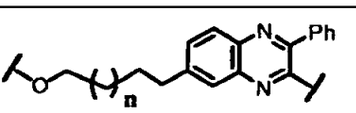
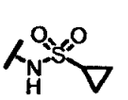
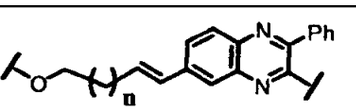
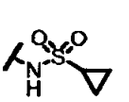
Representative compounds of the invention also include, but are not limited to, the following compounds (Table 2) according to Formula XVI wherein R, L-Ar, n, R' and G are delineated for each example in Table 2.

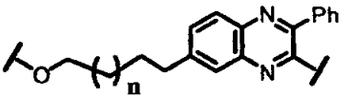
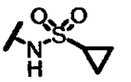
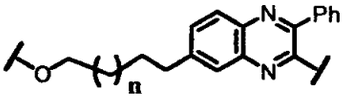
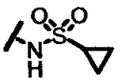
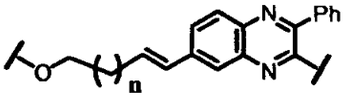
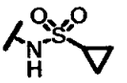
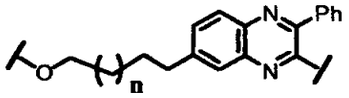
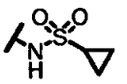
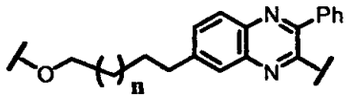
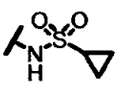
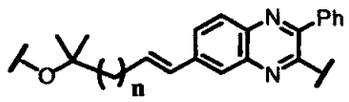
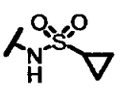
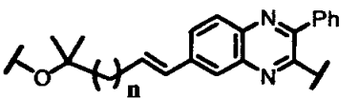
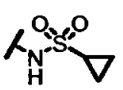
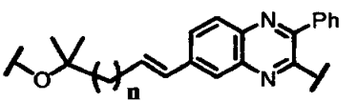
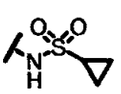
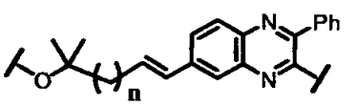
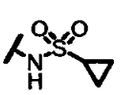
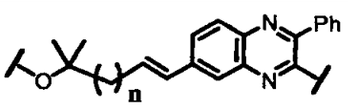
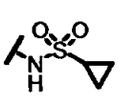
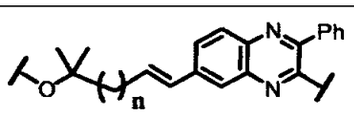
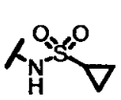
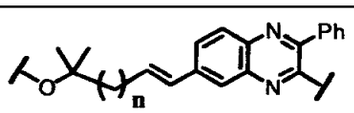
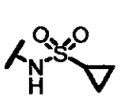
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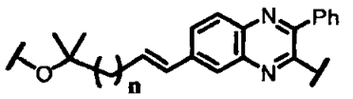
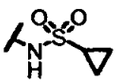
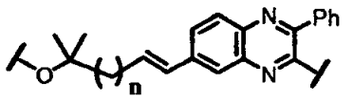
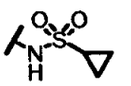
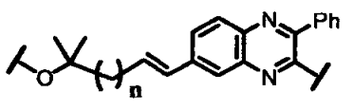
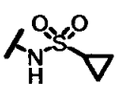
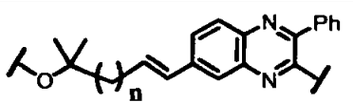
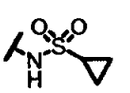
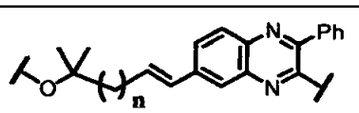
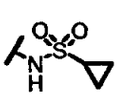
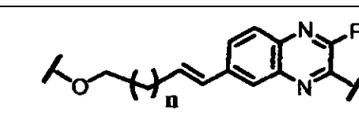
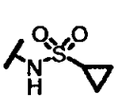
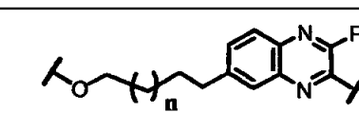
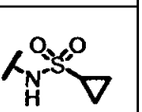
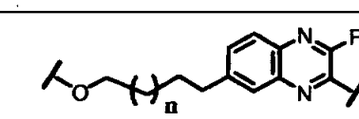
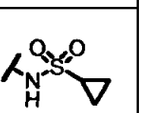
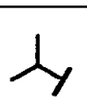
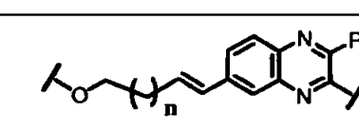
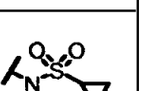
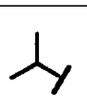
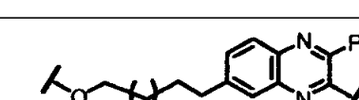
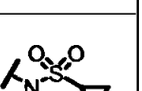
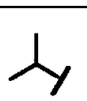
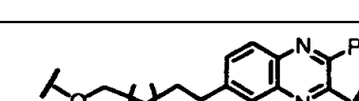
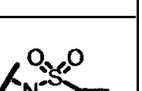
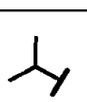
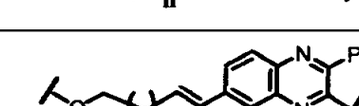
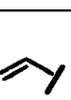
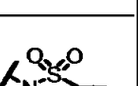


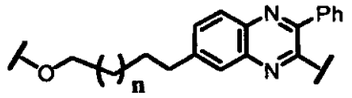
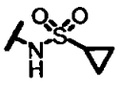
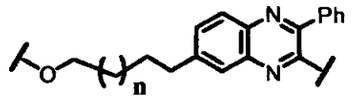
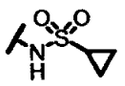
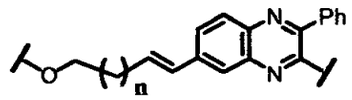
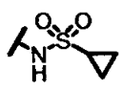
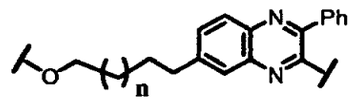
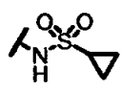
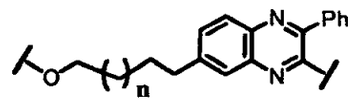
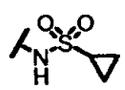
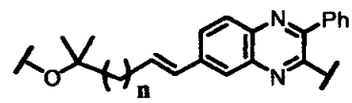
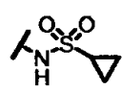
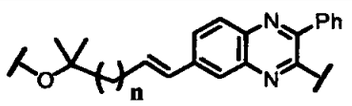
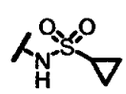
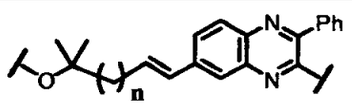
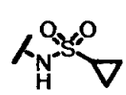
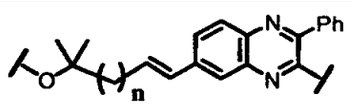
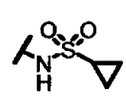
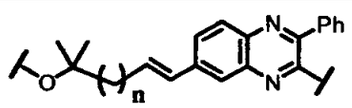
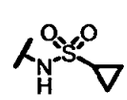
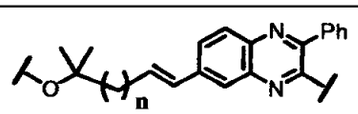
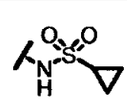
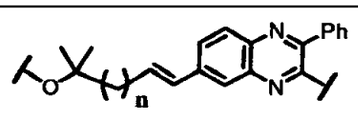
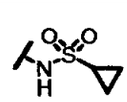
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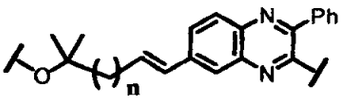
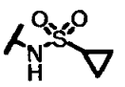
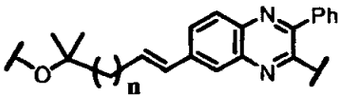
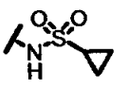
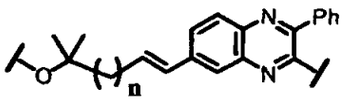
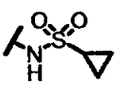
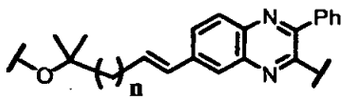
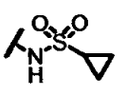
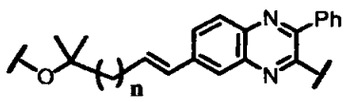
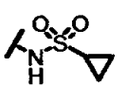
TABLE 2

Example#	R	L-Ar	n	R'	G
1507.			4		
1508.			4		
1509.			4		
1510.			3		
1511.			3		
1512.			3		
1513.			2		

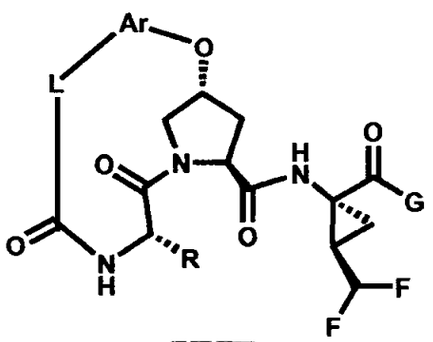
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1515.			2		
1516.			1		
1517.			1		
1518.			1		
1519.			4		
1520.			4		
1521.			4		
1522.			3		
1523.			3		
1524.			3		
1525.			2		

1526.			2		
1527.			2		
1528.			1		
1529.			1		
1530.			1		
1531.			4		
1532.			4		
1533.			4		
1534.			3		
1535.			3		
1536.			3		
1537.			2		

1538.			2		
1539.			2		
1540.			1		
1541.			1		
1542.			1		
1543.			4		
1544.			4		
1545.			4		
1546.			3		
1547.			3		
1548.			3		
1549.			2		

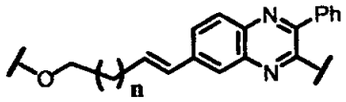
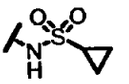
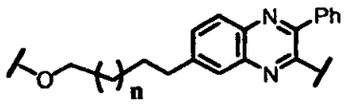
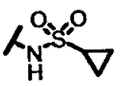
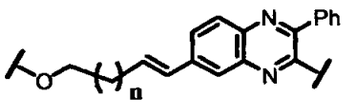
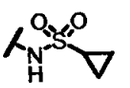
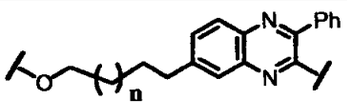
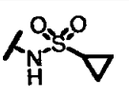
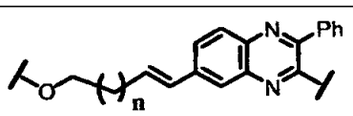
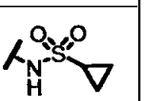
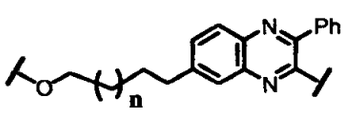
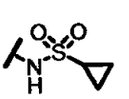
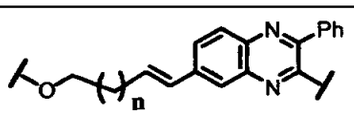
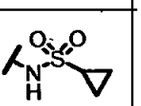
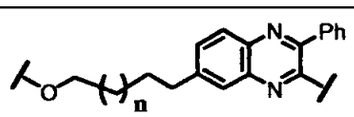
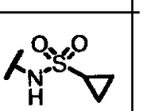
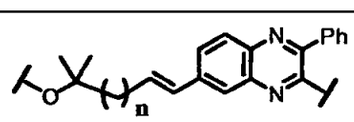
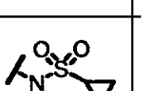
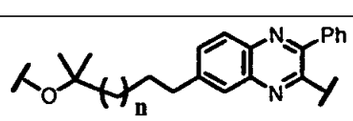
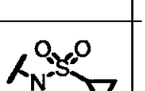
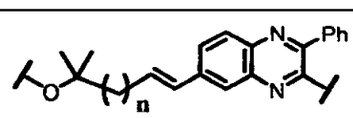
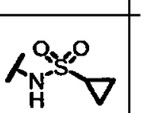
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1554.			1		

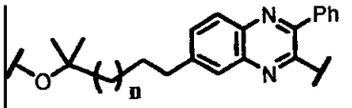
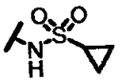
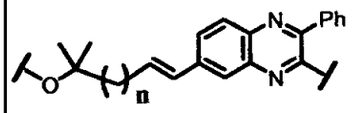
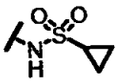
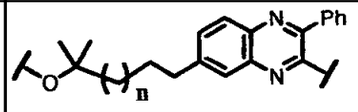
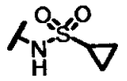
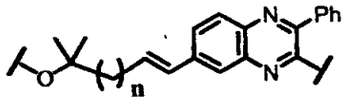
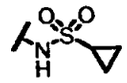
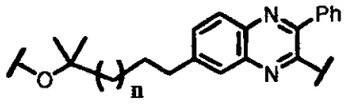
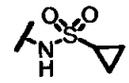
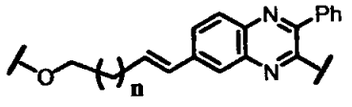
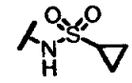
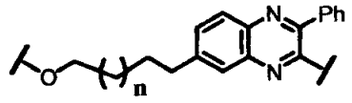
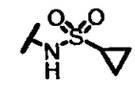
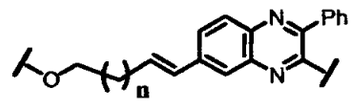
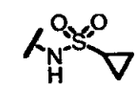
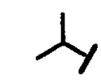
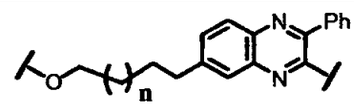
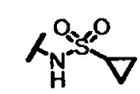
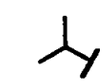
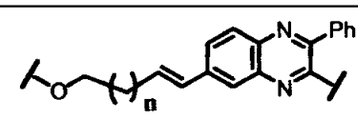
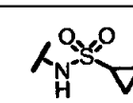
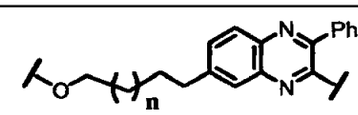
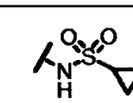
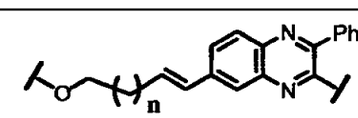
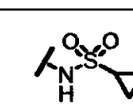
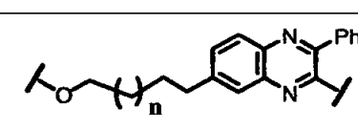
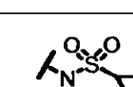
Representative compounds of the invention also include, but are not limited to, the following compounds (Table 3) according to Formula XVII wherein R, L-Ar, n and G are delineated for each example in Table 3.

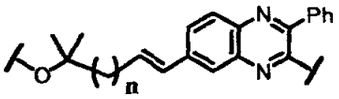
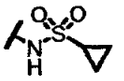
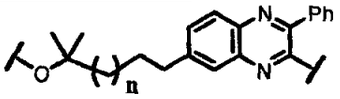
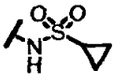
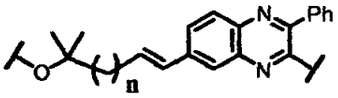
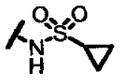
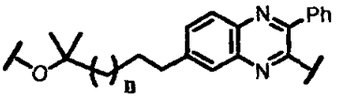
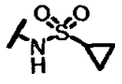
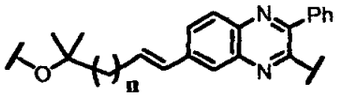
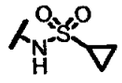
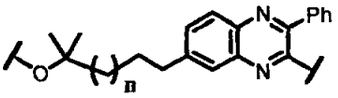
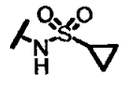
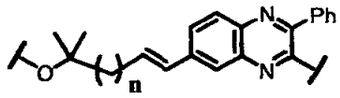
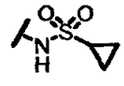
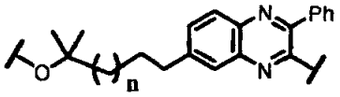
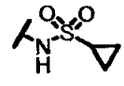


(XVII)

TABLE 3

Example #	R	L-Ar	n	G
1555.			4	
1556.			4	
1557.			3	
1558.			3	
1559.			2	
1560.			2	
1561.			1	
1562.			1	
1563.			4	
1564.			4	
1565.			3	

1566.			3	
1567.			2	
1568.			2	
1569.			1	
1570.			1	
1571.			4	
1572.			4	
1573.			3	
1574.			3	
1575.			2	
1576.			2	
1577.			1	
1578.			1	

1579.			4	
1580.			4	
1581.			3	
1582.			3	
1583.			2	
1584.			2	
1585.			1	
1586.			1	

The present invention also features pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, ester or prodrug thereof.

Compounds of the present invention can be administered as the sole active pharmaceutical agent, or used in combination with one or more agents to treat or prevent hepatitis C infections or the symptoms associated with HCV infection. Other agents to be administered in combination with a compound or combination of compounds of the invention include therapies for disease caused by HCV infection that suppresses HCV viral replication by direct or indirect mechanisms. These include agents such as host immune modulators (for example, interferon-alpha, pegylated interferon-alpha, interferon-beta,

interferon-gamma, CpG oligonucleotides and the like), or antiviral compounds that inhibit host cellular functions such as inosine monophosphate dehydrogenase (for example, ribavirin and the like). Also included are cytokines that modulate immune function. Also included are vaccines comprising HCV antigens or antigen adjuvant combinations directed against HCV. Also included are agents that interact with host cellular components to block viral protein synthesis by inhibiting the internal ribosome entry site (IRES) initiated translation step of HCV viral replication or to block viral particle maturation and release with agents targeted toward the viroporin family of membrane proteins such as, for example, HCV P7 and the like. Other agents to be administered in combination with a compound of the present invention include any agent or combination of agents that inhibit the replication of HCV by targeting proteins of the viral genome involved in the viral replication. These agents include but are not limited to other inhibitors of HCV RNA dependent RNA polymerase such as, for example, nucleoside type polymerase inhibitors described in WO01 90121(A2), or U.S. Pat. No. 6,348,587B1 or WO0160315 or WO0132153 or non-nucleoside inhibitors such as, for example, benzimidazole polymerase inhibitors described in EP 1162196A1 or WO0204425 or inhibitors of HCV protease such as, for example, peptidomimetic type inhibitors such as BILN2061 and the like or inhibitors of HCV helicase.

Other agents to be administered in combination with a compound of the present invention include any agent or combination of agents that inhibit the replication of other viruses for co-infected individuals. These agent include but are not limited to therapies for disease caused by hepatitis B (HBV) infection such as, for example, adefovir, lamivudine, and tenofovir or therapies for disease caused by human immunodeficiency virus (HIV) infection such as, for example, protease inhibitors: ritonavir, lopinavir, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, tipranavir, TMC-114, fosamprenavir; reverse transcriptase inhibitors: zidovudine, lamivudine, didanosine, stavudine, tenofovir, zalcitabine, abacavir, efavirenz, nevirapine, delavirdine, TMC-125; integrase inhibitors: L-870812, S-1360, or entry inhibitors: enfuvirtide (T-20), T-1249.

Accordingly, one aspect of the invention is directed to a method for treating or preventing an infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment one or more agents selected from the group consisting of a host immune modulator and a second antiviral agent, or a combination thereof, with a

therapeutically effective amount of a compound or combination of compounds of the invention, or a pharmaceutically acceptable salt, stereoisomer, tautomer, prodrug, salt of a prodrug, or combination thereof. Examples of the host immune modulator are, but not limited to, interferon-alpha, pegylated-interferon-alpha, interferon-beta, interferon-gamma, a cytokine, a vaccine, and a vaccine comprising an antigen and an adjuvant, and said second antiviral agent inhibits replication of HCV either by inhibiting host cellular functions associated with viral replication or by targeting proteins of the viral genome.

Further aspect of the invention is directed to a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment an agent or combination of agents that treat or alleviate symptoms of HCV infection including cirrhosis and inflammation of the liver, with a therapeutically effective amount of a compound or combination of compounds of the invention, or a pharmaceutically acceptable salt, stereoisomer, tautomer, prodrug, salt of a prodrug, or combination thereof. Yet another aspect of the invention provides a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment one or more agents that treat patients for disease caused by hepatitis B (HBV) infection, with a therapeutically effective amount of a compound or a combination of compounds of the invention, or a pharmaceutically acceptable salt, stereoisomer, tautomer, prodrug, salt of a prodrug, or combination thereof. An agent that treats patients for disease caused by hepatitis B (HBV) infection may be for example, but not limited thereto, L- deoxythymidine, adefovir, lamivudine or tenfovir, or any combination thereof. Example of the RNA-containing virus includes, but not limited to, hepatitis C virus (HCV).

Another aspect of the invention provides a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment one or more agents that treat patients for disease caused by human immunodeficiency virus (HIV) infection, with a therapeutically effective amount of a compound or a combination of compounds of the invention, or a pharmaceutically acceptable salt, stereoisomer, tautomer, prodrug, salt of a prodrug, or combination thereof. The agent that treats patients for disease caused by human immunodeficiency virus (HIV) infection may include, but is not limited thereto, ritonavir, lopinavir, indinavir, nelfinavir,

saquinavir, amprenavir, atazanavir, tipranavir, TMC-114, fosamprenavir, zidovudine, lamivudine, didanosine, stavudine, tenofovir, zalcitabine, abacavir, efavirenz, nevirapine, delavirdine, TMC-125, L-870812, S-1360, enfuvirtide (T-20) or T-1249, or any combination thereof. Example of the RNA-containing virus includes, but not limited to, hepatitis C virus (HCV). In addition, the present invention provides the use of a compound or a combination of compounds of the invention, or a therapeutically acceptable salt form, stereoisomer, or tautomer, prodrug, salt of a prodrug, or combination thereof, and one or more agents selected from the group consisting of a host immune modulator and a second antiviral agent, or a combination thereof, to prepare a medicament for the treatment of an infection caused by an RNA-containing virus in a patient, particularly hepatitis C virus. Examples of the host immune modulator are, but not limited to, interferon-alpha, pegylated- interferon-alpha, interferon-beta, interferon-gamma, a cytokine, a vaccine, and a vaccine comprising an antigen and an adjuvant, and said second antiviral agent inhibits replication of HCV either by inhibiting host cellular functions associated with viral replication or by targeting proteins of the viral genome.

When used in the above or other treatments, combination of compound or compounds of the invention, together with one or more agents as defined herein above, can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt form, prodrug, salt of a prodrug, or combination thereof. Alternatively, such combination of therapeutic agents can be administered as a pharmaceutical composition containing a therapeutically effective amount of the compound or combination of compounds of interest, or their pharmaceutically acceptable salt form, prodrugs, or salts of the prodrug, in combination with one or more agents as defined hereinabove, and a pharmaceutically acceptable carrier. Such pharmaceutical compositions can be used for inhibiting the replication of an RNA-containing virus, particularly Hepatitis C virus (HCV), by contacting said virus with said pharmaceutical composition. In addition, such compositions are useful for the treatment or prevention of an infection caused by an RNA-containing virus, particularly Hepatitis C virus (HCV).

Hence, further aspect of the invention is directed to a method of treating or preventing infection caused by an RNA-containing virus, particularly a hepatitis C virus (HCV), comprising administering to a patient in need of such treatment a pharmaceutical

composition comprising a compound or combination of compounds of the invention or a pharmaceutically acceptable salt, stereoisomer, or tautomer, prodrug, salt of a prodrug, or combination thereof, one or more agents as defined hereinabove, and a pharmaceutically acceptable carrier.

When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or within a predetermined period of time, or the therapeutic agents can be given as a single unit dosage form.

Antiviral agents contemplated for use in such combination therapy include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of a virus in a mammal, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a mammal. Such agents can be selected from another anti-HCV agent; an HIV inhibitor; an HAV inhibitor; and an HBV inhibitor.

Other anti-HCV agents include those agents that are effective for diminishing or preventing the progression of hepatitis C related symptoms or disease. Such agents include but are not limited to immunomodulatory agents, inhibitors of HCV NS3 protease, other inhibitors of HCV polymerase, inhibitors of another target in the HCV life cycle and other anti-HCV agents, including but not limited to ribavirin, amantadine, levovirin and viramidine.

Immunomodulatory agents include those agents (compounds or biologicals) that are effective to enhance or potentiate the immune system response in a mammal. Immunomodulatory agents include, but are not limited to, inosine monophosphate dehydrogenase inhibitors such as VX-497 (merimepodib, Vertex Pharmaceuticals), class I interferons, class II interferons, consensus interferons, asialo-interferons pegylated interferons and conjugated interferons, including but not limited to interferons conjugated with other proteins including but not limited to human albumin. Class I interferons are a group of interferons that all bind to receptor type I, including both naturally and synthetically produced class I interferons, while class II interferons all bind to receptor type II. Examples of class I interferons include, but are not limited to, [alpha]-, [beta]-, [delta]-, [omega]-, and [tau]-interferons, while examples of class II interferons include, but are not limited to, [gamma]-interferons.

Inhibitors of HCV NS3 protease include agents (compounds or biologicals) that are effective to inhibit the function of HCV NS3 protease in a mammal. Inhibitors of HCV NS3 protease include, but are not limited to, those compounds described in WO 99/07733, WO 99/07734, WO 00/09558, WO 00/09543, WO 00/59929, WO 03/064416, WO 03/064455, WO 03/064456, WO 2004/030670, WO 2004/037855, WO 2004/039833, WO 2004/101602, WO 2004/101605, WO 2004/103996, WO 2005/028501 , WO 2005/070955, WO 2006/000085, WO 2006/007700 and WO 2006/007708 (all by Boehringer Ingelheim), WO 02/060926, WO 03/053349, WO03/099274, WO 03/099316, WO 2004/032827, WO 2004/043339, WO 2004/094452, WO 2005/046712, WO 2005/051410, WO 2005/054430 (all by BMS), WO 2004/072243, WO 2004/093798, WO 2004/113365, WO 2005/010029 (all by Enanta), WO 2005/037214 (Intermune) and WO 2005/051980 (Schering), and the candidates identified as VX-950, ITMN-191 and SCH 503034.

Inhibitors of HCV polymerase include agents (compounds or biologicals) that are effective to inhibit the function of an HCV polymerase. Such inhibitors include, but are not limited to, non-nucleoside and nucleoside inhibitors of HCV NS5B polymerase. Examples of inhibitors of HCV polymerase include but are not limited to those compounds described in: WO 02/04425, WO 03/007945, WO 03/010140, WO 03/010141 , WO 2004/064925, WO 2004/065367, WO 2005/080388 and WO 2006/007693 (all by Boehringer Ingelheim), WO 2005/049622 (Japan Tobacco), WO 2005/014543 (Japan Tobacco),WO 2005/012288 (Genelabs), WO 2004/087714 (IRBM), WO 03/101993 (Neogenesis), WO 03/026587 (BMS), WO 03/000254 (Japan Tobacco), and WO 01/47883 (Japan Tobacco), and the clinical candidates XTL-2125, HCV 796, R-1626 and NM 283.

Inhibitors of another target in the HCV life cycle include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of HCV other than by inhibiting the function of the HCV NS3 protease. Such agents may interfere with either host or HCV viral mechanisms necessary for the formation and/or replication of HCV. Inhibitors of another target in the HCV life cycle include, but are not limited to, entry inhibitors, agents that inhibit a target selected from a helicase, a NS2/3 protease and an internal ribosome entry site (IRES) and agents that interfere with the function of other viral targets including but not limited to an NS5A protein and an NS4B protein.

It can occur that a patient may be co-infected with hepatitis C virus and one or more

other viruses, including but not limited to human immunodeficiency virus (HIV), hepatitis A virus (HAV) and hepatitis B virus (HBV). Thus also contemplated is combination therapy to treat such co-infections by co-administering a compound according to the present invention with at least one of an HIV inhibitor, an HAV inhibitor and an HBV inhibitor.

According to yet another embodiment, the pharmaceutical compositions of the present invention may further comprise inhibitor(s) of other targets in the HCV life cycle, including, but not limited to, helicase, polymerase, metalloprotease, and internal ribosome entry site (IRES).

According to another embodiment, the pharmaceutical compositions of the present invention may further comprise another anti-viral, anti-bacterial, anti-fungal or anti-cancer agent, or an immune modulator, or another thearapeutic agent.

According to still another embodiment, the present invention includes methods of treating viral infection such as, but not limited to, hepatitis C infections in a subject in need of such treatment by administering to said subject an effective amount of a compound of the present invention or a pharmaceutically acceptable salt, ester, or prodrug thereof.

According to a further embodiment, the present invention includes methods of treating hepatitis C infections in a subject in need of such treatment by administering to said subject an anti-HCV virally effective amount or an inhibitory amount of a pharmaceutical composition of the present invention.

An additional embodiment of the present invention includes methods of treating biological samples by contacting the biological samples with the compounds of the present invention.

Yet a further aspect of the present invention is a process of making any of the compounds delineated herein employing any of the synthetic means delineated herein.

The cytochrome P450 monooxygenase inhibitor used in this invention is expected to inhibit metabolism of the compounds of the invention. Therefore, the cytochrome P450 monooxygenase inhibitor would be in an amount effective to inhibit metabolism of the protease inhibitor. Accordingly, the CYP inhibitor is administered in an amount such that the bioavailiablity of the protease inhibitor is increased in comparison to the bioavailability in the absence of the CYP inhibitor.

In one embodiment, the invention provides methods for improving the pharmacokinetics of compounds of the invention. The advantages of improving the pharmacokinetics of drugs are recognized in the art (US 2004/0091527; US 2004/0152625; US 2004/0091527). Accordingly, one embodiment of this invention provides a method for administering an inhibitor of CYP3A4 and a compound of the invention. Another embodiment of this invention provides a method for administering a compound of the invention and an inhibitor of isozyme 3A4 ("CYP3A4"), isozyme 2C19 ("CYP2C19"), isozyme 2D6 ("CYP2D6"), isozyme 1A2 ("CYP1A2"), isozyme 2C9 ("CYP2C9"), or isozyme 2E1 ("CYP2E1"). In a preferred embodiment, the CYP inhibitor preferably inhibits CYP3A4. Any CYP inhibitor that improves the pharmacokinetics of the relevant NS3/4A protease may be used in a method of this invention. These CYP inhibitors include, but are not limited to, ritonavir (WO 94/14436), ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, clomethiazole, cimetidine, itraconazole, fluconazole, miconazole, fluvoxamine, fluoxetine, nefazodone, sertraline, indinavir, nelfinavir, amprenavir, fosamprenavir, saquinavir, lopinavir, delavirdine, erythromycin, VX-944, and VX-497. Preferred CYP inhibitors include ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazole.

It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each formulation, containing within a package insert instructing the patient to the correct use of the invention is a desirable additional feature of this invention.

According to a further aspect of the invention is a pack comprising at least a compound of the invention and a CYP inhibitor of the invention and an information insert containing directions on the use of the combination of the invention. In an alternative embodiment of this invention, the pharmaceutical pack further comprises one or more of additional agent as described herein. The additional agent or agents may be provided in the same pack or in separate packs.

Another aspect of this nvention is a packaged kit for a patient to use in the treatment of HCV infection or in the prevention of HCV infection, comprising: a single or a plurality of pharmaceutical formulation of each pharmaceutical component; a container housing the

pharmaceutical formulation (s) during storage and prior to administration; and instructions for carrying out drug administration in a manner effective to treat or prevent HCV infection.

Accordingly, this invention provides kits for the simultaneous or sequential administration of a NS3/4A protease inhibitor of the invention and a CYP inhibitor (and optionally an additional agent) or derivatives thereof are prepared in a conventional manner. Typically, such a kit will comprise, e. g. a composition of each inhibitor and optionally the additional agent (s) in a pharmaceutically acceptable carrier (and in one or in a plurality of pharmaceutical formulations) and written instructions for the simultaneous or sequential administration.

In another embodiment, a packaged kit is provided that contains one or more dosage forms for self administration; a container means, preferably sealed, for housing the dosage forms during storage and prior to use; and instructions for a patient to carry out drug administration. The instructions will typically be written instructions on a package insert, a label, and/or on other components of the kit, and the dosage form or forms are as described herein. Each dosage form may be individually housed, as in a sheet of a metal foil- plastic laminate with each dosage form isolated from the others in individual cells or bubbles, or the dosage forms may be housed in a single container, as in a plastic bottle. The present kits will also typically include means for packaging the individual kit components, i. e. , the dosage forms, the container means, and the written instructions for use. Such packaging means may take the form of a cardboard or paper box, a plastic or foil pouch, etc.

DEFINITIONS

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "viral infection" refers to the introduction of a virus into cells or tissues, e.g., hepatitis C virus (HCV). In general, the introduction of a virus is also associated with replication. Viral infection may be determined by measuring virus antibody titer in samples of a biological fluid, such as blood, using, e.g., enzyme immunoassay. Other suitable diagnostic methods include molecular based techniques, such as RT-PCR, direct hybrid capture assay, nucleic acid sequence based amplification, and the like. A virus may infect an

organ, e.g., liver, and cause disease, e.g., hepatitis, cirrhosis, chronic liver disease and hepatocellular carcinoma.

The term "anti-cancer agent" refers to a compound or drug capable of preventing or inhibiting the advancement of cancer. Examples of such agents include cis-platin, actinomycin D, doxorubicin, vincristine, vinblastine, etoposide, amsacrine, mitoxantrone, tenipaside, taxol, colchicine, cyclosporin A, phenothiazines or thioxantheres.

The term "anti-fungal agent" shall used to describe a compound which may be used to treat a fungus infection other than 3-AP, 3-AMP or prodrugs of 3-AP and 3-AMP according to the present invention. Anti-fungal agents according to the present invention include, for example, terbinafine, fluconazole, itraconazole, posaconazole, clotrimazole, griseofulvin, nystatin, tolnaftate, caspofungin, amphotericin B, liposomal amphotericin B, and amphotericin B lipid complex.

The term "antibacterial agent" refers to both naturally occurring antibiotics produced by microorganisms to suppress the growth of other microorganisms, and agents synthesized or modified in the laboratory which have either bactericidal or bacteriostatic activity, e.g., β-lactam antibacterial agents, glycopeptides, macrolides, quinolones, tetracyclines, and aminoglycosides. In general, if an antibacterial agent is bacteriostatic, it means that the agent essentially stops bacterial cell growth (but does not kill the bacteria); if the agent is bacteriocidal, it means that the agent kills the bacterial cells (and may stop growth before killing the bacteria).

The term "immune modulator" refers to any substance meant to alter the working of the humoral or cellular immune system of a subject. Such immune modulators include inhibitors of mast cell-mediated inflammation, interferons, interleukins, prostaglandins, steroids, cortico-steroids, colony-stimulating factors, chemotactic factors, etc.

The term "C_1-C_6 alkyl," or "C_1-C_8 alkyl," as used herein, refer to saturated, straight- or branched-chain hydrocarbon radicals containing between one and six, or one and eight carbon atoms, respectively. Examples of C_1-C_6 alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, n-hexyl radicals; and examples of C_1-C_8 alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, n-hexyl, heptyl, octyl radicals.

The term "C_2-C_6 alkenyl," or "C_2-C_8 alkenyl," as used herein, denote a group derived from a hydrocarbon moiety, wherein the hydrocarbon moiety has at least one carbon-carbon double bond and contains from two to six, or two to eight carbon atoms, respectively. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl and the like.

The term "C_2-C_6 alkynyl," or "C_2-C_8 alkynyl," as used herein, denote a group derived from a hydrocarbon moiety, wherein the hydrocarbon moiety has at least one carbon-carbon triple bond and contains from two to six, or two to eight carbon atoms, respectively. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butynyl, heptynyl, octynyl and the like.

The term "C_3-C_8-cycloalkyl", or "C_3-C_{12}-cycloalkyl," as used herein, denotes a group derived from a monocyclic or polycyclic saturated carbocyclic ring, where the saturated carbocyclic ring compound has from 3 to 8, or from 3 to 12, ring atoms, respectively. Examples of C_3-C_8-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl and cyclooctyl; and examples of C_3-C_{12}-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl.

The term "C_3-C_8-cycloalkenyl", or "C_3-C_{12}-cycloalkenyl" as used herein, denote a group derived from a monocyclic or polycyclic carbocyclic ring compound having at least one carbon-carbon double, where the carbocyclic ring compound has from 3 to 8, or from 3 to 12, ring atoms, respectively. Examples of C_3-C_8-cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like; and examples of C_3-C_{12}-cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like.

The term "aryl," as used herein, refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, idenyl and the like.

The term "arylalkyl," as used herein, refers to a C_1–C_3 alkyl or C_1–C_6 alkyl residue attached to an aryl ring. Examples include, but are not limited to, benzyl, phenethyl and the like.

The term "heteroaryl," as used herein, refers to a mono-, bi-, or tri-cyclic aromatic radical or ring having from five to ten ring atoms of which at least one ring atom is selected from S, O and N; wherein any N or S contained within the ring may be optionally oxidized. Heteroaryl includes, but is not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl, and the like.

The term "heteroarylalkyl," as used herein, refers to a C_1–C_3 alkyl or C_1–C_6 alkyl residue residue attached to a heteroaryl ring. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl and the like.

The term "substituted" as used herein, refers to independent replacement of one, two, or three or more of the hydrogen atoms thereon with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, $-NO_2$, -CN, $-NH_2$, N_3, protected amino, alkoxy, thioalkoxy, oxo, -halo- C_1-C_{12}-alkyl, -halo- C_2-C_{12}-alkenyl, -halo- C_2-C_{12}-alkynyl, -halo-C_3-C_{12}-cycloalkyl, -NH -C_1-C_{12}-alkyl, -NH -C_2-C_{12}-alkenyl, -NH -C_2-C_{12}-alkynyl, -NH -C_3-C_{12}-cycloalkyl, -NH -aryl, -NH -heteroaryl, -NH -heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C_1-C_{12}-alkyl, -O-C_2-C_{12}-alkenyl, -O-C_2-C_{12}-alkynyl, -O-C_3-C_{12}-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)- C_1-C_{12}-alkyl, -C(O)- C_2-C_{12}-alkenyl, -C(O)- C_2-C_{12}-alkynyl, -C(O)-C_3-C_{12}-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, $-CONH_2$, -CONH- C_1-C_{12}-alkyl, -CONH- C_2-C_{12}-alkenyl, -CONH-C_2-C_{12}-alkynyl, -CONH-C_3-C_{12}-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, $-OCO_2$- C_1-C_{12}-alkyl, $-OCO_2$- C_2-C_{12}-alkenyl, $-OCO_2$- C_2-C_{12}-alkynyl, $-OCO_2$-C_3-C_{12}-cycloalkyl, $-OCO_2$-aryl, $-OCO_2$-heteroaryl, $-OCO_2$-heterocycloalkyl, $-OCONH_2$, -OCONH- C_1-C_{12}-alkyl, -OCONH- C_2-C_{12}-alkenyl, -OCONH- C_2-C_{12}-alkynyl, -OCONH- C_3-C_{12}-cycloalkyl, -OCONH- aryl, -OCONH- heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)- C_1-C_{12}-alkyl, -NHC(O)-C_2-C_{12}-alkenyl, -NHC(O)-C_2-C_{12}-alkynyl, -NHC(O)-C_3-C_{12}-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, $-NHCO_2$- C_1-C_{12}-alkyl, $-NHCO_2$- C_2-C_{12}-alkenyl, $-NHCO_2$- C_2-C_{12}-alkynyl, $-NHCO_2$- C_3-C_{12}-cycloalkyl, $-NHCO_2$- aryl, $-NHCO_2$- heteroaryl, $-NHCO_2$-heterocycloalkyl, $-NHC(O)NH_2$, -NHC(O)NH- C_1-C_{12}-alkyl, -NHC(O)NH-C_2-C_{12}-alkenyl, -NHC(O)NH-C_2-C_{12}-alkynyl, -NHC(O)NH-C_3-C_{12}-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, $NHC(S)NH_2$, -NHC(S)NH- C_1-C_{12}-

alkyl, -NHC(S)NH-C_2-C_{12}-alkenyl, -NHC(S)NH-C_2-C_{12}-alkynyl, -NHC(S)NH-C_3-C_{12}-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH_2, -NHC(NH)NH- C_1-C_{12}-alkyl, -NHC(NH)NH-C_2-C_{12}-alkenyl, -NHC(NH)NH-C_2-C_{12}-alkynyl, -NHC(NH)NH-C_3-C_{12}-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C_1-C_{12}-alkyl, -NHC(NH)-C_2-C_{12}-alkenyl, -NHC(NH)-C_2-C_{12}-alkynyl, -NHC(NH)-C_3-C_{12}-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C_1-C_{12}-alkyl, -C(NH)NH-C_2-C_{12}-alkenyl, -C(NH)NH-C_2-C_{12}-alkynyl, -C(NH)NH-C_3-C_{12}-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C_1-C_{12}-alkyl, - S(O)-C_2-C_{12}-alkenyl, - S(O)-C_2-C_{12}-alkynyl, - S(O)-C_3-C_{12}-cycloalkyl, - S(O)-aryl, - S(O)-heteroaryl, - S(O)-heterocycloalkyl -SO_2NH_2, -SO_2NH- C_1-C_{12}-alkyl, -SO_2NH-C_2-C_{12}-alkenyl, -SO_2NH- C_2-C_{12}-alkynyl, -SO_2NH- C_3-C_{12}-cycloalkyl, -SO_2NH- aryl, -SO_2NH- heteroaryl, -SO_2NH- heterocycloalkyl, -$NHSO_2$-C_1-C_{12}-alkyl, -$NHSO_2$-C_2-C_{12}-alkenyl, - $NHSO_2$-C_2-C_{12}-alkynyl, -$NHSO_2$-C_3-C_{12}-cycloalkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -$NHSO_2$-heterocycloalkyl, -CH_2NH_2, -$CH_2SO_2CH_3$, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C_3-C_{12}-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C_1-C_{12}-alkyl, -S-C_2-C_{12}-alkenyl, -S-C_2-C_{12}-alkynyl, -S-C_3-C_{12}-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, methylthiomethyl, or –L'–R', wherein L' is C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, and R' is aryl, heteroaryl, heterocyclic, C_3-C_{12}cycloalkyl or C_3-C_{12}cycloalkenyl. It is understood that the aryls, heteroaryls, alkyls, and the like can be further substituted. In some cases, each substituent in a substituted moiety is additionally optionally substituted with one or more groups, each group being independently selected from -F, -Cl, -Br, -I, -OH, -NO_2, -CN, or -NH_2. When there is at least two replacements of the hydrogen atoms with substituents, the two substitutents can be taken together to form a cycloalkyl, cycloalkenyl or heterocyclic ring.

In accordance with the invention, any of the aryls, substituted aryls, heteroaryls and substituted heteroaryls described herein, can be any aromatic group. Aromatic groups can be substituted or unsubstituted.

It is understood that any alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl moiety described herein can also be an aliphatic group, an alicyclic group or a heterocyclic group.

An "aliphatic group" is non-aromatic moicty that may contain any combination of carbon atoms, hydrogen atoms, halogen atoms, oxygen, nitrogen or other atoms, and optionally contain one or more units of unsaturation, e.g., double and/or triple bonds. An aliphatic group may be straight chained, branched or cyclic and preferably contains between about 1 and about 24 carbon atoms, more typically between about 1 and about 12 carbon atoms. In addition to aliphatic hydrocarbon groups, aliphatic groups include, for example, polyalkoxyalkyls, such as polyalkylene glycols, polyamines, and polyimines, for example. Such aliphatic groups may be further substituted. It is understood that aliphatic groups may be used in place of the alkyl, alkenyl, alkynyl, alkylene, alkenylene, and alkynylene groups described herein.

The term "alicyclic," as used herein, denotes a group derived from a monocyclic or polycyclic saturated carbocyclic ring compound. Examples include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl. Such alicyclic groups may be further substituted.

The term "heterocycloalkyl" and "heterocyclic" can be used interchangeably and refer to a non-aromatic 3-, 4-, 5-, 6- or 7-membered ring or a bi- or tri-cyclic group fused system, where (i) each ring contains between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, (ii) each 5-membered ring has 0 to 1 double bonds and each 6-membered ring has 0 to 2 double bonds, (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iv) the nitrogen heteroatom may optionally be quaternized, (v) any of the above rings may be fused to a benzene ring, and (vi) the remaining ring atoms are carbon atoms which may be optionally oxo-substituted. Representative heterocycloalkyl groups include, but are not limited to, [1,3]dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, and tetrahydrofuryl. Such heterocyclic groups may be further substituted to give substituted heterocyclic.

It will be apparent that in various embodiments of the invention, the substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, arylalkyl, heteroarylalkyl, and heterocycloalkyl are intended to be monovalent or divalent. Thus, alkylene, alkenylene, and alkynylene, cycloaklylene, cycloalkenylene, cycloalkynylene,

arylalkylene, heterarylalkylene and heterocycloalkylene groups are to be included in the above definitions, and are applicable to provide the formulas herein with proper valency.

The term "hydroxy activating group", as used herein, refers to a labile chemical moiety which is known in the art to activate a hydroxy group so that it will depart during synthetic procedures such as in a substitution or elimination reactions. Examples of hydroxy activating group include, but not limited to, mesylate, tosylate, triflate, *p*-nitrobenzoate, phosphonate and the like.

The term "activated hydroxy", as used herein, refers to a hydroxy group activated with a hydroxy activating group, as defined above, including mesylate, tosylate, triflate, p-nitrobenzoate, phosphonate groups, for example.

The term "protected hydroxy," as used herein, refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups.

The terms "halo" and "halogen," as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- , or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques, which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, et al., Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text

so states; thus a carbon-carbon double bond depicted arbitrarily herein as *trans* may be *cis*, *trans*, or a mixture of the two in any proportion.

The term "subject" as used herein refers to a mammal. A subject therefore refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, and the like. Preferably the subject is a human. When the subject is a human, the subject may be referred to herein as a patient.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art.

The term "hydroxy protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect a hydroxy group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the hydroxy protecting group as described herein may be selectively removed. Hydroxy protecting groups as known in the are described generally in T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of hydroxy protecting groups include benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, methoxycarbonyl, tert-butoxycarbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-furfuryloxycarbonyl, allyloxycarbonyl, acetyl, formyl, chloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, methyl, t-butyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, 1,1-dimethyl-2-propenyl, 3-methyl- 3 -butenyl, allyl, benzyl, para-methoxybenzyldiphenylmethyl, triphenylmethyl (trityl), tetrahydrofuryl, methoxymethyl, methylthiomethyl, benzyloxymethyl, 2,2,2-trichloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, and the like. Preferred hydroxy protecting groups for the present invention are acetyl (Ac or -C(O)CH_3), benzoyl (Bz or -C(O)C_6H_5), and trimethylsilyl (TMS or-Si(CH_3)$_3$).Berge, *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts can be prepared *in situ*

during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts e.g., salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, malcate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

The term "amino protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect an amino group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the amino protecting group as described herein may be selectively removed. Amino protecting groups as known in the are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of amino protecting groups include, but are not limited to, t-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, benzyloxycarbonyl, and the like.

As used herein, the term "pharmaceutically acceptable ester" refers to esters of the compounds formed by the process of the present invention which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a

salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present invention. "Prodrug", as used herein means a compound, which is convertible in vivo by metabolic means (e.g. by hydrolysis) to afford any compound delineated by the formulae of the instant invention. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), Design of Prodrugs, Elsevier (1985); Widder, et al. (ed.), Methods in Enzymology, vol. 4, Academic Press (1985); Krogsgaard-Larsen, et al., (ed). "Design and Application of Prodrugs, Textbook of Drug Design and Development, Chapter 5, 113-191 (1991); Bundgaard, et al., Journal of Drug Deliver Reviews, 8:1-38(1992); Bundgaard, J. of Pharmaceutical Sciences, 77:285 et seq. (1988); Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, American Chemical Society (1975); and Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry And Enzymology," John Wiley and Sons, Ltd. (2002).

The term "acyl" includes residues derived from acids, including but not limited to carboxylic acids, carbamic acids, carbonic acids, sulfonic acids, and phosphorous acids. Examples include aliphatic carbonyls, aromatic carbonyls, aliphatic sulfonyls, aromatic sulfinyls, aliphatic sulfinyls, aromatic phosphates and aliphatic phosphates. Examples of aliphatic carbonyls include, but are not limited to, acetyl, propionyl, 2-fluoroacetyl, butyryl, 2-hydroxy acetyl, and the like.

The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to proton activity, i.e., not acting as a proton-donor. Examples include, but are not limited to, hydrocarbons, such as hexane and toluene, for example, halogenated hydrocarbons, such as,

for example, methylene chloride, ethylene chloride, chloroform, and the like, heterocyclic compounds, such as, for example, tetrahydrofuran and N-methylpyrrolidinone, and ethers such as diethyl ether, bis-methoxymethyl ether. Such solvents are well known to those skilled in the art, and individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of aprotic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

The terms "protogenic organic solvent" or "protic solvent" as used herein, refer to a solvent that tends to provide protons, such as an alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like. Such solvents are well known to those skilled in the art, and individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of protogenic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. In addition, the solvents, temperatures, reaction durations, etc. delineated herein are for purposes of illustration only and variation of the reaction conditions can produce the desired bridged macrocyclic

products of the present invention. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein include, for example, those described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995).

The compounds of this invention may be modified by appending various functionalities via synthetic means delineated herein to enhance selective biological properties. Such modifications include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

PHARMACEUTICAL COMPOSITIONS

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. The pharmaceutical compositions

of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a

solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

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

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

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

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain

silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

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

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes,

paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Antiviral Activity

An inhibitory amount or dose of the compounds of the present invention may range from about 0.01 mg/Kg to about 500 mg/Kg, alternatively from about 1 to about 50 mg/Kg. Inhibitory amounts or doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

According to the methods of treatment of the present invention, viral infections are treated or prevented in a subject such as a human or lower mammal by administering to the subject an anti-hepatitis C virally effective amount or an inhibitory amount of a compound of the present invention, in such amounts and for such time as is necessary to achieve the desired result. An additional method of the present invention is the treatment of biological samples with an inhibitory amount of a compound of composition of the present invention in such amounts and for such time as is necessary to achieve the desired result.

The term "anti-hepatitis C virally effective amount" of a compound of the invention, as used herein, mean a sufficient amount of the compound so as to decrease the viral load in a biological sample or in a subject (e.g., resulting in at least 10%, preferably at least 50%, more preferably at least 80%, and most preferably at least 90% or 95%, reduction in viral load). As well understood in the medical arts, an anti-hepatitis C virally effective amount of a compound of this invention will be at a reasonable benefit/risk ratio applicable to any medical treatment.

The term "inhibitory amount" of a compound of the present invention means a sufficient amount to decrease the hepatitis C viral load in a biological sample or a subject (e.g., resulting in at least 10%, preferably at least 50%, more preferably at least 80%, and most preferably at least 90% or 95%, reduction in viral load). It is understood that when said inhibitory amount of a compound of the present invention is administered to a subject it will be at a reasonable benefit/risk ratio applicable to any medical treatment as determined by a physician. The term "biological sample(s)," as used herein, means a substance of biological origin intended for administration to a subject. Examples of biological samples include, but are not limited to, blood and components thereof such as plasma, platelets, subpopulations of blood cells and the like; organs such as kidney, liver, heart, lung, and the like; sperm and ova; bone marrow and components thereof; or stem cells. Thus, another embodiment of the present invention is a method of treating a biological sample by contacting said biological sample with an inhibitory amount of a compound or pharmaceutical composition of the present invention.

Upon improvement of a subject's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. The subject may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific inhibitory dose for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The total daily inhibitory dose of the compounds of this invention administered to a subject in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in single or multiple doses.

Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art. All publications, patents, published patent applications, and other references mentioned herein are hereby incorporated by reference in their entirety.

Abbreviations

Abbreviations which have been used in the descriptions of the schemes and the examples that follow are:

ACN for acetonitrile;

BME for 2-mercaptoethanol;

BOP for benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate;

COD for cyclooctadiene;

DAST for diethylaminosulfur trifluoride;

DABCYL for 6-(N-4'-carboxy-4-(dimethylamino)azobenzene)- aminohexyl-1-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite;

DCM for dichloromethane;

DIAD for diisopropyl azodicarboxylate;

DIBAL-H for diisobutylaluminum hydride;

DIEA for diisopropyl ethylamine;

DMAP for N,N-dimethylaminopyridine;

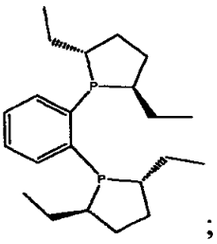
DME for ethylene glycol dimethyl ether;

DMEM for Dulbecco's Modified Eagles Media;

DMF for N,N-dimethyl formamide;

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DMSO for dimethylsulfoxide;

DUPHOS for  ;

EDANS for 5-(2-Amino-ethylamino)-naphthalene-1-sulfonic acid;

EDCI or EDC for 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride;

EtOAc for ethyl acetate;

HATU for O (7-Azabenzotriazole-1-yl)-N,N,N',N' – tetramethyluronium hexafluorophosphate;

Hoveyda's Cat. for Dichloro(*o*-isopropoxyphenylmethylene) (tricyclohexylphosphine)ruthenium(II);

KHMDS is potassium bis(trimethylsilyl) amide;

Ms for mesyl;

NMM for N-4-methylmorpholine;

PyBrOP for Bromo-tri-pyrolidino-phosphonium hexafluorophosphate;

Ph for phenyl;

RCM for ring-closing metathesis;

RT for reverse transcription;

RT-PCR for reverse transcription-polymerase chain reaction;

TEA for triethyl amine;

TFA for trifluoroacetic acid;

THF for tetrahydrofuran;

TLC for thin layer chromatography;

TPP or PPh_3 for triphenylphosphine;

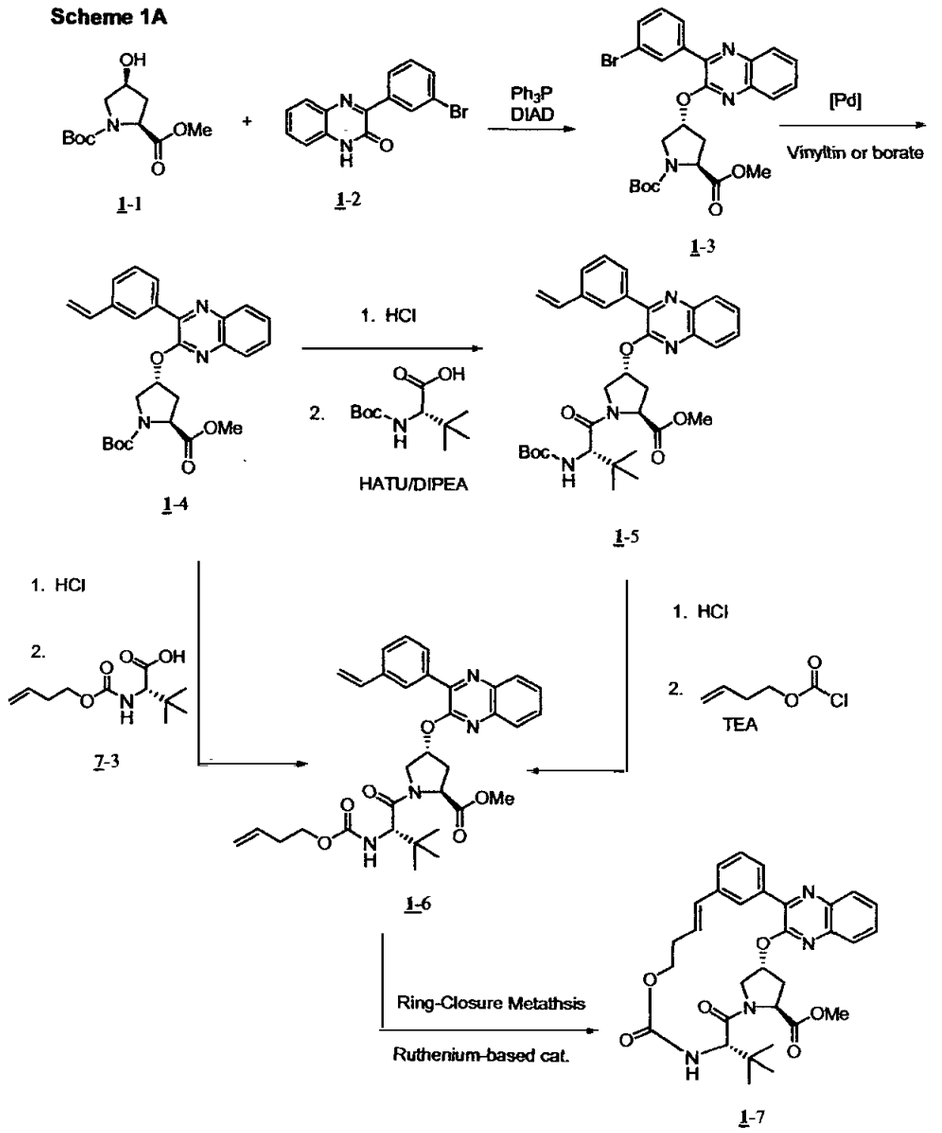
tBOC or Boc for tert-butyloxy carbonyl; and

Xantphos for 4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene.

Synthetic Methods

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes that illustrate the methods by which the compounds of the invention may be prepared, which are intended as an illustration only and not to limit the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

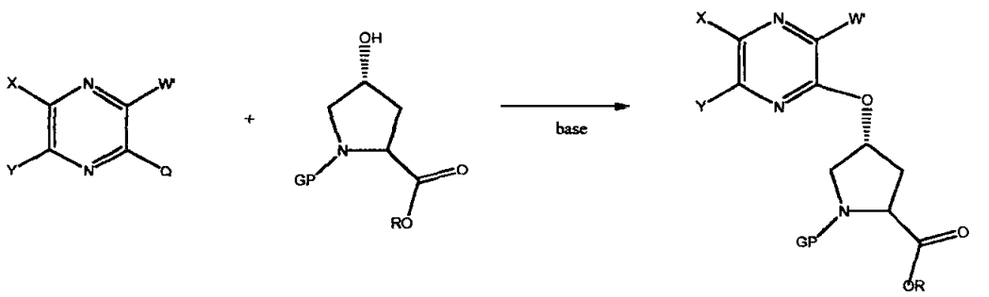
Scheme 1A



1-1 1-2 1-3 1-4 1-5 7-3 1-6 1-7

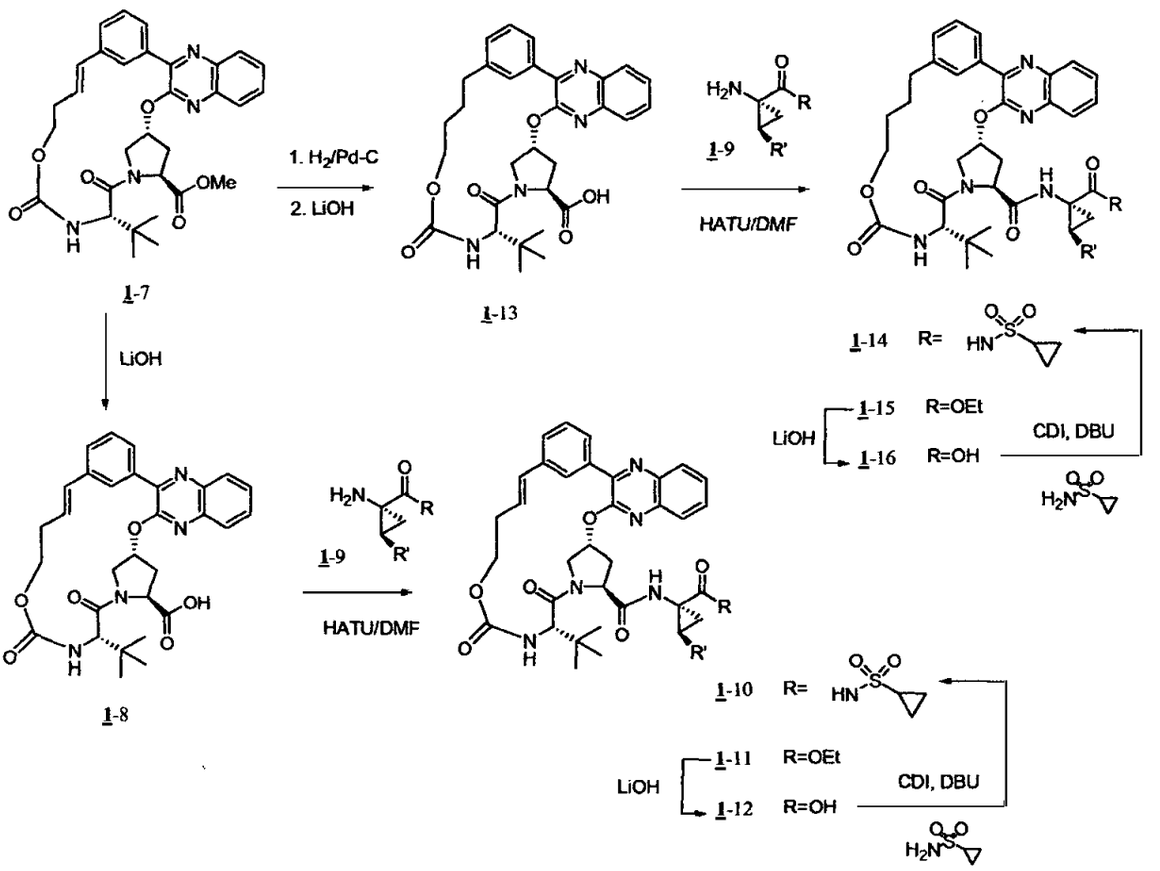
The preparation of quinoxalinyl macrocyclic core compounds is exemplified in Scheme 1A. Commercially available Boc-hydroxyproline 1-1was coupled with quinoxaline derivative 1-2 (for the preparation of quinoxaline analogs, see Schemes 3-6) under Mitsunobu conditions giving compound 1-3. Attachment at the carbonyl oxygen was observed to form the desired compound. A detailed discussion of the identification and characterization of the unexpected oxo Mitosunobu addition product appears in the examples herein. For further details on the Mitsunobu reaction, see O. Mitsunobu, *Synthesis* **1981,** 1-28; D. L. Hughes, *Org. React.* **29,** 1-162 (1983); D. L. Hughes, *Organic Preparations and Procedures Int.* **28,** 127-164 (1996); and J. A. Dodge, S. A. Jones, *Recent Res. Dev. Org. Chem.* **1,** 273-283 (1997). Introduction of vinyl group was accomplished via Suzuki (vinylborate/palladium) or Still (vinyltin/Palladium) reaction to afford compound 1-4. Deprotection of 1-4 with HCl followed by coupling reaction (HATU/DMF) with Boc-L-tert.-leucine gave compound 1-5. Deprotection of 1-5 with HCl followed by reacting with 3-butenyl chloroformate resulted in the macrocyclic compound precursor 1-6. Alternatively, compound 1-6 can be prepared from the direct coupling of intermediate 1-4 (after deprotection of Boc group) with the corresponding carbamate aminoacid 7-3 (for the preparation of the carbamate aminoacid derivatives see Scheme 7). Ring-closing metathesis of compound 1-6 with a ruthenium-based catalyst gives the desired macrocyclic intermediate 1-7 (for further details on ring closing metathesis see recent reviews: Grubbs et al., *Acc. Chem. Res.*, **1995**, *28*, 446; Shrock et al., *Tetrahedron* **1999**, *55*, 8141; Furstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012; Trnka et al., *Acc. Chem. Res.* **2001**, *34*, 18, and Hoveyda et al., *Chem. Eur. J.* **2001**, *7*, 945).

Scheme 1B



An alternate route to quinoxaline core structures is set forth in Scheme 1B, which illustrates the displacement reaction of a substituted quinoxaline halide with amino-protected hydroxyproline in the presence of base, such as NaH or NaO^{t}Bu. In this scheme, PG is an amino protecting group, Q is a halogen, preferably bromine, chlorine or iodine, X and Y have the meanings given for these variables in Formula I, W' has the meanings given for L_{101}-W_{101}- in Formula I and Z-W- in Formula II and R is hydrogen or alkyl.

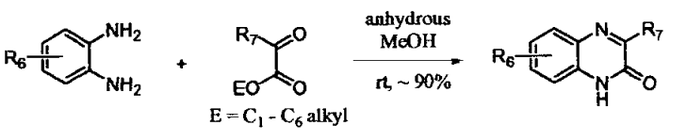
Scheme 2



The syntheses of quinoxalinyl macrocyclic compounds as HCV protease inhibitors are exemplified in Scheme 2. Hydrolysis of compound 1-7 gives the corresponding carboxylic acid 1-8, which is coupled with amino sulfinimide or amino acid ester 1-9 (for the preparation, see Schemes 8 and 9) to afford compound 1-10 or ester 1-11. Hydrolysis of 1-

11 gives 1-12. Compound 1-10 can also be prepared from the acid 1-12 as shown in scheme 2. Hydrogenation of 1-7 gives compound 1-13, which is transformed into compounds 1-14 and 1-16 using the same chemistry as in the preparation of compounds 1-10 and 1-12.

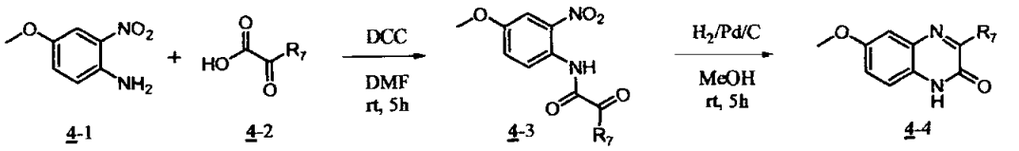
Scheme 3



3-1 3-2 3-3

Various quinoxaline derivatives of compound 1-2 (i.e. formula 3-3) can be made via the condensation of phenyl diamines of formula 3-1, wherein R_6 is previously defined, with keto acids or esters of formula 3-2, wherein R_7 is W-Z as previously defined, in anhydrous methanol at room temperature (see Bekerman et al., *J. Heterocycl. Chem.* **1992**, *29*, 129-133 for further details of this reaction). Examples of phenyl diamines suitable for creating quinoxaline derivatives of formula 3-3 include, but are not limited to, 1,2-diamino-4-nitrobenze, o –phenylenediamine, 3,4-diaminotoluene, 4-chloro-1,2-phenylenediamine, methyl-3,4-diaminobenzoate, benzo[1,3]dioxole-5,6-diamine, 1,2-diamino-4,5-methylene dioxybenzene, 4-chloro-5-(trifluoromethyl)-1,2-benzenediamine, and the like. Examples of keto acids suitable for the reaction described in Scheme 3 include, but are not limited to, benzoylformic acid, phenylpyruvic acid, indole-3-glyoxylic acid, indole-3-pyruvic acid, nitrophenylpyruvic acid, (2-furyl)glyoxylic acid, and the like. Examples of keto esters suitable for the reaction described in Scheme 3 include, but are not limited to ethyl thiophene-2-glyoxylate, ethyl 2-oxo-4-phenylbutyrate, ethyl 2-(formylamino)-4-thiazolyl glyoxylate, ethyl-2-amino-4-thiozolyl glyoxylate, ethyl-2-oxo-4-phenylbutyrate, ethyl-(5-bromothien-2-yl)glyoxylate, ethyl-3-indolylglyoxylate, ethyl-2-methylbenzoyl formate, ethyl-3-ethylbenzoyl formate, ethyl-3-ethylbenzoyl formate, ethyl-4-cyano-2-oxobutyrate, methyl(1-methylindolyl)-3-glyoxylate, and the like.

Scheme 4

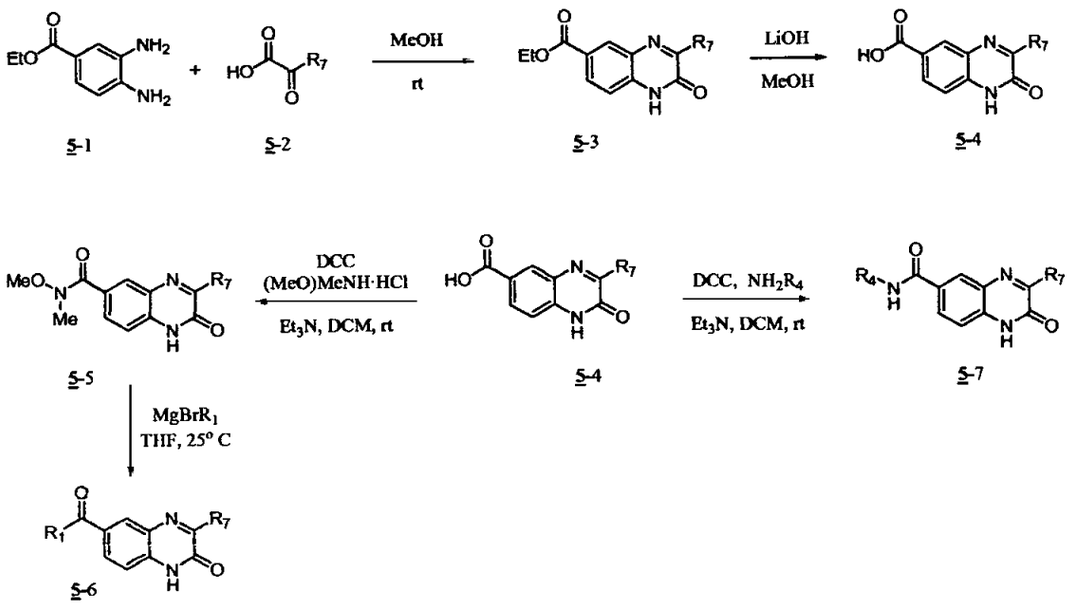


4-1 4-2 4-3 4-4

3,6-substituted quinoxalin-2-ones of formula 4-4, wherein R_7 is W-Z as previously defined, can be made in a regioselective manner to favor the 6-position substitution beginning with the amide coupling of 4-methoxy-2-nitro aniline 4-1 and substituted glyoxylic acid 4-2 to yield compound 4-3. The 3,6-substituted quinoxalin-2-one 4-4 was created via catalytic reduction of the nitro of compound 4-3 followed by condensation. Other substituents may be introduced into 4-4 through the use of other 2-nitroanilines. Examples of keto acids suitable for the reaction described in Scheme 4 include, but are not limited to, benzoylformic acid, phenylpyruvic acid, indole-3-glyoxylic acid, indole-3-pyruvic acid, nitrophenylpyruvic acid, (2-furyl)glyoxylic acid, and the like. Examples of 2-nitro anilines suitable for the reaction described in Scheme 4 include, but are not limited to, 4-ethoxy-2-nitroaniline, 4-amino-3-nitrobenzotrifluoride, 4,5-dimethyl-2-nitroaniline, 4-fluoro-2-nitroaniline, 4-chloro-2-nitroaniline, 4-amino-3-nitromethylbenzoate, 4-benzoyl-2-nitroaniline, 3-bromo-4-methoxy-2-nitroaniline, 3'-amino-4'-methyl-2-nitroacetophenone, 5-ethoxy-4-fluoro-2-nitroaniline, 4-bromo-2-nitroaniline, 4-(trifluoromethoxy)- 2-nitroaniline, ethyl-4-amino3-nitrobenzoate, 4-bromo-2-methyl-6-nitroaniline, 4-propoxy-2-nitroaniline, 5-(propylthio)- 2-nitroaniline, and the like.

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Scheme 5



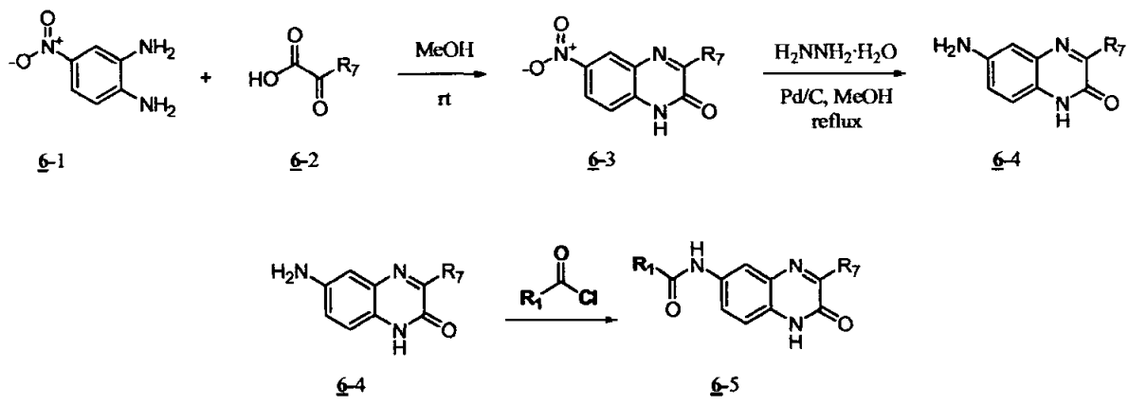
The 3-substituted 2-oxo-1,2-dihydro-quinoxaline-6-carboxylic acid intermediate 5-4 can be formed via condensation of ethyl 3,4-diaminobenzoate (5-1) with oxo acetic acid of formula 5-2, wherein R_7 = W-Z as previously defined, using the method described previously in Scheme 3 (see Bekerman et al., *J. Heterocycl. Chem.* **1992**, *29*, 129-133 for further details). The resulting ethyl ester 5-3 was then hydrolyzed with LiOH in MeOH at room temperature to yield carboxylic acid intermediate 5-4.

Carboxylic acid 5-4 then may be converted to substituted ketone 5-6 (wherein R_1 is as previously defined) via Weinreb's amide 5-5 and subsequent treatment with various Grignard Reagents (see Weinreb et al. *Tetrahedron Lett.* **1977**, 33, 4171; Weinreb et al, *Synth. Commun.* **1982**, *12*, 989 for details of the formation and use of Weinreb's amide; and see B.S. Furniss, A.J. Hannaford, P.W.G. Smith, A.R. Tatchell, Vogel's Textbook of Practical Organic Chemistry, 5th ed., Longman, 1989). The addition was performed in an inert solvent, generally at low temperatures. Suitable solvents include, but are not limited to, tetrahydrofuran, diethylether, 1,4-dioxane, 1,2-dimethoxyethane, and hexanes. Preferably the solvent was tetrahydrofuran or diethylether. Preferably the reaction was carried out at –78°C to 0°C.

Alternatively, carboxylic acid 5-4 may be used to form various amides of formula 5-7, wherein R_4 is as previously defined, in a manner generally described in Scheme 5. All of the various quinoxalin-2-one compounds described in Scheme 5 are further coupled to the macrocyclic precursor via the Mitsunobu conditions described above.

Scheme 6

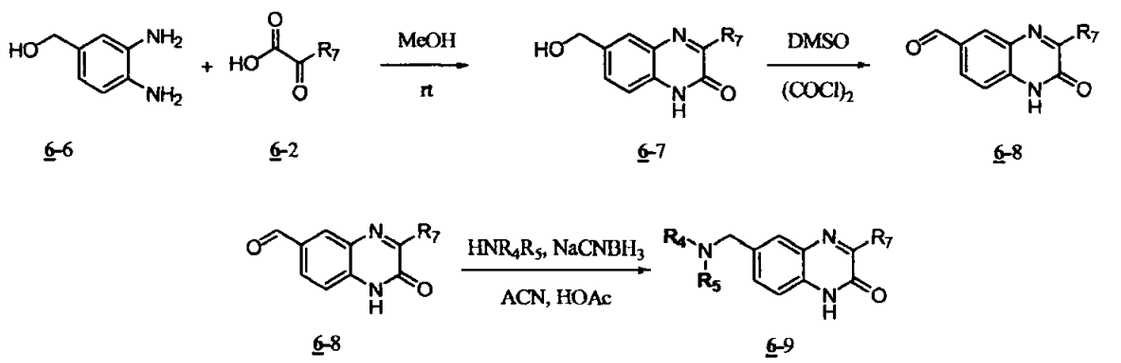
A



6-1 6-2 6-3 6-4

6-4 6-5

B



6-6 6-2 6-7 6-8

6-8 6-9

Further 6-substituted quinoxalin-2-one compounds can be made via the general procedures set forth in Scheme 6.

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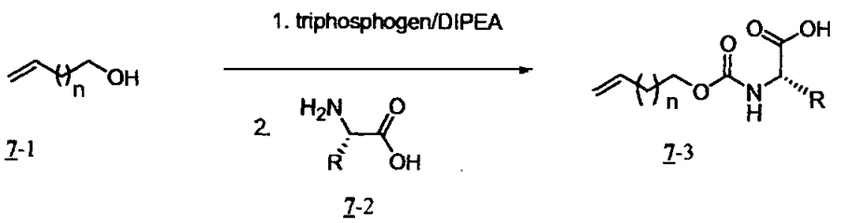
A. Reduction of 6-nitro and Amide Formation

6-nitro-1H-quinoxalin-2-one (6-3) can be formed in the manner previously described from 3,4-diaminonitrobenzene and the oxo acetic acid of formula 6-2, wherein R_7 = W-Z as is previously described. Reduction of the nitro group at the 6-position can be achieved via Pd/C with $H_2NNH_2 \bullet H_2O$ in refluxing MeOH. The 6-position of amine 6-4 then can be treated with a wide array of acid chlorides to give various amides of formula 6-5 where R_1 is as previously defined.

B. Oxidation of Benzyl alcohol and Reductive Amination

Quinoxalin-2-one of formula 6-7 can be formed via the condensation of 3,4-diaminobenzyl alcohol and various oxo acetic acids of formula 6-2, wherein R_7 = W-Z as is previously described. The resulting benzyl alcohol 6-7 may then be oxidized under Swern conditions, or any other oxidation conditions, to generate aldehyde of formula 6-8. For further details concerning the Swern reaction see A. J. Mancuso, D. Swern, *Synthesis* **1981**, 165-185 *passim;* T. T. Tidwell, *Org. React.* **1990**, *39*, 297-572 *passim*. For other oxidation conditions see B.S. Furniss, A.J. Hannaford, P.W.G. Smith, A.R. Tatchell, Vogel's Textbook of Practical Organic Chemistry, 5th ed., Longman, 1989. Subsequent reductive amination reactions with primary or secondary amines in the presence of $NaCNBH_3$ and acetic acid can yield compounds of formula 6-9 wherein R_4 and R_5 are as previously defined.

Scheme 7

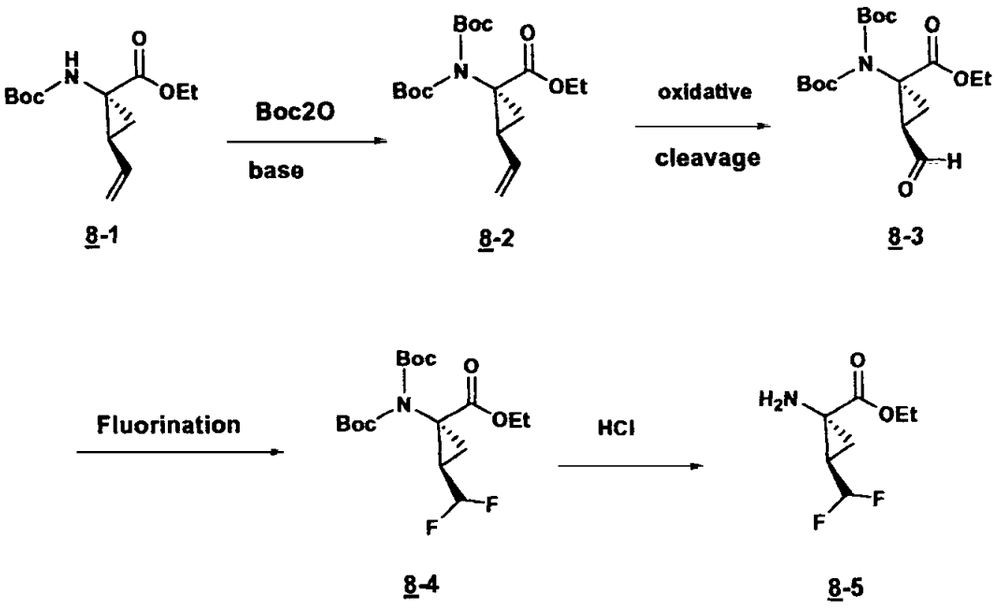


7-1 7-2 7-3

The preparation of carbamate amino acids 7-3 is shown in Scheme 7; n is an integer from 0 to 5. The corresponding olefin alcohol reacts with triphosphogen in presence of DIPEA, followed by adding the appropriate amino acids 7-2 to give the desired carbamate aminoacids 7-3.

000179

Scheme 8

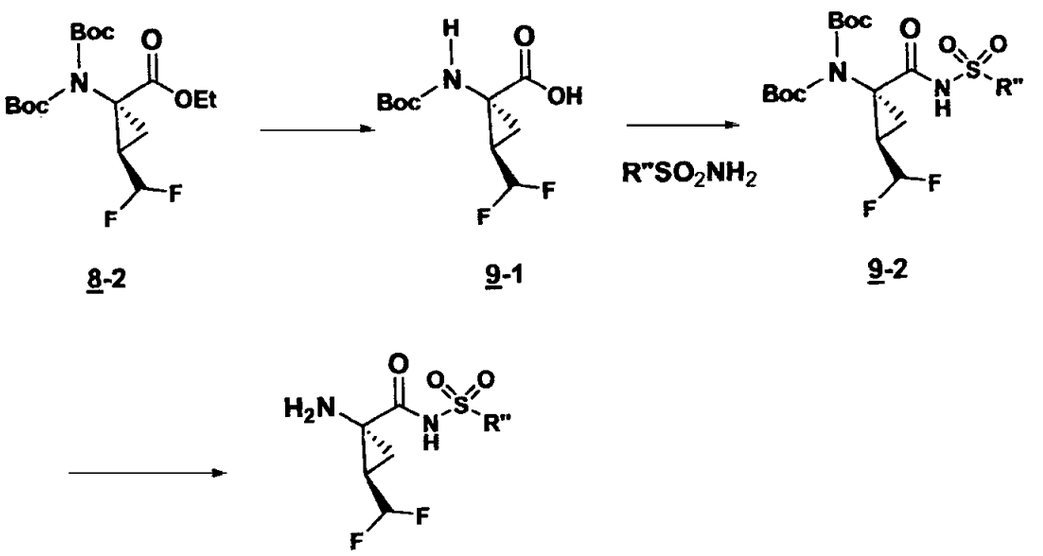


8-1 8-2 8-3

8-4 8-5

The synthesis of difluoromethyl P1 amino acid derivatives 8-5 (i.e. 1-9 with R=OEt and R'=CF_2H) is outlined in Scheme 8. Mono-Boc amino acid ester was further protected as bis-Boc aminoacid ester 8-2. Oxidative cleavage of compound 8-2 resulted in the aldehyde 8-3, which was then converted to difuoromethyl compound 8-4 using aminosulfur trifluoride derivatives such as diethylminosulfur trifluoride (DAST). Deprotection of 8-4 using HCl afforded the desired difluoromethyl P1 compound 8-5.

Scheme 9



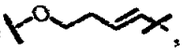
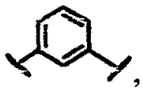
Difluoromethyl P1 sulfonamide derivative 9-3 (i.e. 1-9 with R=NHS(O)$_2$R" and R'=CF_2H) was prepared as shown in Scheme 9. The hydrolysis of compound 8-2 gave the acid 9-1, which was converted to 9-2 using CDI/R"SO_2NH_2/DBU or EDC/DMAP/ R"SO_2NH_2. Deprotection of 9-2 afforded the desired intermediate 9-3.

All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, internet web sites, databases, patents, and patent publications.

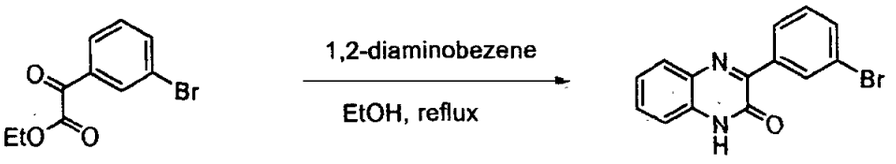
Examples

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not to limit the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents,

derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

Example 1. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G =OH

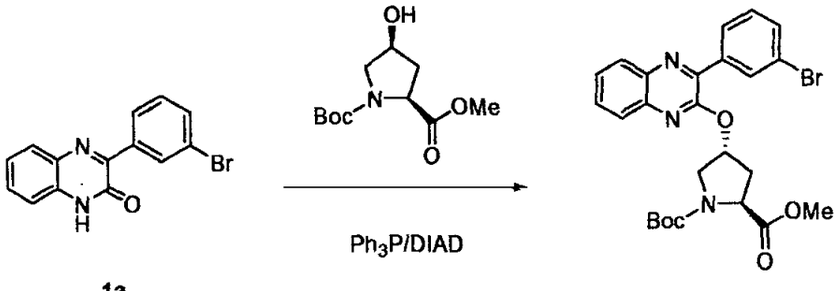
Step 1A



1a-1 **1a**

A mixture of compound **1a-1** (0.84g, 7.77mmol), 1,2-diaminobenzene (2g, 7.77mmol) and ethanol (10m) was heated under reflux for 2h, cooled to room temperature, filtered, washed with cold ethanol and dried under reduced pressure to afford compound **1a** (2.12g) directly used in nexs step.

Step **1B**

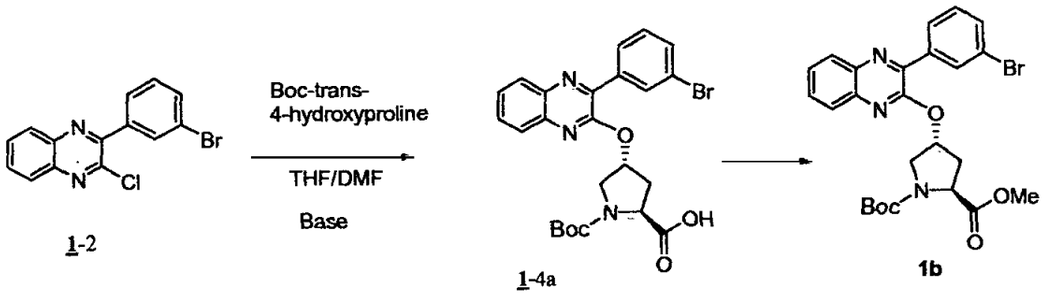


1a **1b**

To a mixture of the above **1a** (1.02g, 3.39mmol), Boc-L-cis-hydroxyproline methyl ester (0.831g, 3.38mmol) and triphenylphosphine (1.8g, 6.86mmol) in THF at 0°C was added dropwise DIAD (1.33ml, 6.76mmol). The resulting mixture was held at 0°C for 15 min. before being warmed to room temperature. After 18 hours, the mixture was

concentrated under vacuum and the residue was purified by chromatography (Hexane/EtOAC = 1:0 to 4:1) to give **1b** (1.74g). MS(ESI): m/e 528.02 (M+H).

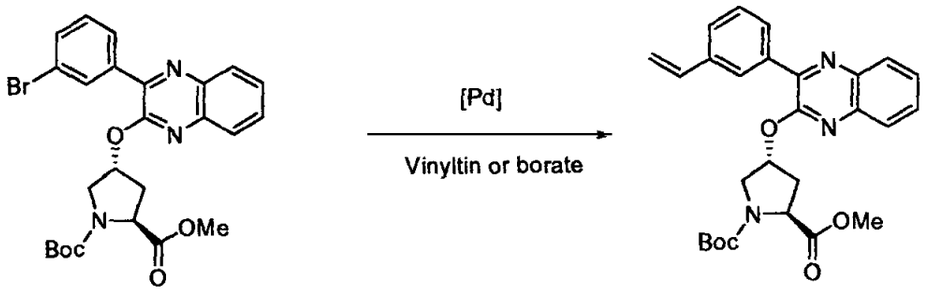
Alternatively, intermediate **1b** was prepared from 1-2 as shown below:



1-2 1-4a **1b**

A 12L round bottom flask was charged with Boc-trans-4-hydroxyproline (141g, 0.61 mol), THF (3.3L). The mixture was cooled to 0°C, a solution of NaOtBu (175.9g, 1.83 mol) in DMF (0.8L) was added slowly via addition funnel while the internal temperature did not exceed 10°C. The ice bath was removed and the mixture was stirred at room temperature for 1.5h. The reaction flask was placed again at 0°C, and compound 1-2 (195g, 0.61 mol) was added portion wise. Thin layer chromatography showed no starting material left after 2h. The reaction mixture was quenched with water (2L) and concentrated to remove most of the THF. Another 2L of water was added, and the mixture was extracted with t-butylmethyl ether twice (4L+3L). 4L of EtOAc was added to the aqueous layer, 10% citric acid was added slowly to adjust the pH to 4-5. Two phases were separated, the aqueous layer was extracted with EtOAc (2X 3L). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford a brown oil (356g). This crude material was disolved in MeOH/CH_2Cl_2 (1.5L/1.6L), cooled to 0°C, and $Me_3SiCH_2N_2$ (2M in hexane, 640mL, 1.28 mol) was added dropwise. After 3.5h the addition was completed and thin layer chromatography showed starting material left. The reaction mixture was concentrated and the residue was crystallized from MeOH (~500mL) to yield 275g of compound **1b**. The mother liquor was purified with silica gel column to afford 22g more of the product. (combined yield: 88% from 1-2).

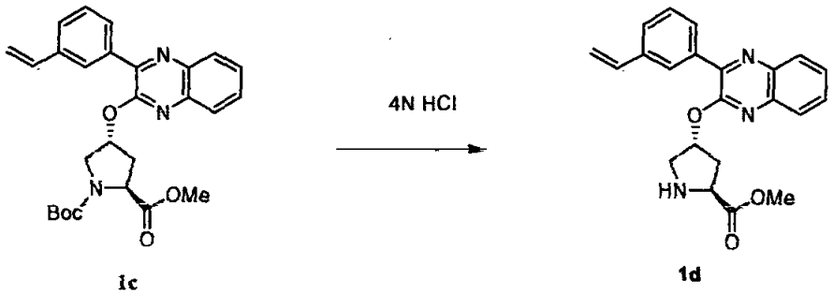
Step **1C**



1b **1c**

To a mixture of compound **1b** (0.6g, 1mmol), potassium vinyltrifluoroborate (0.52g, 2mmol), triethylamine (0.55ml) and ethanol (20ml) was added 1,1'-bis(diphenylphopshino)ferrocene palladium (II) chloride complex with CH_2Cl_2(40mg, 0.048mmol). The resulting mixture was stirred at 75°C for 15h, cooled to room temperature, quenched with 10% KHSO4 aq. solution, extracted with ethyl acetate (3x). The combined oranic layers were dried (MgSO4), concentrated under vacuum, and the residue was purified by chromatography (Hexane/EtOAC = 1:0 to 4:1) to give **1c** (0.49g). MS(ESI): m/z 476.21(M+H).

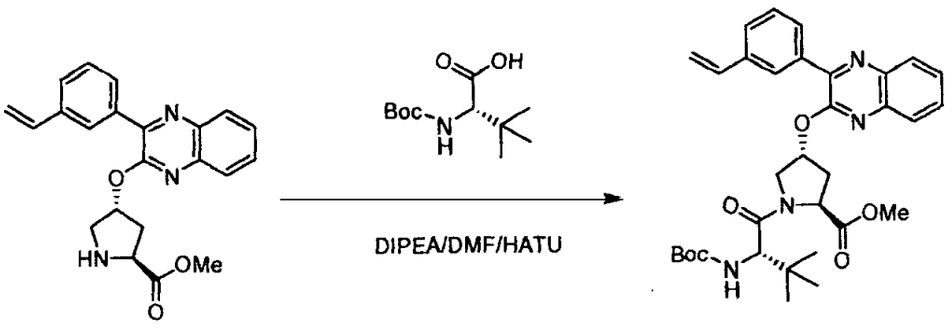
Step**1D**



1c **1d**

A solution of compound **1c** (1mmol) in dichloromethane (2ml) was treated with 4M HCl/dioxane (4ml, 16mmol). The resulting mixture was stirred at room temperature for 1 hour, and concentrated in vacuo to dryness to afford HCl salt of compound **1d** (100%). MS (ESI): m/e 376.15 (M+H).

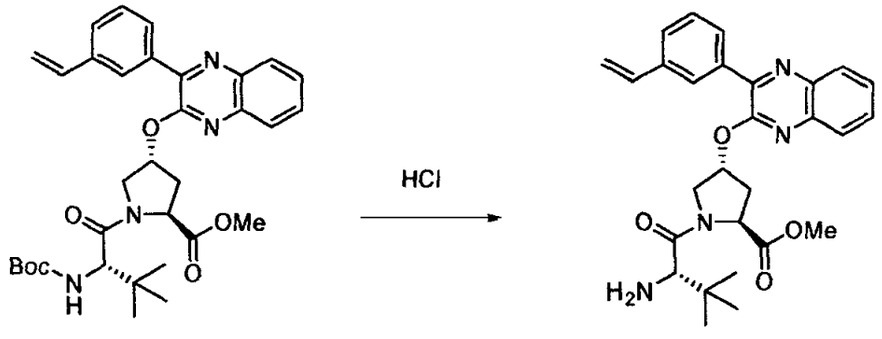
Step1E



1d 1e

To a solution of compound **1d** (HCl salt, 100mg, 0.223mmol), Boc-L-t-leucine (67mg, 0.29mmol) and DIPEA (0.24ml, 1.37mmol) in DMF (3ml) at 0 °C was added HATU (110mg, 0.29mmol). The mixture was stirred at rt for 18h, diluted with EtOAc and washed with half-sat.-aq. NaCl four times. The organic phase was dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo*. The resudue was purified by silica gel chromatography (Hexane/EtOAC = 9 : 1 to 4 : 1) to afford compound **1e** (128mg). MS (ESI): m/e 589.44 (M+H), 489.36 (M-Boc).

Step1F

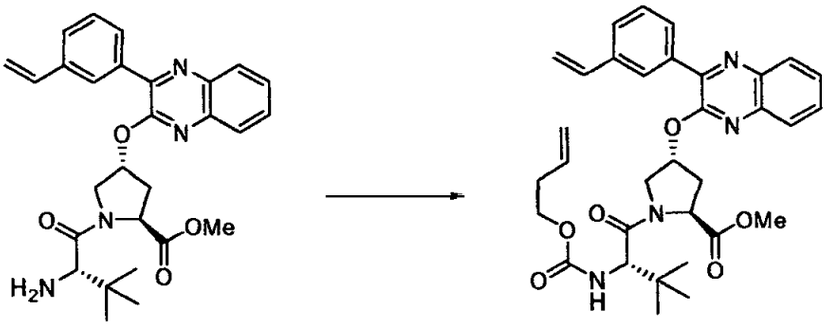


1e 1f

A solution of compound **1e** (117mg, 0.2mmol) in dichloromethane (1ml) was treated with 4M HCl/dioxane (3ml, 12mmol). The resulting mixture was stirred at room temperature for 1 hour, and concentrated in vacuo to dryness to afford HCl salt of compound **1f** (100%). MS (ESI): m/z 489.45(M+H).

000185

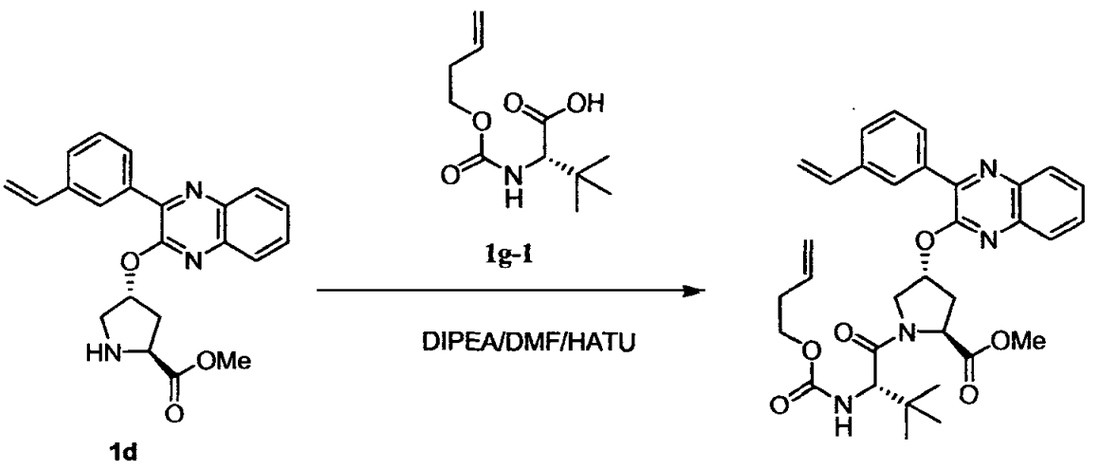
Step1G



1f 1g

Compound **1f** (0.198mmol) was dissolved in dichloromethane (3m), cooled to 0°C, treated with triethylamine (120ul, 4eq.) followed by 3-butenyl chloroformate (0.041ml, 0.33mmol). The mixture was stirred at room temperature for 0.5 to 1 hour, diluted with ethyl acetate, washed with half-sat.-aq. NaCl twice, dried (MgSO4) and concentrated in vacuo. The residue was purified by silica gel chromatography (Hexanes/ EtOAc = 6 : 1 to 4: 1) to give compound **1g** (95mg). MS(ESI): m/z 587.47 (M+H).

Alternatively, compound **1g** was prepared from the coupling of compound **1d** and **1g-1** as shown below:

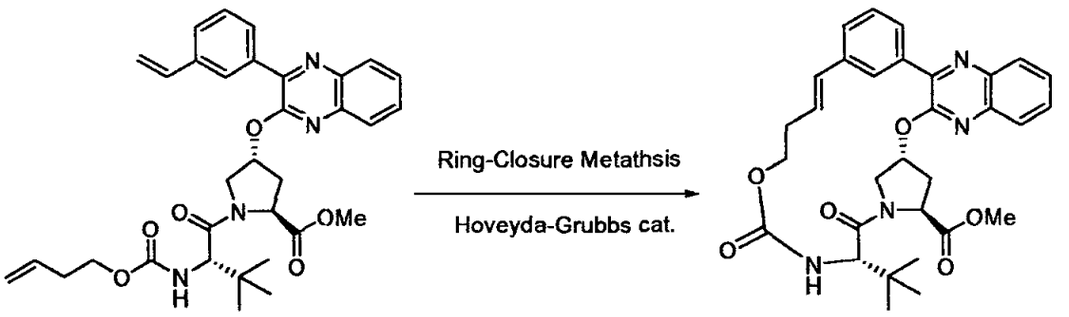


1d 1g-1 1g

To a solution of compound **1d** (HCl salt, 10.78mmol), **1g-1** (2.97g, 13.12mmol) and DIPEA

(5.6ml, 32.3mmol) in DMF (30ml) at 0 °C was added in portions HATU (5.12g, 13.5mmol). The mixture was stirred at rt for 18h, diluted with EtOAc and washed with half-sat.-aq. NaCl four times. The organic phase was dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo*. The resudue was purified by silica gel chromatography (Hexane/EtOAC = 9 : 1 to 4 : 1) to afford compound **1g** (6.1g).

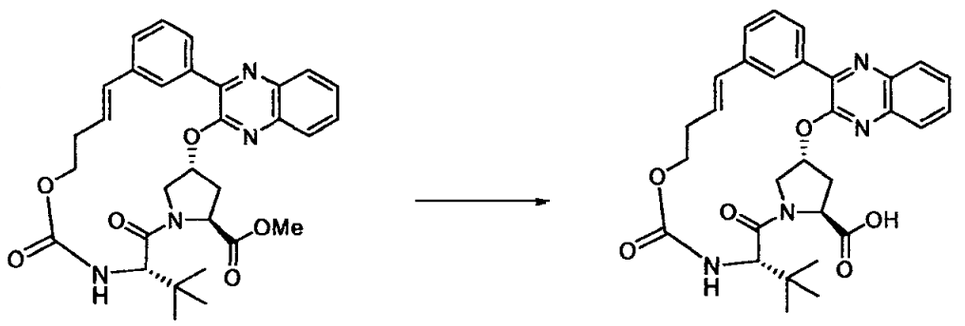
Step**1H**



1g **1h**

To a solution of compound **1g** (95mg, 0.16mmol) in dichloromethane (20ml) was added Hoveyda-Grubbs' 1st generation catalyst or a similar catalyst (5 mol% eq.). The reaction mixture was stirred at 40°C for 20h. The solvent was then evaporated and the residue was purified by silica gel flash chromatography using gradient elution (Hexane/EtOAC = 9 : 1 to 7 : 3) to yield the macrocyclic compound **1h** (58mg). MS (ESI) m/z 559.30 (M+H).

Step **1I**

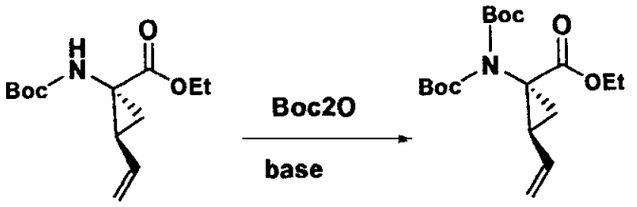


1h **1i**

To a solution of compound **1h** (58mg, 0.103mmol) in THF/MeOH (3ml/1.5ml) was added 1N lithium hydroxide (1.5ml, 1.5mmol). The mixture was stirred at room temperature

for 20 hours. Most organic solvents were evaporated *in vacuo*, and the resulting residue was diluted with water and acidified to pH 5 to 6. The mixture was extracted with EtOAc three times. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford **1i** (100%). MS(ESI): m/z 545.24 (M+H), 551.25 (M+Li).

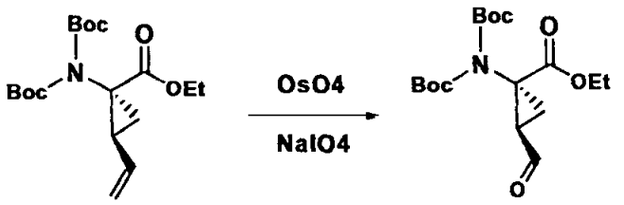
Step **1J**



1j-1 **1j**

To a solution of compound **1j-1** (6.6g, 25.85mmol) in THF (115ml) at -78°C was added slowly NaHMDS (1.0M in THF, 28.5ml, 28.5mmol). After the mixture was stirred at -78°C for an hour, Boc2O (6.8g, 1.2 eq.) in THF (15ml) was added. The resulting mixture was stirred, and the temerature allowed to rise gradually to rt overnight. The reaction mixture was diluted with EtOAc, washed with brine (2x), dried (MgSO4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 1 : 0 to 85 : 15) to afford **1j** (8.05g).

Step **1K**

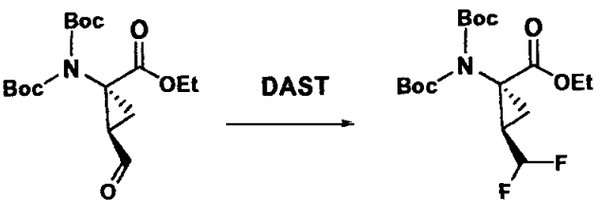


1j **1k**

To a solution of compound **1j** (0.5g, 1.4mmol) in iso-propanol (5ml) was added NaIO4 (0,9g, 4.2mmol), followed by water (5ml). To this vigorously stirred mixture was added OsO4 (0.4% aq. solution, 0.22m, 2.5% eq.). The resulting mixture was stirred at rt for 4h, diluted with EtOAc, washed with aq. NaHCO3, aq. Na2S2O3, brine, dried (MgSO4) and

concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 1:0 to 85:15) to afford **1k** (0.37g).

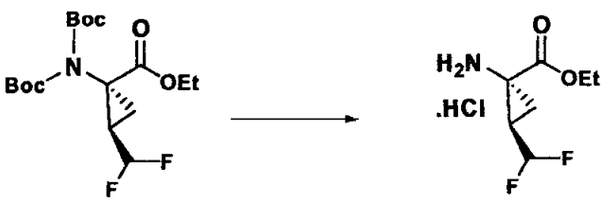
Step **1L**



1k **1l**

To a solution of compound **1k** (2.9g, 8.1mmol) in dichloromethane (25ml) at -78°C was added diethylaminosulfur trifluoride (DAST) (2.7ml, 20.25mmol). The resulting mixture was stirred at -78°C for an hour, then the temperature allowed to rise gradually to rt over 6h, diluted with EtOAc, washed with aq. NaHCO3 (2x), brine, dried (MgSO4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 1 : 0 to 85 : 15) to afford **1l** (1.49g). Recovered starting material **1k** (1.2g).

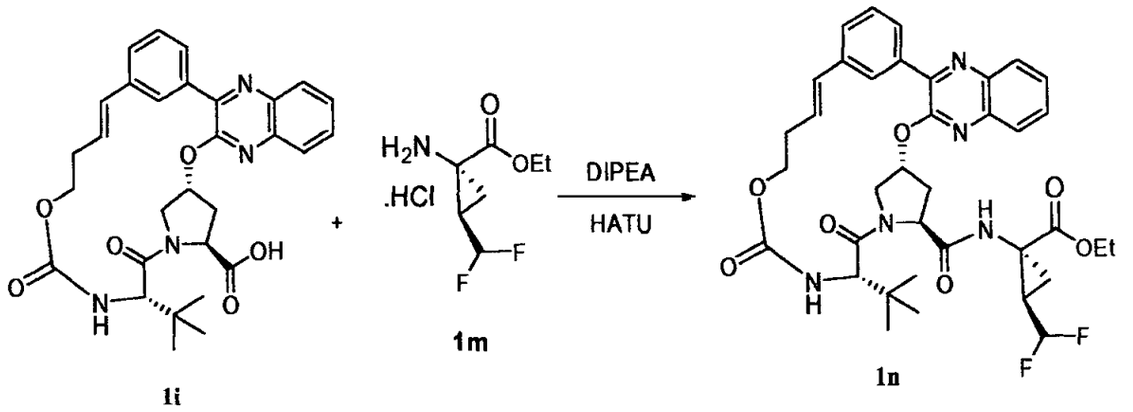
Step **1M**



1l **1m**

A solution of compound **1l** (491mg, 1.29mmol) in dichloromethane (1ml) was treated with 4N HCl in 1, 4-dioxane (6ml, 24mmoL). The mixture was stirred at room temperature for an hour, concentrated to dryness to afford **1m** (~100%).

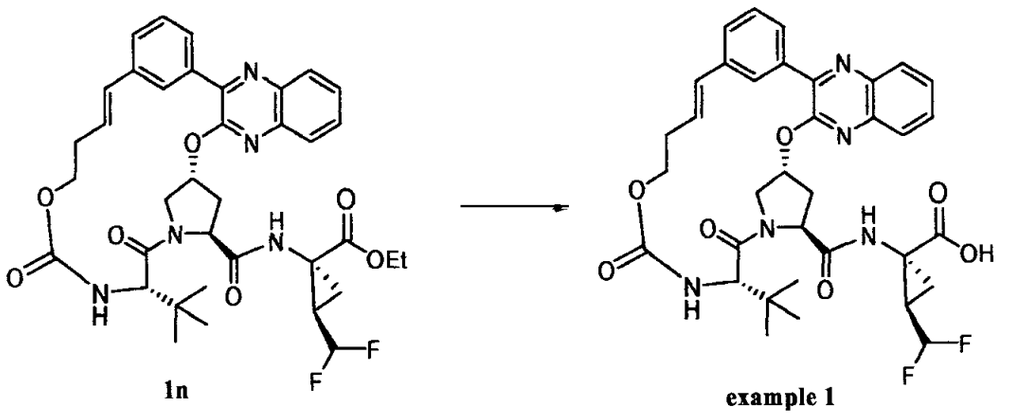
Step **1N**



1i **1m** **1n**

To a solution of **1i** (5.28mmol), compound **1m** (5.808mmol) and DIPEA (3.6ml, 3.9eq.) in DMF (22ml) at 0 °C was added HATU (2.31g, 6.07mmol). The mixture was stirred at room temperature for 4h, diluted with EtOAc and washed with half-sat.-aq. NaCl four times. The organic phase was dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo*. The residue was purified by silica gel column (Hexane/EtOAc = 9 : 1 to 6 : 4) to afford compound **1n** (2.85g). MS (ESI): m/z 706.53 (M+H).

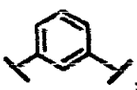
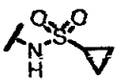
Step **1O**



1n **example 1**

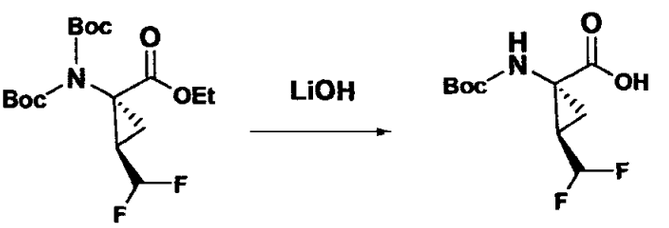
To a solution of compound **1n** (2.85g, 4.04mmol) in THF/MeOH (28ml-12ml) at 0°C was added lithium hydroxide monohydrate (1.02g, 24.2mmol) followed by water (12ml). The mixture was stirred at room temperature for 2 hours, cooled to 0°C, acidified with 1N HCl to pH 5 to 6. Some organic solvents were removed *in vacuo*, and the resulting mixture

was extracted with EtOAc three times (3x 150ml). The combined organic extracts were washed with brine (30ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound (~100%). MS(ESI): m/z 678.41 (M+H).

Example 2. Compound of Formula XV, wherein R =  , M-L = , Ar=  , R'=CF_2H, G = 

Method I

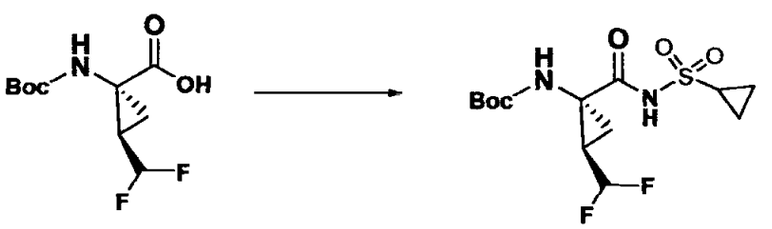
Step **2A**



1l **2a**

Ethyl ester **1l** (50 g, 132 mmol) was dissolved in THF (400 mL), then further diluted with MeOH (160 mL) and water (160 mL). $LiOH{\cdot}H_2O$ (27.6 g, 660 mmol) was added and the reaction mixture was stirred at rt overnight. The solution was acidified to pH ~ 2 using 1 M HCl, then extracted with DCM (3 x 500 mL). The combined organic portions were dried (Na_2SO_4), filtered, and concentrated. The crude carboxylic acid **2a** was carried directly on without any further purification.

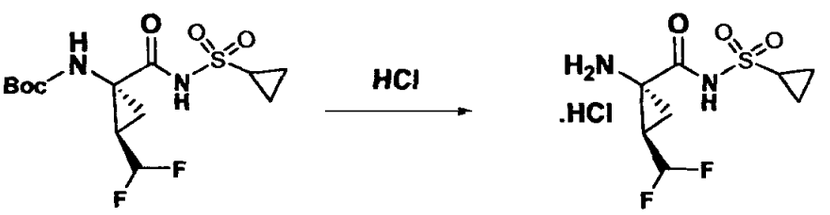
Step **2B**



2a **2b**

Carboxylic acid **2a** (~ 132 mmol) was dissolved in DCM (400 mL) then cooled to 0 °C. DMAP (40.3 g, 330 mmol), sulfonamide (16.0 g, 132 mmol), and EDC (63.3 g, 330 mmol) were added and reaction was stirred at 0 °C for 1 h, warmed to rt, then stirred an additional 48 h. Reaction was diluted with EtOAC (1.5 L) and extracted with 1N HCl (2 x 750 mL). Combined aqueous layers were back-extracted with EtOAc, and the combined EtOAc layers were washed with brine (1 L). Organic portions were dried (Na_2SO_4), filtered, and concentrated. Crude oil was purified via SiO_2 chromatography using a 60% EtOAc/hexanes to yield the desired sulfonimide **2b** (40 g, 85%, two steps).

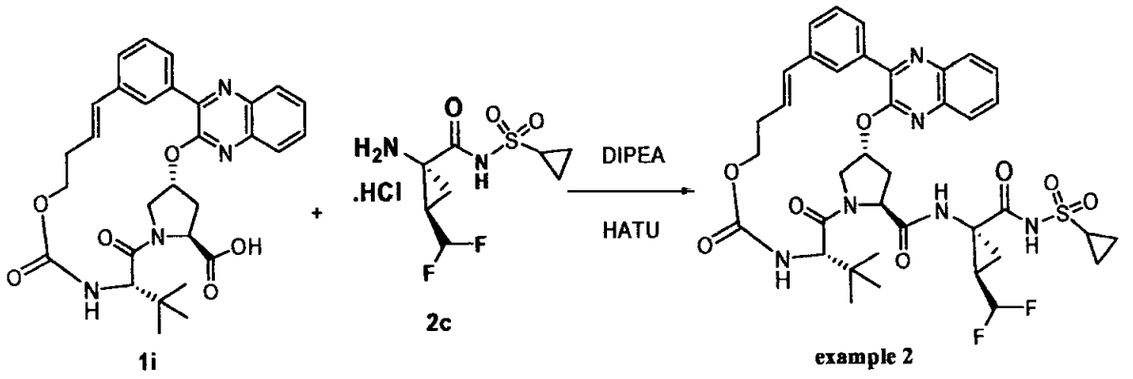
Step **2C**



2b **2c**

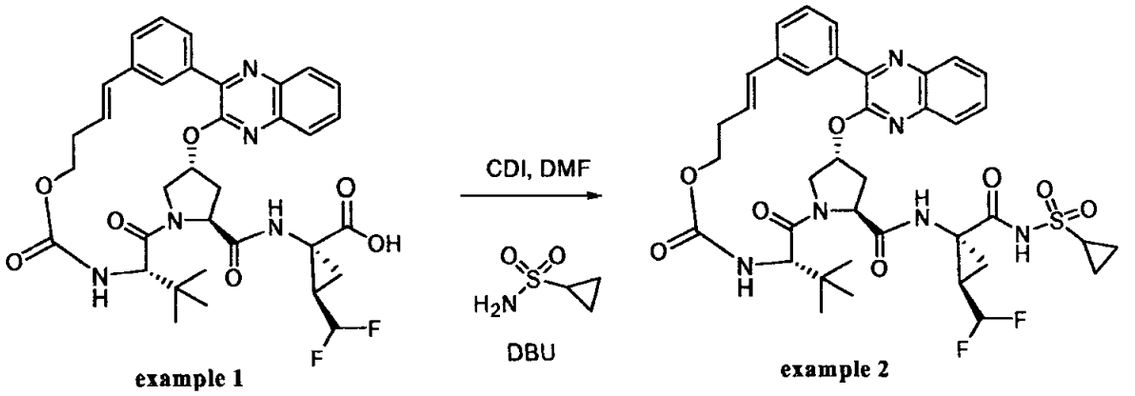
Sulfonimide **2b** (40 g, 112 mmol) was directly charged with a 4M HCl solution in dioxane (282 mL, 1.13 mol), and the resulting solution was stirred at rt for 1.5 h. The reaction mixture was concentrated *in vacuo*, and the crude oil dissolved in a minimum amount of DCM, and triturated with hexane (hexane/DCM = 3.5/1.5). The solid was then filtered and dried to give 32.4 g of the targeted compound **2c**.

Step2D



To a solution of compound 1i (11mg, 0.02mmol), 2c (1 eq.) and DIPEA (0.05ml, 0.287mmol) in DMF (1ml) at 0 °C was added HATU (24mg, 0.063mmol). The mixture was stirred at room temperature for 18h, diluted with EtOAc and washed with half-sat.-aq. NaCl four times. The organic phase was dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the title compound (6mg). MS(ESI); m/z 781.20 (M+H).

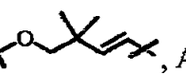
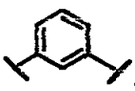
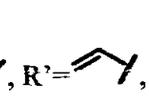
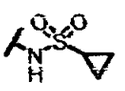
Method II



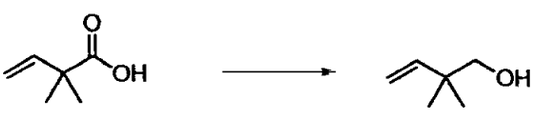
Compound of example 1 (2.78g, 4.04 mmol) and carbonyldiimidazole (1.11g, 6.85mmol) were dissolved in 22 ml of anhydrous DMF and the resulting solution was stirred at 40°C for 1 hour. Cyclopropylsulfonamide (1.22g, 10.06mmol) was added to the reaction followed by DBU (0.96ml, 6.4mmol). The reaction mixture was stirred at 40°C for 5 hours. The reaction mixture was diluted with ethyl acetate (400ml), washed with water (2x50ml), 0.5M KH_2PO_4

000193

(2x50ml), saturated-aqueous NaCl solution (50ml), dried over anhydrous ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexans/ EtOAc = 1 : 1 to 0 : 1) to give the title compound (2.4g). MS(ESI); m/z 781.20 (M+H).

Example 3. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

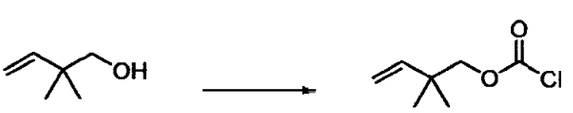
Step**3A**



3a-1 **3a**

To a solution of compound **3a-1** (21.7g, 0.19mole) in diethyl ether (100ml) at 5-10°C was added dropwise LAH (1M in ether, 200ml, 0.2mole). The mixture was then stirred at rt for 1h, cooled to 0-5°C. EtOAc (5ml) was added slowly, followed by careful addition of 6N HCl (200ml), water (50ml) and ether (50ml). The separated aq. phase was further extracted with ether (2x250ml). the combined organic layers were washed with brine (75ml), dried (sodium sulfate) and concentrated at 0°C to remove ether. Distillation under reduced pressure afforded compound **3a** (10.5g).

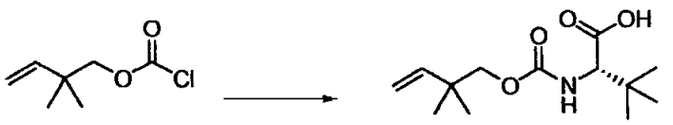
Step3B



3a **3b**

To a solution of phosgene solution in toluene (20% wt. 100ml, 188mmol) at 10°C was added dropwise compound **3a** over 20min. The mixture was stirred at rt for 3h, co-evaporated with methylene chloride (5x40ml) to afford compound **3b** (15.6g, 77% puity).

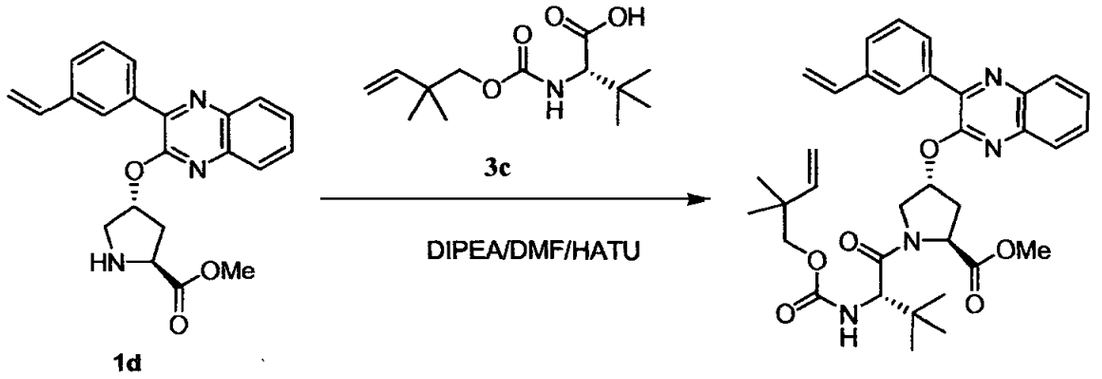
Step3C



3b **3c**

To a mixture of L-tert-leucine (5.36g, 40.8mmol) and 1,4-dioxane (22m) was added slowly 2N NaOH while the internal temperature did not excedd 30°C. The mix. was cooed to 10-15°C, compound **3b** (10.6g, 77%, 49mmol) was added slowly. The mixture was stirred at rt for 15h, then at 60°C for 3h, cooled to rt, washed with methylene chloride (3x35ml), The aqueous phase was adjusted to pH 2 to 3 with 6N HCl, extracted with EtOAc (3x70ml). The combined EtOAc layers were washed with brine (20ml), dried (sodiun sulfate) and concentrated to dryness to afford compound **3c** (8.3g).

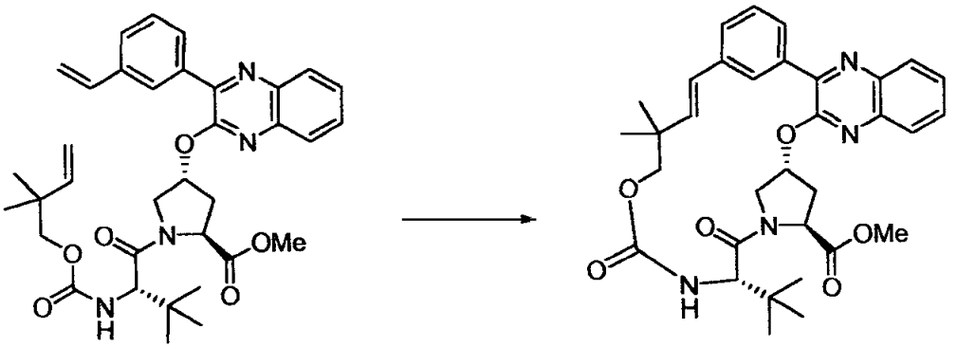
Step**3D**



1d **3d**

To a solution of compound **1d** (HCl salt, 13.57mmol), **3c** (3.84g, 14.9mmol) and DIPEA (7.1ml, 40.7mmol) in DMF (45ml) at 0 °C was added in portions HATU (5.95g, 15.6mmol). The mixture was stirred at rt for 18h, diluted with EtOAc (400m) and washed with water, half-sat.-aq. NaCl four times. The organic phase was dried over anhydrous Na_2SO_4, filtered, and then concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexanc/EtOAC = 9 : 1 to 4 : 1) to afford compound **3d** (8.6g).

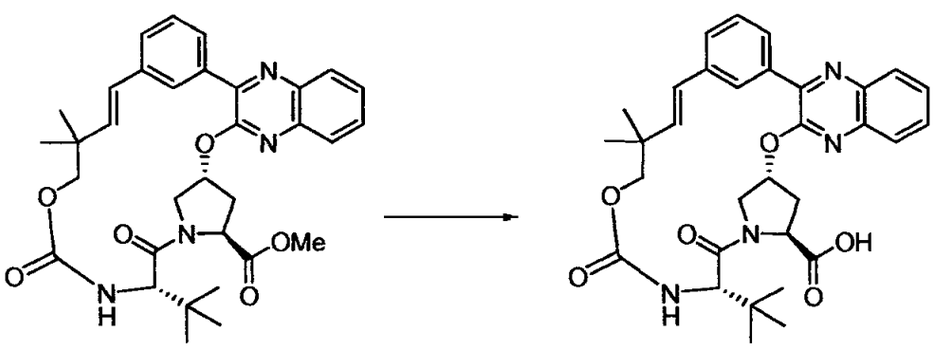
Step3E



3d 3e

A solution of compound **3d** (4.04g, 6.75mmol) in toluene (1200ml) was purged with nitrogen for 0.5h and ruthenium-based catalyst Zhan 1B (0.5g 0.675mmol) was added. The mixture was stirred at 110°C for 8h, cooled to rt, 2-mercaptonicotinic acid (1.014g, 6.7mmo) and DIPEA (1.2ml, 6.75mmol) were added. The mixture was stirred at rt for 16h, filtered and concentrated. The residue was dissolved in EtOAc, washed with aq. $NaHCO_3$, brine, dried (sodium sulfate). The solvent was then evaporated and the residue was purified by silica gel flash chromatography using gradient elution (EtOAc/Hexane 0% to 25%) to yield compound **3e** (2.6g). MS (ESI) m/z 587.30 (M+H).

Step 3F

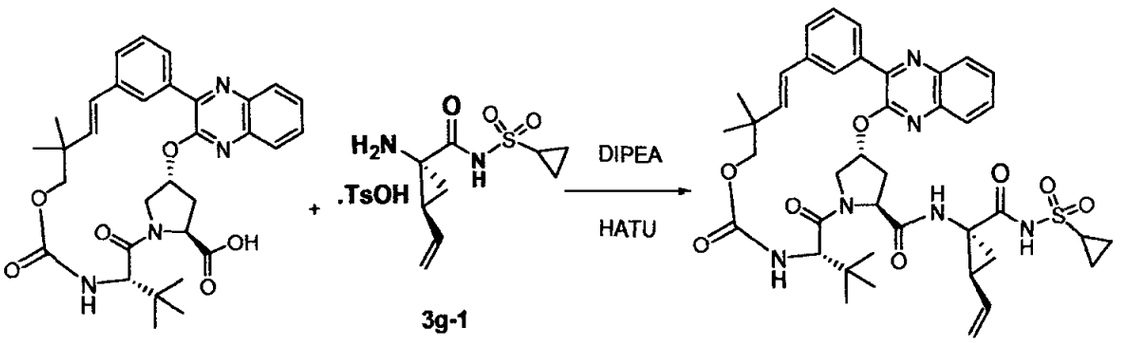


3e 3f

To a solution of compound **3e** (3.1g, 5.28mmol) in THF/MeOH (32ml/14ml) at 0°C was added lithium hydroxide hydrate (1.11g, 26.45mmol), followed by water (14ml). The

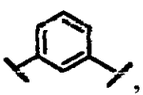
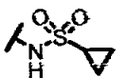
mixture was stirred at room temperature for an hour, placed at 0°C, 1N HCl (~ 29ml) was added dropwise until the mixture 's pH = ~5. The mixture was extracted with EtOAc (3x80ml). the combined organic layers were washed with brine (30ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford **3f** (~100%). MS(ESI): m/z 573.39 (M+H).

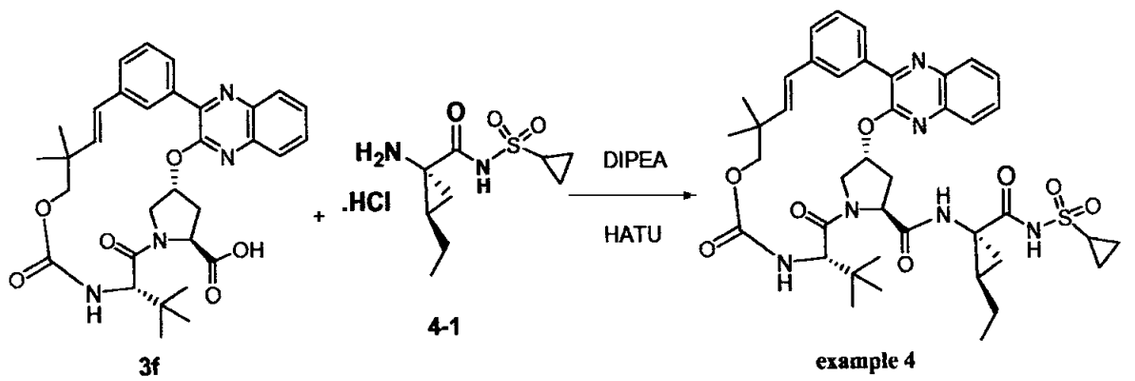
Step3G



3f **3g-1** **example 3**

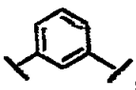
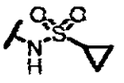
To a solution of compound **3f** (16mg, 0.028mmol), **3g-1** (14mg, 0.034.) and DIPEA (0.025ml, 0.14mmol) in DMF (1.8ml) at 0 °C was added HATU (15mg, 0.039mmol). The mixture was stirred at room temperature for 2h, and purified by preparative HPLC to afford the title compound (16mg). MS(ESI): m/z 785.26 (M+H).

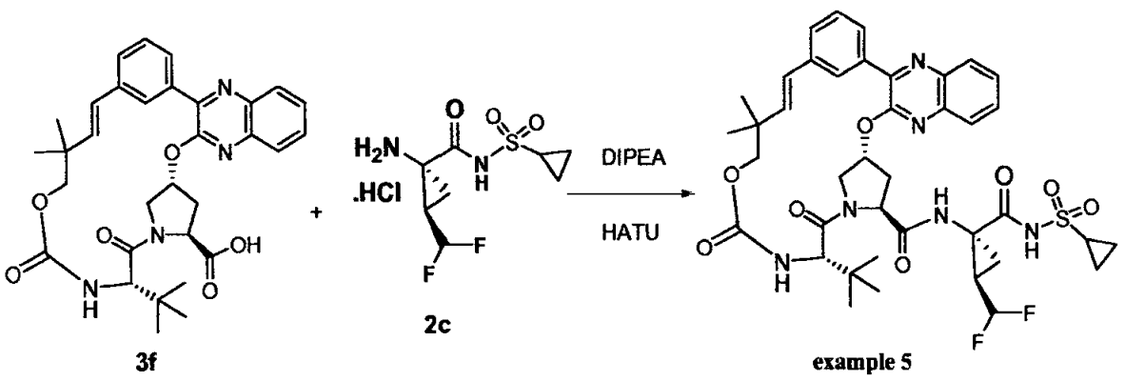
Example 4. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 



3f 4-1 example 4

To a solution of compound **3f** (15mg, 0.026mmol), **4-1** (8.4mg, 0.031.) and DIPEA (0.025ml, 0.14mmol) in DMF (1.8ml) at 0 °C was added HATU (15mg, 0.039mmol). The mixture was stirred at room temperature for 2h, and purified by preparative HPLC to afford the title compound (15mg). MS(ESI): m/z 787.39 (M+H).

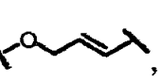
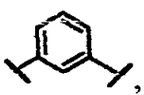
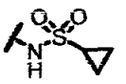
Example 5. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'= CF_2H, G = 



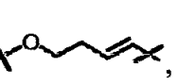
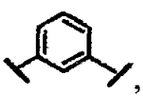
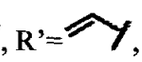
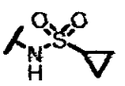
3f 2c example 5

To a solution of compound **3f** (1.284g, 2.07mmol), **2c** (0.681g, 2.34mmol) and DIPEA (1.1ml, 3eq.) in DMF (16ml) at 0 °C was added in portions HATU (0.914g, 2.4mmol). The mixture was stirred at room temperature for 1h, diluted with EtOAc (180ml), and washed with water (20ml), half-sat.-aq. NaCl (20ml), aq. 0.5M KH_2PO_4 (2x20ml), brine (20ml). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated *in*

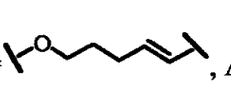
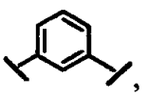
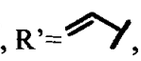
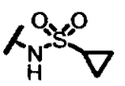
vacuo. The residue was purified by silica gel chromatography (EtOAc/Hexane 25% to 50%) to afford the title compound (1.3g). MS(ESI); m/z 809.55 (M+H).

Example 6. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'= CF_2H, G = 

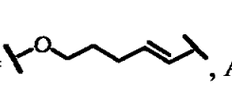
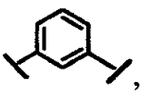
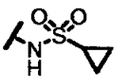
This compound was prepared by the same procedures as described in Example 2 or Example 5. MS (ESI): m/e 767.35 (M+H).

Example 7. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

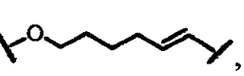
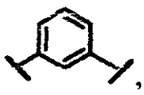
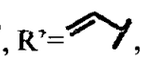
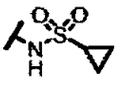
This compound was prepared by the same procedures as described in Example 3. MS (ESI): m/e 757.51 (M+H).

Example 8. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

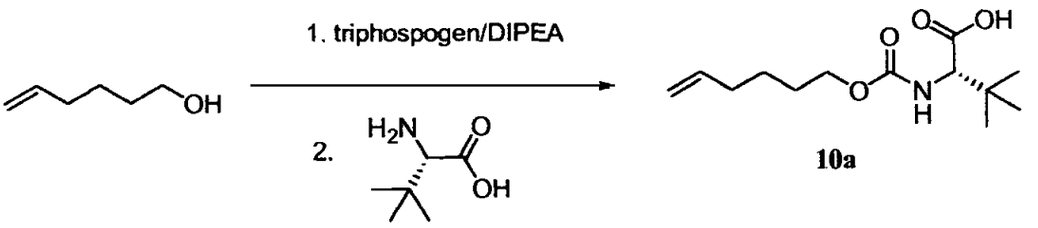
This compound was prepared by the same proceduress as described in Example 3. MS (ESI): m/z 771.23 (M+H).

Example 9. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'= CF_2H, G = 

This compound was prepared by the same procedures as described in Example 2 or Example 5. MS (ESI): m/z 795.34 (M+H).

Example 10. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

Step**10A**

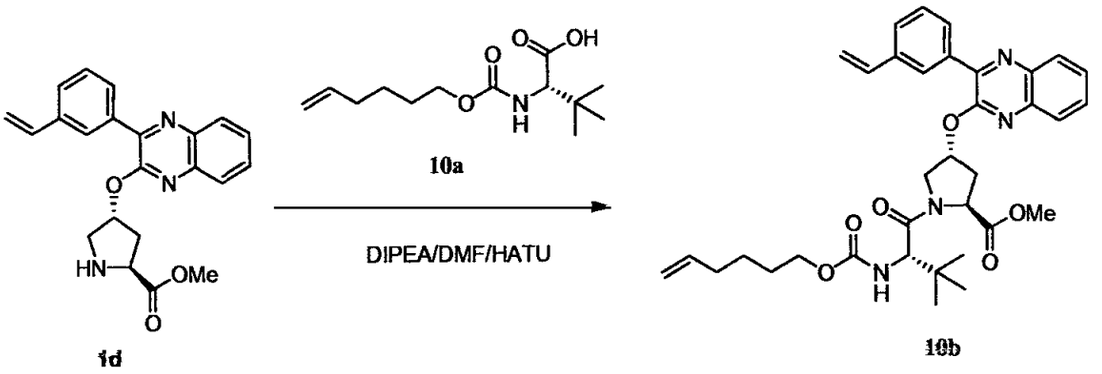


10a

To a solution of hex-5-en-1-ol (1.3ml, 10.9mol), triphosphogen (1.46g, 4.92mmol) in 1,4-dioxane (21ml) at 0°C was added dropwise DIPEA (1.7ml, 9.72mmol). The mixture was stirred at room temperature for an hour, cooled to 0°C. To this was added slowly L-t-leucine (1.28g, 9.72mmol) dissolved in 1N NaOH (9.8ml). The resulting mixture was stirred at room temperature overnight, concentrated to remove half volume of dioxane, treated with 1N NaOH (25ml), washed with ether (3x30ml). The aqueous phase was acidified to pH 2~3 with 6N HCl, then extracted with dichloromethane (3x30ml). The combined oranic layers were dried (MgSO4), concentrated to dryness to give compound **10a** (2.5g) directly used in next step.

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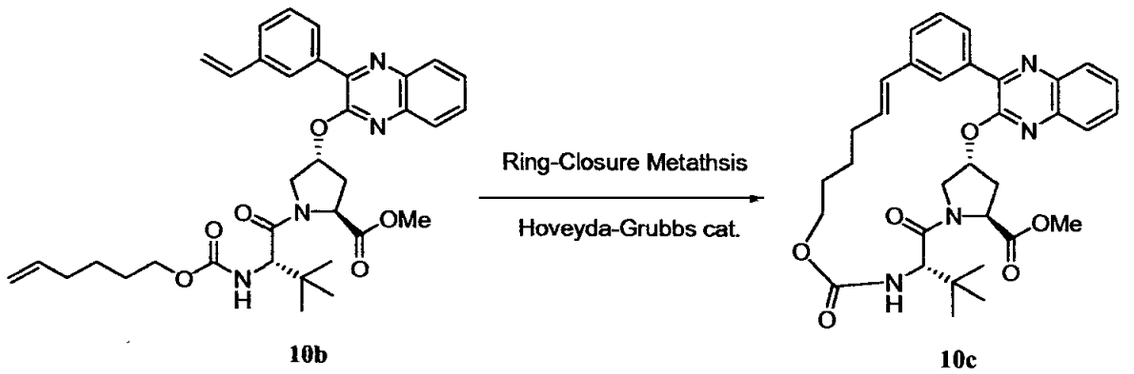
Step**10B**



1d **10b**

To a solution of compound **1d** (HCl salt, 98mg, 0.218mmol), compound **10a** (90mg, 0.35mmol) and DIPEA (0.24ml, 1.37mmol) in DMF (3ml) at 0 °C was added HATU (133mg, 0.35mmol). The mixture was stirred at rt for 18h, diluted with EtOAc and washed with half-sat.-aq. NaCl four times. The organic phase was dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo*. The resudue was purified by silica gel chromatography (Hexane/EtOAC = 6 : 1 to 4 : 1) to afford compound **10b** (119mg). MS (ESI): m/e 615.45 (M+H).

Step**10C**

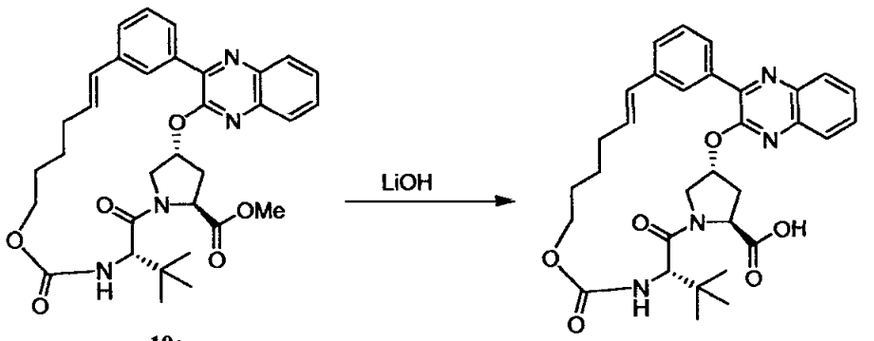


10b **10c**

To a solution of compound **10b** (119mg, 0.19mmol) in dichloromethane (20ml) was added Hoveyda-Grubbs' 1st generation catalyst (5 mol% eq.). The reaction mixture was stirred at 40°C for 20h. The solvent was then evaporated and the residue was purified by silica gel flash chromatography using gradient elution (Hexane/EtOAC = 9 : 1 to 7 : 3) to yield the macrocyclic compound **10c** (58mg). MS (ESI) m/z 587.44 (M+H).

000201

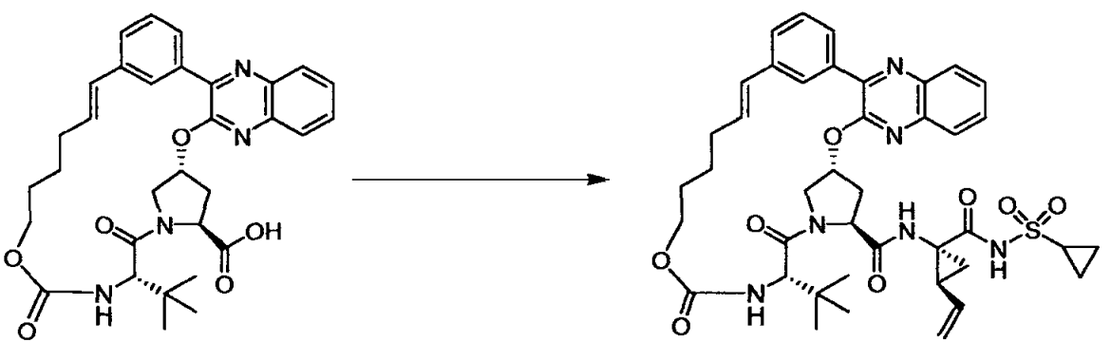
Step **10D**



10c **10d**

To a solution of compound **10c** (58mg, 0.099mmol) in THF/MeOH (3ml/1.5ml) was added 1N lithium hydroxide (1.5ml, 1.5mmol). The mixture was stirred at room temperature for 20 hours. Most organic solvents were evaporated *in vacuo*, and the resulting residue was diluted with water and acidified to pH 5 to 6. The mixture was extracted with EtOAc three times. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford **10d** (100%). MS(ESI): m/z 573.31 (M+H), 579.32 (M+Li).

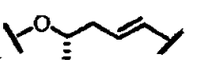
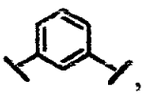
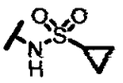
Step**10E**



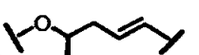
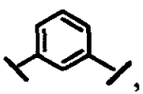
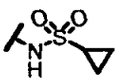
10d **example 10**

This compound was prepared from **10d** by the same procedure as described in Example 3. MS (ESI): m/z 785.31 (M+H).

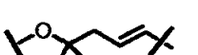
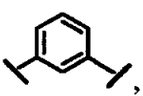
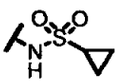
000202

Example 11. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'= CF_2H, G = 

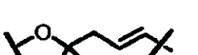
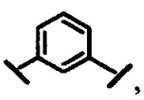
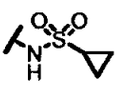
This compound was prepared by the same procedures as described in Example 2 or Example 5. MS (ESI): m/z 795.53 (M+H).

Example 12. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'= CF_2H, G = 

This compound was prepared by the same procedures as described in Example 2 or Example 5. MS (ESI): m/z 795.58 (M+H).

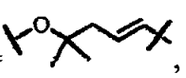
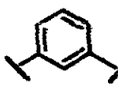
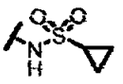
Example 13. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

This compound was prepared by the same procedures as described in Example 3. MS (ESI): m/z 785.29 (M+H).

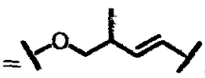
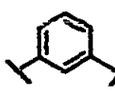
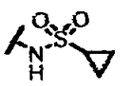
Example 14. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

This compound was prepared by the same procedures as described in Example 4. MS (ESI): m/z 787.39 (M+H).

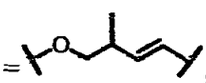
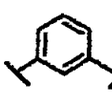
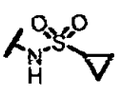
000203

Example 15. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

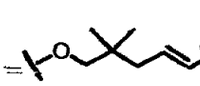
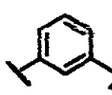
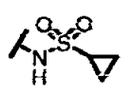
This compound was prepared by the same procedures as described in Example 2 or Example 5. MS (ESI): m/e 809.28 (M+H).

Example 16. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

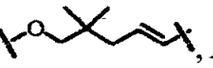
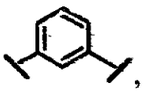
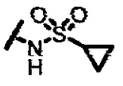
This compound was prepared by the same procedures as described in Example 3. MS (ESI): m/e 771.11 (M+H).

Example 17. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

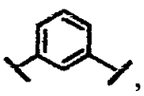
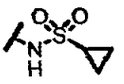
This compound was prepared by the same procedure as described in Example 2 or Example 5. MS (ESI): m/z 795.21 (M+H).

Example 18. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

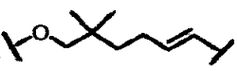
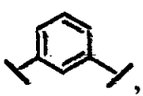
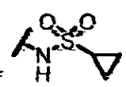
This compound was prepared by the same procedures as described in Example 3. MS (ESI): m/z 799.25 (M+H).

Example 19. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

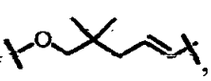
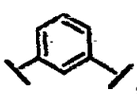
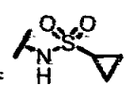
This compound was prepared by the same procedures as described in Example 4. MS (ESI): m/z 801.22 (M+H).

Example 20. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

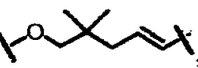
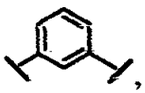
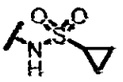
This compound was prepared by the same procedures as described in Example 2 or Example 5. MS (ESI): m/z 823.21 (M+H).

Example 21. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

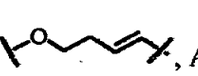
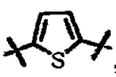
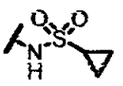
This compound was prepared by the same procedures as described in Example 3. MS (ESI): m/z 813.42 (M+H).

Example 22. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

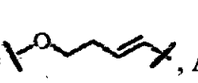
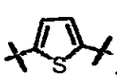
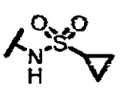
This compound was prepared by the same procedures as described in Example 4. MS (ESI): m/z 815.43 (M+H).

Example 23. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

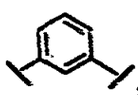
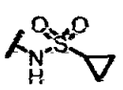
This compound was prepared by the same procedures as described in Example 2 or Example 5. MS (ESI): m/z 837.41 (M+H).

Example 24. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

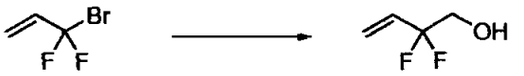
This compound was prepared by the same procedures as described in Example 3. MS (ESI): m/z 763.25 (M+H).

Example 25. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

This compound was prepared by the same procedures as described in Example 2 or Example 5. MS (ESI): m/z 787.22 (M+H).

Example 26. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

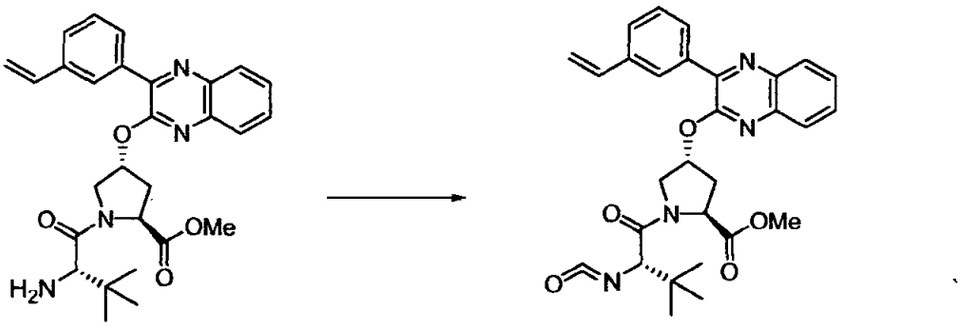
Step**26A**



26a-1 **26a**

To a solution of **26a-1** (3.4g, 21.6mmol), HCOOEt (3.5ml, 43.2mmol) in THF (100ml)-ether (30ml)-pentane (30ml) at -95°C (liquid N2 and toluene bath) was added dropwise n-BuLi (2.5 M in hexane, 10ml, 25mmol). The mix. was stirred at that temperature for 1.5hand the bath temperature was allowed to rise gradually to 0°C over 2 -3h, quenched with aq . solution of NH4Cl (1.4g in 20ml of water). The mix. was stirred for 15min. To the separated organic layer was added MeOH (50ml), followed by adding $NaBH_4$ (1g) in portions at 0°C. The mixture was stirred at rt for 0.5h, cooled to 0°C, quenched carefully with 1N HCl, to pH ~3, extracted with ether (3x). The combined organic layers were washed with aq. NaHCO3, brine, dried (Na2SO4) and concentrated at 0°C. The residue was purified by distillation to yield **26a** (1.3g).

Step **26B**

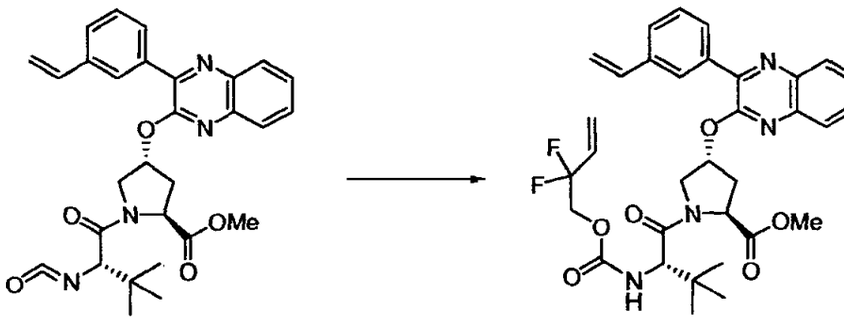


1f **26b**

To a solution of compound **1f** (6.23g, 11.10mmol) in methylene chloride (100ml) at 0°C was added pyridine (5.4ml, 67mmol), followed by dropwose addition of phosgene solution (20% wt. in toluene, 17mmol) over a period of 0.5h. the mixture was stirred at rt for 0.5h, diluted with EtOAc (500ml), washed with water (70ml), brine (2x70ml), dried (sodiun sulfate), filtered and concentrated to dryness to afford compound **26b** (5.3g). MS(ESI): m/z 515.28 (M+H)

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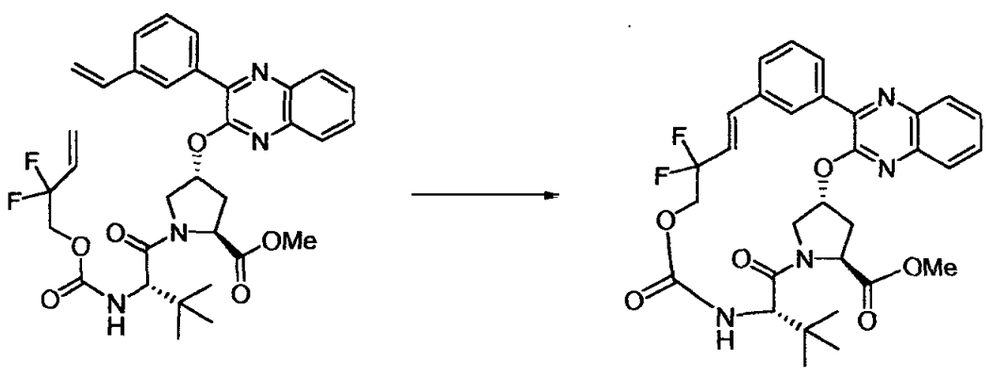
Step **26C**



26b **26c**

To a solution of compound **26b** (4.89g, 9.5mmol) and **26a** (~1.4eq.) in methylene chloride (65ml) was added molecular sieve (4A, 5g). After the mixture was stirred at rt for 0.5h, DBU (2.1ml, 16=4mmol) was dded. The resulting mixture was stirred at rt for 2h and concentrated. The residue was purified by silica gel flash chromatography using gradient elution (EtOAC/Hexane 0% to 25%) to yield compound **26c** (6.1g). MS (ESI) m/z 623.34 (M+H).

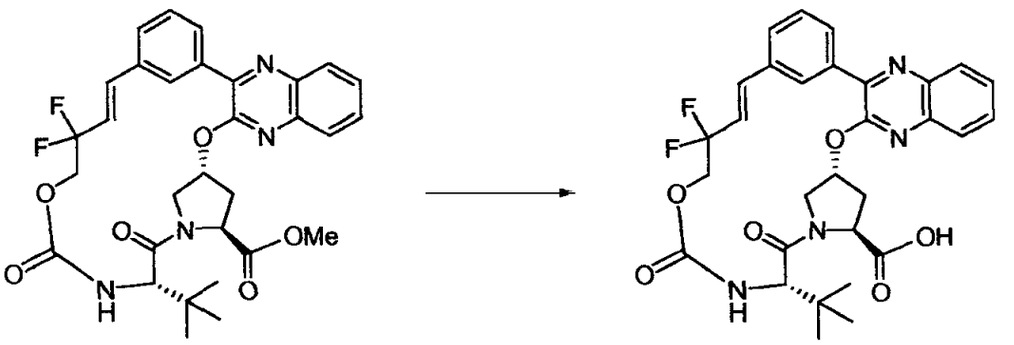
Step **26D**



26c **26d**

Compound **26d** was prepared from compound **26c** by the same procedure as described in Step3E of example 3. MS (ESI) m/z 595.01 (M+H).

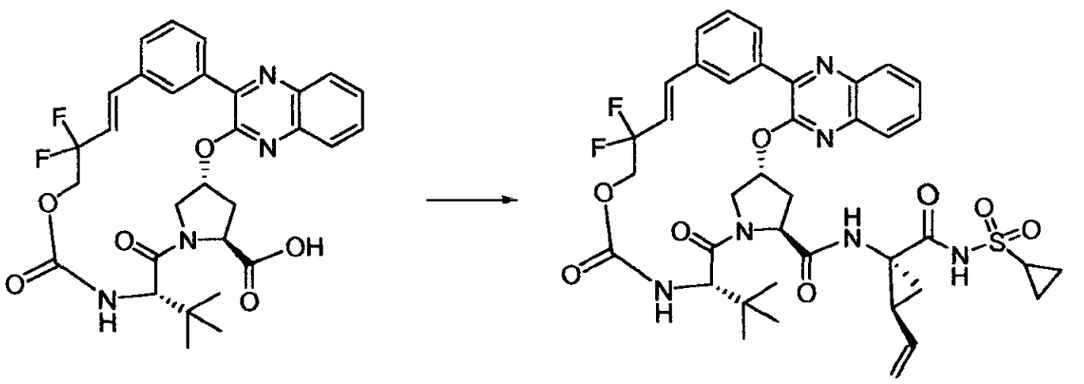
Step **26E**



26d **26e**

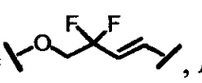
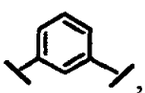
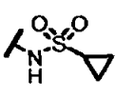
Compound **26e** was prepared from compound **26d** by the same procedure as described in Step3F of example 3. MS (ESI) m/z 581.15 (M+H).

Step **26F**

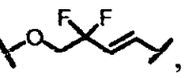
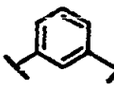
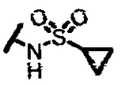


26e **example 26**

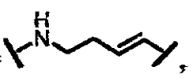
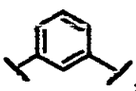
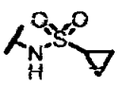
Compound example 26 was prepared from **26e** by the same procedures as described in Example 3. MS (ESI): m/z 793.20 (M+H).

Example 27. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

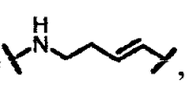
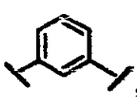
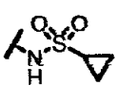
This compound was prepared from compound **26e** by the same procedures as described in Example 4. MS (ESI): m/z 795.43 (M+H).

Example 28. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

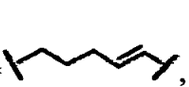
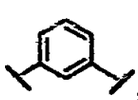
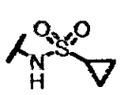
This compound was prepared from compound **26e** by the same procedures as described in Example 5. MS (ESI): m/z 817.27 (M+H).

Example 29. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

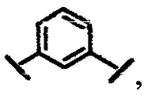
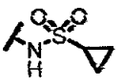
This compound was prepared by the same procedures as described in Example 3. MS (ESI): m/z 756.23 (M+H).

Example 30. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

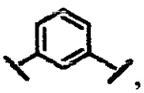
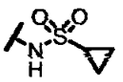
This compound was prepared by the same procedures as described in Example 2 or Example 5. MS (ESI): m/z 780.19 (M+H).

Example 31. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

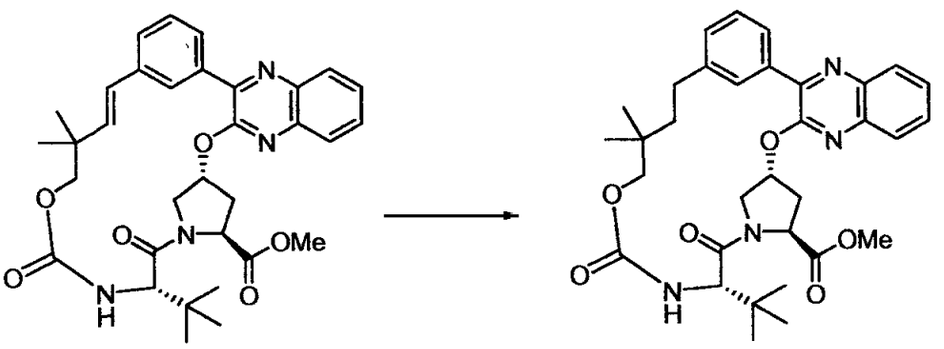
This compound was prepared by the same procedures as described in Example 3. MS (ESI): m/z 755.13 (M+H).

Example 32. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

This compound was prepared by the same procedures as described in Example 2 or Example 5. MS (ESI): m/z 779.26 (M+H).

Example 33. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

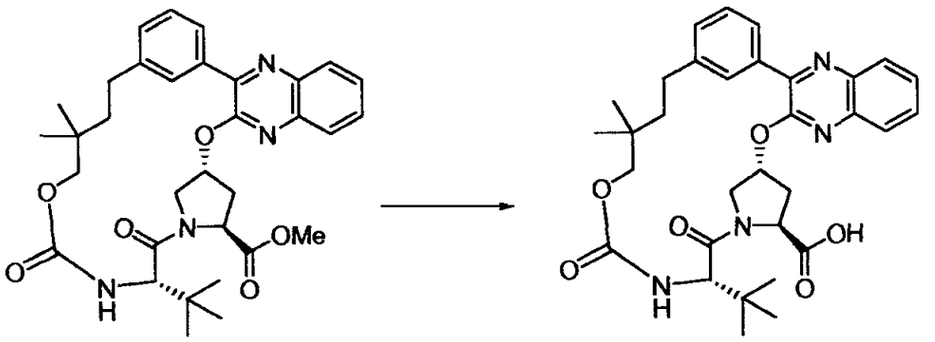
Step **33A**



3e **33a**

A mixture of **3e** (1.52g, 2.59mmol), Pd-C (10% wt. 182mg) and EtOAc (38ml) was hydrogenated for 10h, filtered and concentrated. The residue was purified by silica gel flash chromatography using gradient elution (EtOAC/Hexane 0% to 25%) to yield compound **33a** (1.3g). MS (ESI): m/z 589.27 (M+H).

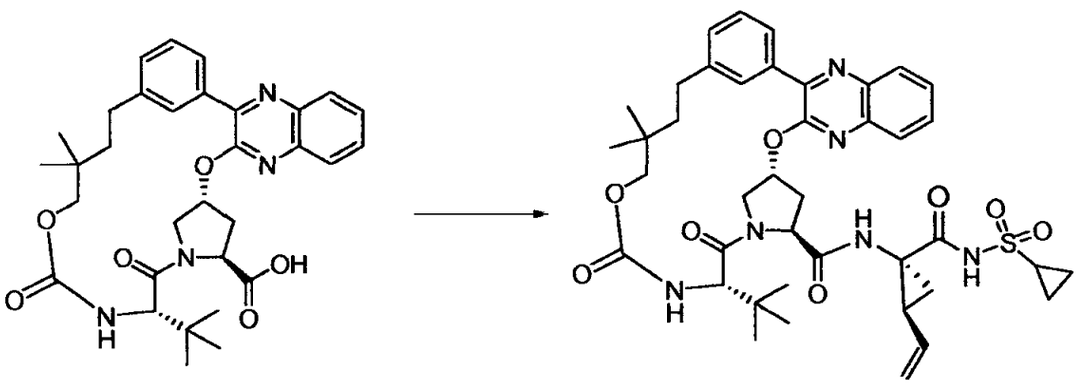
Step **33B**



33a **33b**

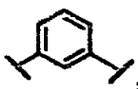
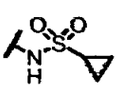
Compound **33b** was prepared from **33a** by the same procedures as described in Step3F of Example 3. MS(ESI): m/z 575.15 (M+H).

Step **33C**

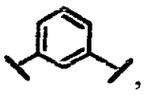
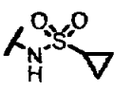


33b **example 33**

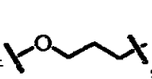
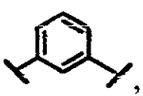
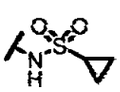
Compound of example 33 was prepared from **33b** by the same procedures as described in Example 3. MS (ESI): m/z 778.39 (M+H).

Example 34. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

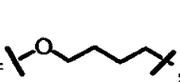
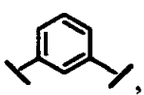
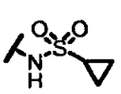
This compound was prepared from **33b** by the same procedures as described in Example 4. MS (ESI): m/z 789.37 (M+H).

Example 35. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

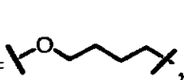
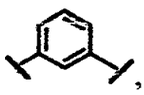
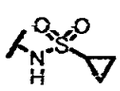
This compound was prepared from **33b** by the same procedures as described in Example 5. MS (ESI): m/z 811.26 (M+H).

Example 36. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

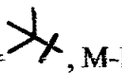
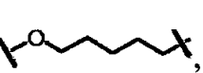
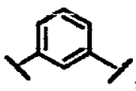
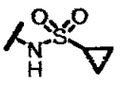
This compound was prepared by the same procedures as described in Example 35. MS (ESI): m/z 769.35 (M+H).

Example 37. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

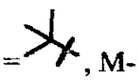
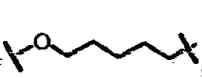
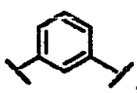
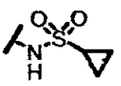
This compound was prepared by the same procedures as described in Example 34. MS (ESI): m/z 761.62 (M+H).

Example 38. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

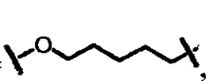
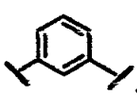
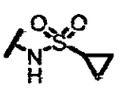
This compound was prepared by the same procedures as described in Example 35. MS (ESI): m/z 783.38 (M+H).

Example 39. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

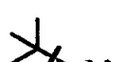
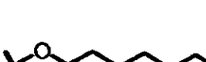
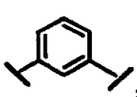
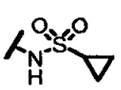
This compound was prepared by the same procedures as described in Example 33. MS (ESI): m/z 773.49 (M+H).

Example 40. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

This compound was prepared by the same procedures as described in Example 34. MS (ESI): m/z 775.36 (M+H).

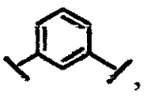
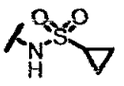
Example 41. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

This compound was prepared by the same procedures as described in Example 35. MS (ESI): m/z 797.34 (M+H).

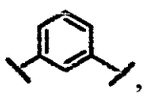
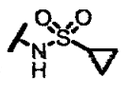
Example 42. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

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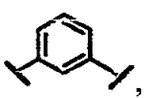
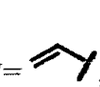
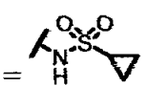
This compound was prepared by the same procedures as described in Example 33. MS (ESI): m/z 787.41 (M+H).

Example 43. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

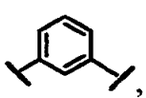
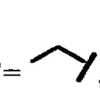
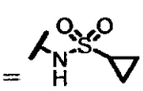
This compound was prepared by the same procedures as described in Example 34. MS (ESI): m/z 789.26 (M+H).

Example 44. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

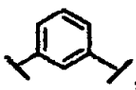
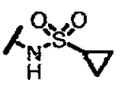
This compound was prepared by the same procedures as described in Example 35. MS (ESI): m/z 811.28 (M+H).

Example 45. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

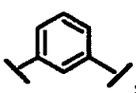
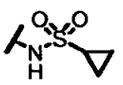
This compound was prepared by the same procedures as described in Example 33. MS (ESI): m/z 801.57 (M+H).

Example 46. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

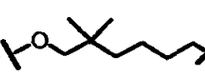
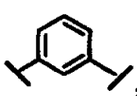
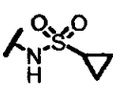
This compound was prepared by the same procedures as described in Example 34. MS (ESI): m/z 803.57 (M+H).

Example 47. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

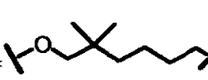
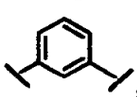
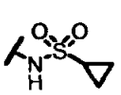
This compound was prepared by the same procedures as described in Example 35. MS (ESI): m/z 825.50 (M+H).

Example 48. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

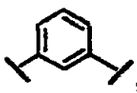
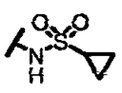
This compound was prepared by the same procedures as described in Example 33. MS (ESI): m/z 815.46 (M+H).

Example 49. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

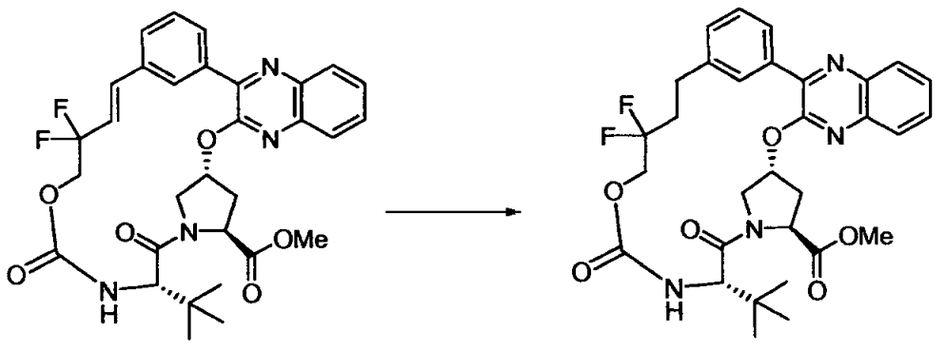
This compound was prepared by the same procedures as described in Example 34. MS (ESI): m/z 817.46 (M+H).

Example 50. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

This compound was prepared by the same procedures as described in Example 35. MS (ESI): m/z 839.46 (M+H).

Example 51. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

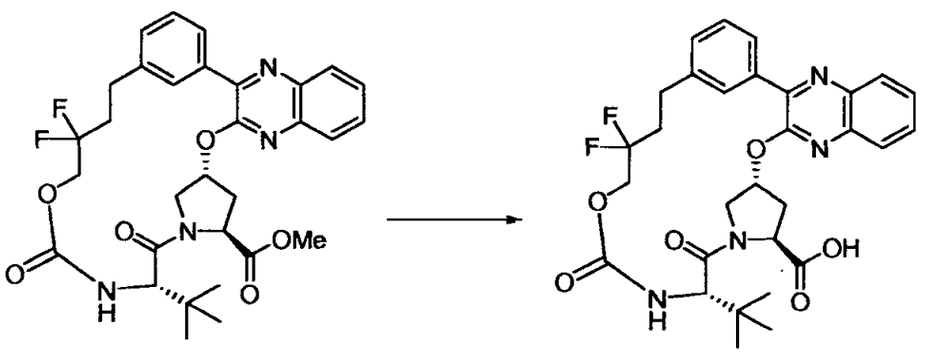
Step **51A**



26d **51a**

A mixture of **26d** (2.55g, 4.286mmol), Pd-C (10% wt. 255mg), DIPEA (1.5ml) and EtOAc (65ml) was hydrogenated for 4h, filtered and concentrated. The residue was purified by silica gel flash chromatography using gradient elution (EtOAC/Hexane 0% to 25%) to yield compound **51a** (1.83g). MS (ESI): m/z 597.05 (M+H).

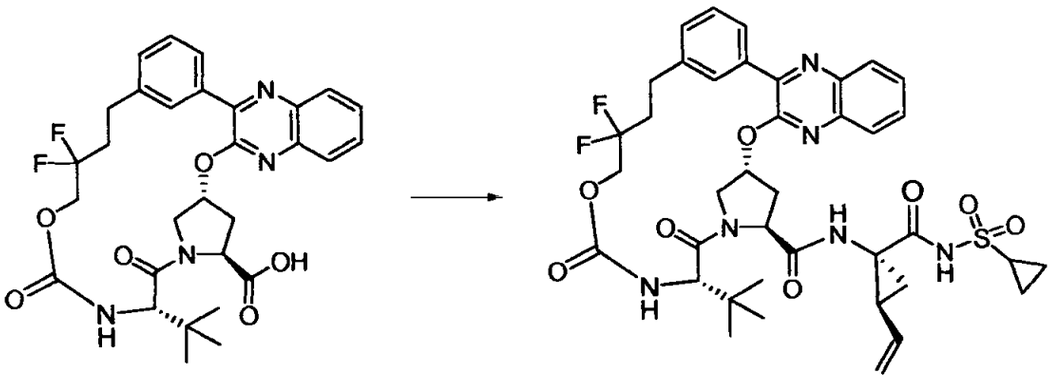
Step **51B**



51a **51b**

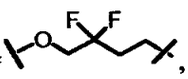
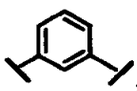
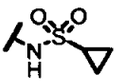
Compound **51b** was prepared from compound **51a** by the same procedure as described in Step3F of example 3. MS (ESI) m/z 583.04 (M+H).

Step **51C**

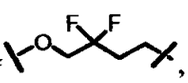
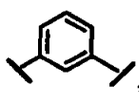
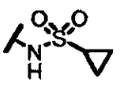


51b **example 51**

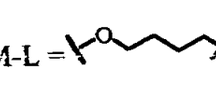
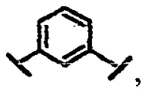
Compound of example 51 was prepared from **51b** by the same procedures as described in Example 3. MS (ESI): m/z 795.27 (M+H).

Example 52. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

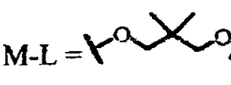
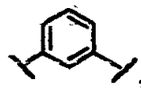
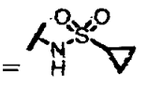
This compound was prepared from **51b** by the same procedures as described in Example 4. MS (ESI): m/z 797.43 (M+H).

Example 53. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

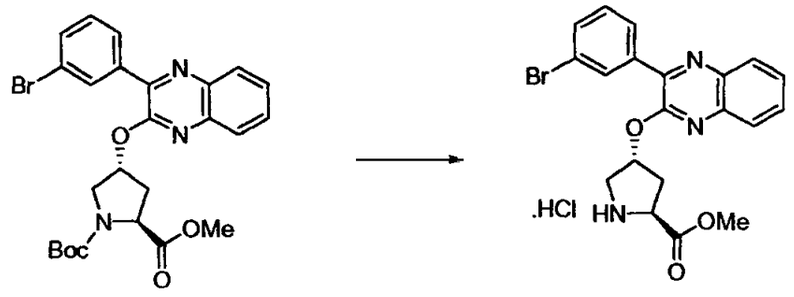
This compound was prepared from **51b** by the same procedures as described in Example 5. MS (ESI): m/z 819.43 (M+H).

Example 54. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = OH

This compound was prepared by the same procedures as described in Example 1. MS (ESI): m/z 680.46 (M+H).

Example 55. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

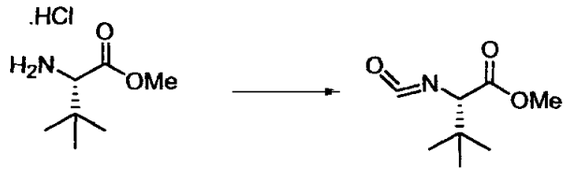
Step **55A**



1b **55a**

A solution of compound **1b** (1g, 1.9mmol) in dichloromethane (1ml) was treated with 4M HCl/dioxane (6ml, 24mmol). The resulting mixture was stirred at room temperature for 2 hours, and concentrated in vacuo to dryness to afford HCl salt compound **55a** (100%).

Step **55B**

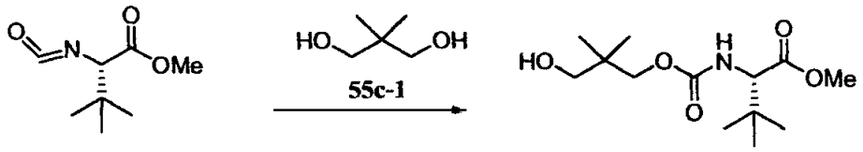


55b-1 **55b**

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To a solution of compound **55b-1** (1.046g, 5.5mmol) in dichloromethane (30ml) at 0°C was added pyridine (2.23ml), followed by dropwise addition of phosgene solution (in toluene, 20% wt., 4.4ml, 8.3mmol). The mixture was stirred at 0°C for 2h, diluted with EtOAc, washed with 1N HCl, brine, dried (sodium sulfate) and concentrated to dryness to afford **55b** (0.95g).

Step **55C**



55b **55c**

To a solution of compound **55b** (0.228g, 1.33mmol) and **55c-1** (1.4g, 13.3mmol) in dichloromethane (10ml) - DMF (2ml) at rt was added DBU (0.3ml, 2.18mmo). The mixture was stirred at rt for 16h, diluted with EtOAc, washed with water, brine twice, 1N HCl, brien, dried (sodium sulfate) and concentrated. The residue was purified by silica gel flash chromatography using gradient elution (EtOAC/Hexane 0% to 30%) to yield compound **55c** (0.303g).

Step **55D**

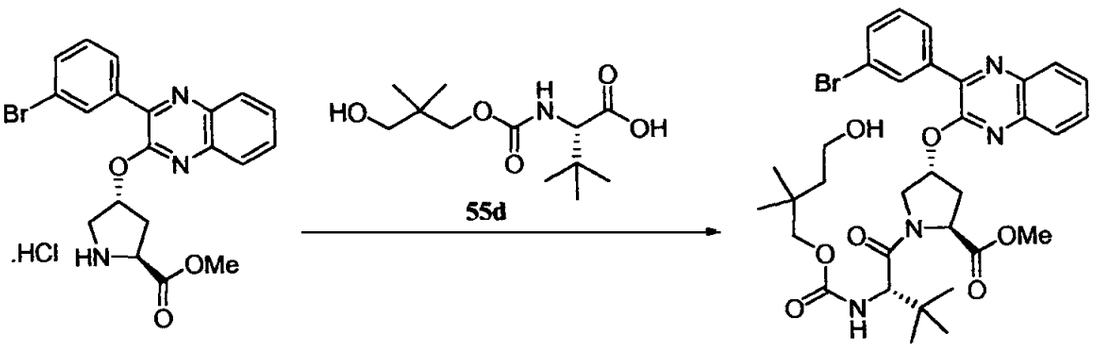


55c **55d**

To a solution of compound **55c** (0.255g, 0.93mmol) in THF/MeOH (6ml/2.6ml) at 0°C was lithium hydroxide hydrate (0.195g, 4.6mmol), followed by water (2.6ml). The mixture was stirred at room temperature for 16h, placed at 0°C, 1N HCl was added dropwise until the mixture 's pH = ~3. The mixture was extracted with EtOAc three times. the combined

organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford **55d** (0.227g).

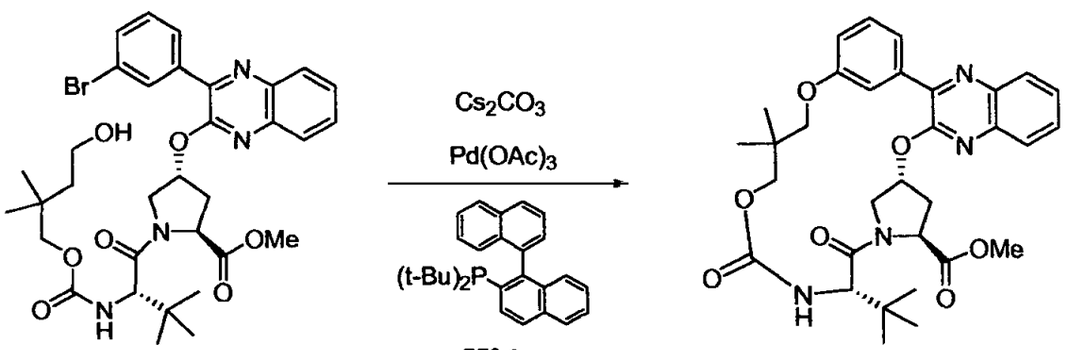
Step **55E**



55a **55e**

To a solution of compound **55a** (0.52g, 1.1mmol), **55d** (0.93mmol) and DIPEA (0.81ml, 5eq.) in DMF (8ml) at 0 °C was added in portions HATU (0.407g, 1.07mmol). The mixture was stirred at room temperature for 16h, diluted with EtOAc, washed with water once, brine four times. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc/Hexane 0% to 40%) to afford **55e** (0.328g). MS(ESI); m/z 671.32, 673.32 (M+H).

Step **55F**

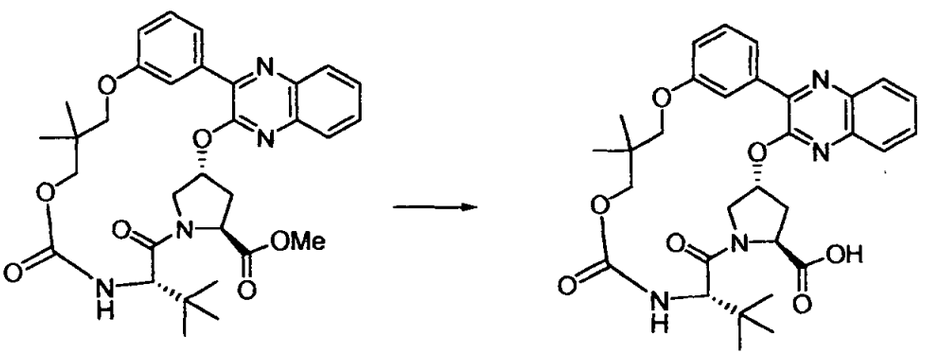


55e **55f-1** **55f**

000221

A mixture of compound **55e** (0.161g, 0.24mmol), cesium carbonate (0.156g, 0.48mmol) and toluene (10ml) was purged with nitrogen for 5min. Palladium acetate (11mg, 0.049mmol) and ligand **55f-1** (24mg, 0.06mmol) were added. The mixture was stirred at 80°C for 19h, cooled to rt, filtered, washed with EtOAc and concentrated. The residue was purified by silica gel chromatography (EtOAc/Hexane 0% to 25%) to afford **55f** (0.035g). MS(ESI); m/z 591.61(M+H).

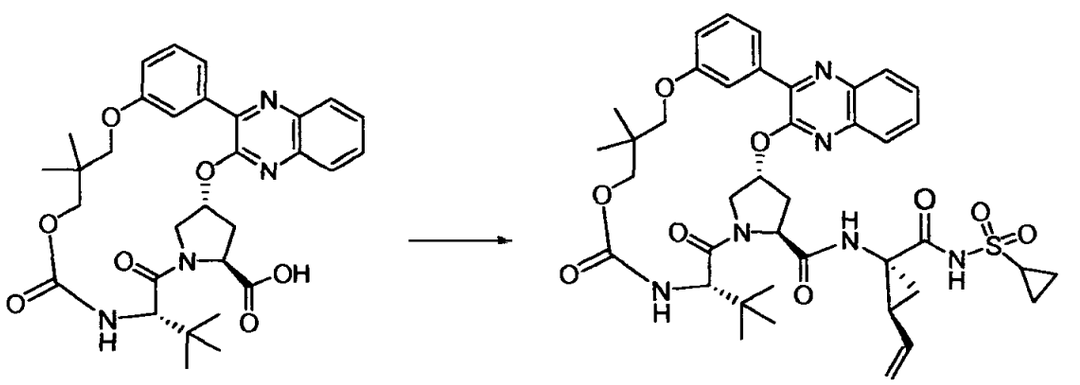
Step **55G**



55f **55g**

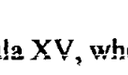
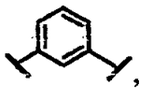
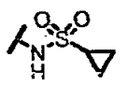
Compound **55g** was prepared from compound **55f** by the same procedure as described in Step3F of example 3. MS(ESI): m/z 577.55 (M+H).

Step **55H**

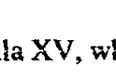
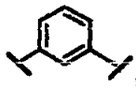
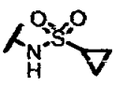


55g **example 55**

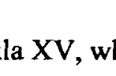
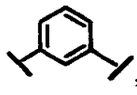
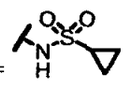
Compound of example 55 was prepared from **55g** by the same procedures as described in Example 3. MS (ESI): m/z 789.34 (M+H).

Example 56. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

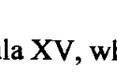
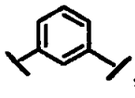
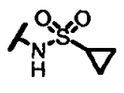
This compound was prepared from **55g** by the same procedures as described in Example 4. MS (ESI): m/z 790.92 (M+H).

Example 57. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

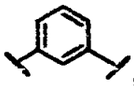
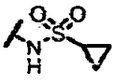
This compound was prepared from **55g** by the same procedures as described in Example 5. MS (ESI): m/z 813.74 (M+H).

Example 58. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

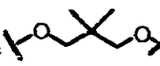
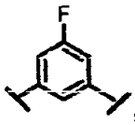
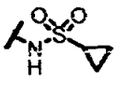
This compound was prepared by the same procedures as described in Example 55. MS (ESI): m/z 787.20 (M+H).

Example 59. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

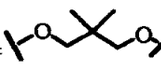
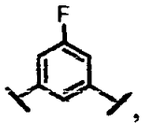
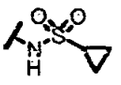
This compound was prepared by the same procedures as described in Example 56. MS (ESI): m/z 789.22 (M+H).

Example 60. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

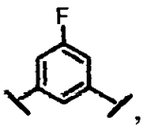
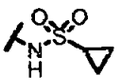
This compound was prepared by the same procedures as described in Example 57. MS (ESI): m/z 811.59 (M+H).

Example 61. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

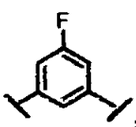
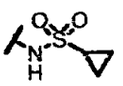
This compound was prepared by the same procedures as described in Example 55. MS (ESI): m/z 807.17 (M+H).

Example 62. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

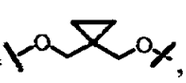
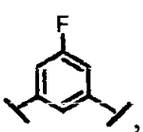
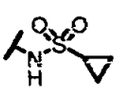
This compound was prepared by the same procedures as described in Example 56. MS (ESI): m/z 809.10 (M+H).

Example 63. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

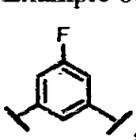
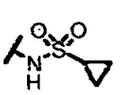
This compound was prepared by the same procedures as described in Example 57. MS (ESI): m/z 831.24 (M+H).

Example 64. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

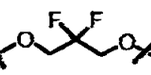
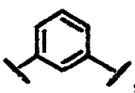
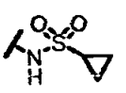
This compound was prepared by the same procedures as described in Example 55. MS (ESI): m/z 805.14 (M+H).

Example 65. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

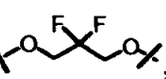
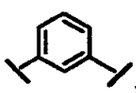
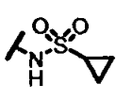
This compound was prepared by the same procedures as described in Example 56. MS (ESI): m/z 807.03 (M+H).

Example 66. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

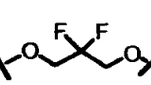
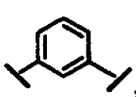
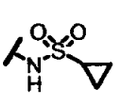
This compound was prepared by the same procedures as described in Example 57. MS (ESI): m/z 828.97 (M+H).

Example 67. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

This compound was prepared by the same procedures as described in Example 55. MS (ESI): m/z 797.11 (M+H).

Example 68. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=  , G = 

This compound was prepared by the same procedures as described in Example 56. MS (ESI): m/z 799.06 (M+H).

Example 69. Compound of Formula XV, wherein R =  , M-L =  , Ar=  , R'=CF_2H, G = 

This compound was prepared by the same procedures as described in Example 57. MS (ESI): m/z 821.54 (M+H).

Examples 70 to 1506, compounds of Formula XV in Table 1, are made following the procedures described in Examples 1 to 69 and the Synthetic Methods section.

Examples 1507 to 1554, compounds of Formula XVI in Table 2, are made following the procedures described in Examples 1 to 69 and the Synthetic Methods section.

Examples 1555 to 1586, compounds of Formula XVII in Table 3, are made following the procedures described in Examples 1 to 69 and the Synthetic Methods section.

The compounds of the present invention exhibit potent inhibitory properties against the HCV NS3 protease. The following examples describe assays in which the compounds of the present invention can be tested for anti-HCV effects.

Example 1587. NS3/NS4a Protease Enzyme Assay

HCV protease activity and inhibition is assayed using an internally quenched fluorogenic substrate. A DABCYL and an EDANS group are attached to opposite ends of a short peptide. Quenching of the EDANS fluorescence by the DABCYL group is relieved upon proteolytic cleavage. Fluorescence is measured with a Molecular Devices Fluoromax (or equivalent) using an excitation wavelength of 355 nm and an emission wavelength of 485 nm.

The assay is run in Corning white half-area 96-well plates (VWR 29444-312 [Corning 3693]) with full-length NS3 HCV protease 1b tethered with NS4A cofactor (final enzyme concentration 1 to 15 nM). The assay buffer is complemented with 10 μM NS4A cofactor Pep 4A (Anaspec 25336 or in-house, MW 1424.8). RET S1 (Ac-Asp-Glu-Asp(EDANS)-Glu-Glu-Abu-[COO]Ala-Ser-Lys-(DABCYL)-NH_2, AnaSpec 22991, MW 1548.6) is used as the fluorogenic peptide substrate. The assay buffer contains 50 mM Hepes at pH 7.5, 30 mM NaCl and 10 mM BME. The enzyme reaction is followed over a 30 minutes time course at room temperature in the absence and presence of inhibitors.

The peptide inhibitors HCV Inh 1 (Anaspec 25345, MW 796.8) Ac-Asp-Glu-Met-Glu-Glu-Cys-OH, [-20°C] and HCV Inh 2 (Anaspec 25346, MW 913.1) Ac-Asp-Glu-Dif-Cha-Cys-OH, are used as reference compounds.

IC50 values are calculated using XLFit in ActivityBase (IDBS) using equation 205: y=A+((B-A)/(1+(((C/x)^D))).

Example 1588 - Cell-Based Replicon Assay

Quantification of HCV replicon RNA (HCV Cell Based Assay) is accomplished using the Huh 11-7 cell line (Lohmann, et al Science 285:110-113, 1999). Cells are seeded at $4x10^3$ cells/well in 96 well plates and fed media containing DMEM (high glucose), 10% fetal calf serum, penicillin-streptomycin and non-essential amino acids. Cells are incubated in a 7.5% CO_2 incubator at 37 °C. At the end of the incubation period, total RNA is extracted and purified from cells using Ambion RNAqueous 96 Kit (Catalog No. AM1812). To amplify the HCV RNA so that sufficient material can be detected by an HCV specific probe (below), primers specific for HCV (below) mediate both the reverse transcription of the HCV RNA and the amplification of the cDNA by polymerase chain reaction (PCR) using the TaqMan One-Step RT-PCR Master Mix Kit (Applied Biosystems catalog no. 4309169). The nucleotide sequences of the RT-PCR primers, which are located in the NS5B region of the HCV genome, are the following:

HCV Forward primer "RBNS5bfor"

5'GCTGCGGCCTGTCGAGCT (SEQ ID NO: 1):

HCV Reverse primer "RBNS5Brev"

5'CAAGGTCGTCTCCGCATAC (SEQ ID NO 2).

Detection of the RT-PCR product is accomplished using the Applied Biosystems (ABI) Prism 7500 Sequence Detection System (SDS) that detects the fluorescence that is emitted when the probe, which is labeled with a fluorescence reporter dye and a quencher dye, is degraded during the PCR reaction. The increase in the amount of fluorescence is measured during each cycle of PCR and reflects the increasing amount of RT-PCR product. Specifically, quantification is based on the threshold cycle, where the amplification plot crosses a defined fluorescence threshold. Comparison of the threshold cycles of the sample with a known standard provides a highly sensitive measure of relative template concentration in different samples (ABI User Bulletin #2 December 11, 1997). The data is analyzed using the ABI SDS program version 1.7. The relative template concentration can be converted to

RNA copy numbers by employing a standard curve of HCV RNA standards with known copy number (ABI User Bulletin #2 December 11, 1997).

The RT-PCR product was detected using the following labeled probe:

5' FAM-CGAAGCTCCAGGACTGCACGATGCT-TAMRA (SEQ ID NO: 3)

FAM= Fluorescence reporter dye.

TAMRA:=Quencher dye.

The RT reaction is performed at 48 °C for 30 minutes followed by PCR. Thermal cycler parameters used for the PCR reaction on the ABI Prism 7500 Sequence Detection System are: one cycle at 95 °C, 10 minutes followed by 40 cycles each of which include one incubation at 95 °C for 15 seconds and a second incubation for 60 °C for 1 minute.

To normalize the data to an internal control molecule within the cellular RNA, RT-PCR is performed on the cellular messenger RNA glyceraldehyde-3-phosphate dehydrogenase (GAPDH). The GAPDH copy number is very stable in the cell lines used. GAPDH RT-PCR is performed on the same RNA sample from which the HCV copy number is determined. The GAPDH primers and probesare contained in the ABI Pre-Developed TaqMan Assay Kit (catalog no. 4310884E). The ratio of HCV/GAPDH RNA is used to calculate the activity of compounds evaluated for inhibition of HCV RNA replication.

<u>Activity of compounds as inhibitors of HCV replication (Cell based Assay) in replicon containing Huh-7 cell lines.</u>

The effect of a specific anti-viral compound on HCV replicon RNA levels in Huh-11-7 cells is determined by comparing the amount of HCV RNA normalized to GAPDH (e.g. the ratio of HCV/GAPDH) in the cells exposed to compound versus cells exposed to the DMSO vehicle (negative control). Specifically, cells are seeded at 4x 10^3 cells/well in a 96 well plate and are incubated either with: 1) media containing 1% DMSO (0% inhibition control), or 2) media/1%DMSO containing a fixed concentration of compound. 96 well

plates as described above are then incubated at 37 °C for 4 days (EC50 determination). Percent inhibition is defined as:

% Inhibition= 100-100*S/C1

where

S= the ratio of HCV RNA copy number/GAPDH RNA copy number in the sample;

C1= the ratio of HCV RNA copy number/GAPDH RNA copy number in the 0% inhibition control (media/1%DMSO).

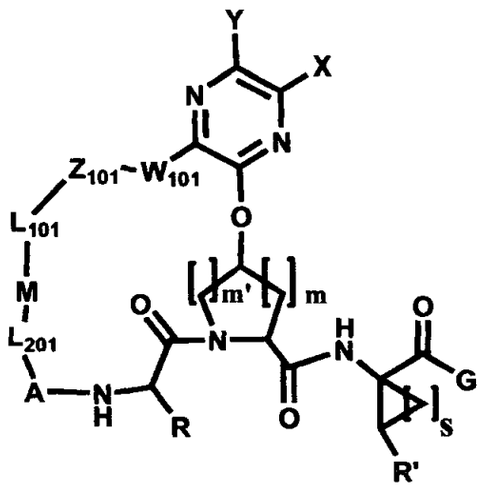
The dose-response curve of the inhibitor is generated by adding compound in serial, three-fold dilutions over three logs to wells starting with the highest concentration of a specific compound at 1.5 uM and ending with the lowest concentration of 0.23 nM. Further dilution series (500 nM to 0.08 nM for example) is performed if the EC50 value is not positioned well on the curve. EC50 is determined with the IDBS Activity Base program "XL Fit" using a 4-paramater, non-linear regression fit (model # 205 in version 4.2.1, build 16).

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

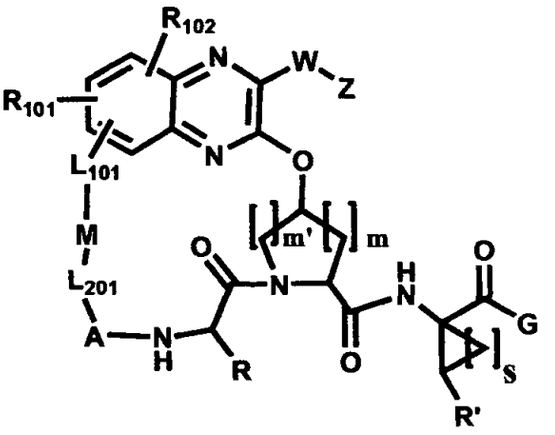
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WHAT IS CLAIMED:

1. A compound of Formula I or II:



(I)



(II)

wherein

A is absent or selected from –(C=O)–, –$S(O)_2$, -C=N-OR_1 or –C(=N-CN);

L_{201} is absent or selected from -C_1-C_8 alkylene, –C_2-C_8 alkenylene, or –C_2-C_8 alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted –C_1-C_8 alkylene, substituted –C_2-C_8 alkenylene, or substituted –C_2-C_8 alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; –C_3-C_{12} cycloalkylene, or substituted –C_3-C_{12} cycloalkylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; –C_3-C_{12} cycloalkenylene, or substituted –C_3-C_{12} cycloalkenylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N;

M is absent or selected from O, S, SO, SO_2 or NR_1; wherein R_1 is selected at each occurrence from the group consisting of:

(i) hydrogen;

(ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

(iii) heterocycloalkyl or substituted heterocycloalkyl;

(iv) $-C_1$-C_8 alkyl, $-C_2$-C_8 alkenyl, or $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1$-C_8 alkyl, substituted $-C_2$-C_8 alkenyl, or substituted $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3$-C_{12} cycloalkyl, or substituted $-C_3$-C_{12} cycloalkyl; $-C_3$-C_{12} cycloalkenyl, or substituted $-C_3$-C_{12} cycloalkenyl;

L_{101} is absent or selected from -C_1-C_8 alkylene, $-C_2$-C_8 alkenylene, or $-C_2$-C_8 alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1$-C_8 alkylene, substituted $-C_2$-C_8 alkenylene, or substituted $-C_2$-C_8 alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3$-C_{12} cycloalkylene, or substituted $-C_3$-C_{12} cycloalkylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3$-C_{12} cycloalkenylene, or substituted $-C_3$-C_{12} cycloalkenylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N;

Z_{101} is absent or selected from aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

W_{101} is absent or selected from $-O-$, $-S-$, $-NR_1$-, -C(O)- or -C(O)NR_1-;

X and Y taken together with the carbon atoms to which they are attached to form a carbocyclic moiety or a heterocyclic moiety selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, or substituted heterocylic;
or X and Y together form a C_2- C_8-alkylene group or a C_2-C_8-heteroalkylene group;

R_{101} and R_{102} are independently selected from the group consisting of:

(i) hydrogen, halogen, CN, CF_3, N_3, NO_2, OR_1, SR_1, SO_2R_2, $-NHS(O)_2-R_2$, $-NH(SO_2)NR_3R_4$, NR_3R_4, CO_2R_1, COR_1, $CONR_1R_2$, $N(R_1)COR_2$;

(ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

(iii) heterocycloalkyl or substituted heterocycloalkyl;

(iv) $-C_1$-C_8 alkyl, $-C_2$-C_8 alkenyl, or $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1$-C_8 alkyl, substituted $-C_2$-C_8 alkenyl, or substituted $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3$-C_{12} cycloalkyl, or substituted $-C_3$-C_{12} cycloalkyl; $-C_3$-C_{12} cycloalkenyl, or substituted $-C_3$-C_{12} cycloalkenyl;

R and R' are each independently selected from the group consisting of:

(i) $-C_1$-C_8 alkyl, $-C_2$-C_8 alkenyl, or $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1$-C_8 alkyl, substituted $-C_2$-C_8 alkenyl, or substituted $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3$-C_{12} cycloalkyl, or substituted $-C_3$-C_{12} cycloalkyl; $-C_4$-C_{12} alkylcycloalkyl, or substituted $-C_4$-C_{12} alkylcycloalkyl; $-C_3$-C_{12} cycloalkenyl, or substituted $-C_3$-C_{12} cycloalkenyl; $-C_4$-C_{12} alkylcycloalkenyl, or substituted $-C_4$-C_{12} alkylcycloalkenyl;

(ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

(iii) heterocycloalkyl or substituted heterocycloalkyl;

(iv) hydrogen; deuterium;

G is selected from $-OH$, $-NHS(O)_2-R_2$, $-NH(SO_2)NR_3R_4$, and NR_3R_4;

R_2 is selected from:

(i) aryl; substituted aryl; heteroaryl; substituted heteroaryl

(ii) heterocycloalkyl; substituted heterocycloalkyl;

(iii) $-C_1$-C_8 alkyl, $-C_2$-C_8 alkenyl, or $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N, substituted $-C_1$-C_8 alkyl, substituted

$-C_2$-C_8 alkenyl, or substituted $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3$-C_{12} cycloalkyl, or substituted $-C_3$-C_{12} cycloalkyl; $-C_3$-C_{12} cycloalkenyl, or substituted $-C_3$-C_{12} cycloalkenyl; heterocylic; substituted heterocyclic;

R_3 and R_4 are independently selected from:

(i) hydrogen;

(ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

(iii) heterocycloalkyl or substituted heterocycloalkyl;

(iv) $-C_1$-C_8 alkyl, $-C_2$-C_8 alkenyl, or $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1$-C_8 alkyl, substituted $-C_2$-C_8 alkenyl, or substituted $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3$-C_{12} cycloalkyl, or substituted $-C_3$-C_{12} cycloalkyl; $-C_3$-C_{12} cycloalkenyl, or substituted $-C_3$-C_{12} cycloalkenyl; heterocyclic, or substitututed heterocyclic;

alternatively, R_3 and R_4 are taken together with the nitrogen they are attached to form a heterocyclic or substituted heterocyclic;

Z is selected from the groups consisting of:

(i) hydrogen;

(ii) CN;

(iii) N_3;

(iv) halogen;

(v) $-NH-N=CHR_1$;

(vi) aryl, substituted aryl;

(vii) heteroaryl, substituted heteroaryl;

(viii) $-C_3$–C_{12} cycloalkyl, substituted $-C_3$–C_{12} cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl;

(ix) $-C_1-C_6$ alkyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

(x) $-C_2-C_6$ alkenyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

(xi) $-C_2-C_6$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

W is absent, or selected from alkylene, alkenylene, alkynylene, –O–, –S–, $-NR_1-$, $-C(O)NR_1-$, or -C(O)-;

m is 0, 1, 2 or 3;

m' is 0, 1, 2 or 3; and

s is 1, 2, 3 or 4.

2. A compound according to claim 1 wherein:

M is absent or selected from O or NR_1;

Z_{101} is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

W_{101} is absent, or selected from –O–, –S–, –NH-, -N(Me)-, -C(O)NH-, or -C(O)N(Me)-;

X and Y taken together with the carbon atoms to which they are attached to form a cyclic moiety which selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocylic;

R_{101} and R_{102} are independently selected from the group consisting of:

(i) hydrogen, halogen, CN, CF_3, NO_2, OR_1, SR_1, $-NHS(O)_2-R_2$, $-NH(SO_2)NR_3R_4$, NR_3R_4, CO_2R_1, COR_1, $CONR_1R_2$, $N(R_1)COR_2$;

(ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

(iii) heterocycloalkyl or substituted heterocycloalkyl;

(iv) $-C_1$-C_8 alkyl, $-C_2$-C_8 alkenyl, or $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1$-C_8 alkyl, substituted $-C_2$-C_8 alkenyl, or substituted $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3$-C_{12} cycloalkyl, or substituted $-C_3$-C_{12} cycloalkyl; $-C_3$-C_{12} cycloalkenyl, or substituted $-C_3$-C_{12} cycloalkenyl;

R_3 and R_4 are independently selected from:

(i) hydrogen;

(ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

(iii) heterocycloalkyl or substituted heterocycloalkyl;

(iv) $-C_1$-C_8 alkyl, $-C_2$-C_8 alkenyl, or $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1$-C_8 alkyl, substituted $-C_2$-C_8 alkenyl, or substituted $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3$-C_{12} cycloalkyl, or substituted $-C_3$-C_{12} cycloalkyl; $-C_3$-C_{12} cycloalkenyl, or substituted $-C_3$-C_{12} cycloalkenyl; heterocyclic, or substituted heterocyclic;

W is absent, or selected from alkylene, alkenylene, alkynylene, –O–, –S–, –NH-, -N(Me)-, -C(O)NH-, or -C(O)N(Me)-;

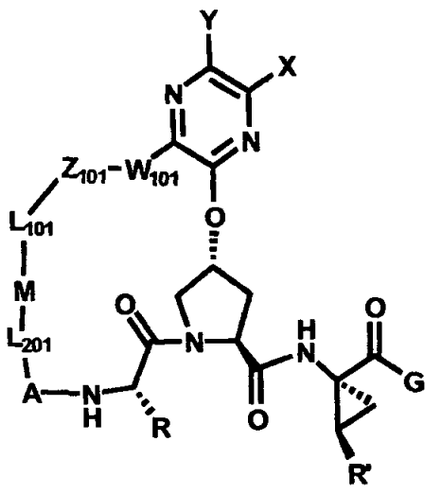
m = 0, 1, or 2;

m' = 1 or 2; and

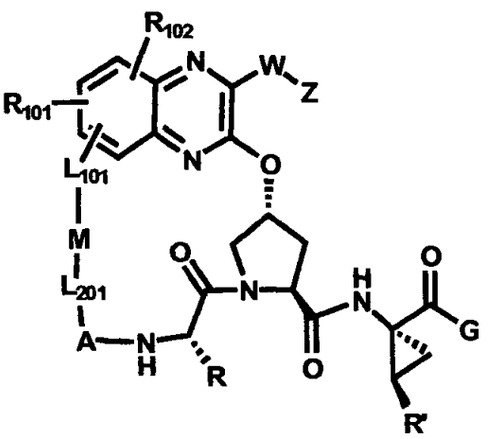
s is 1.

3. The compound of claim 1, wherein R' is $-CHQ_1Q_2$, wherein Q_1 and Q_2 are independently selected from F, Cl and Br.

4. The compound of claim 1, wherein the compound is of Formula III or IV:



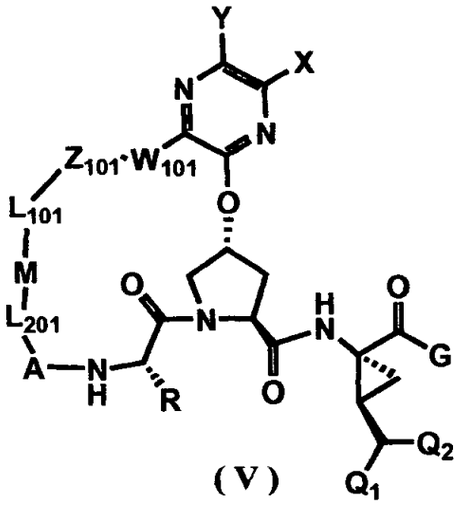
(III)



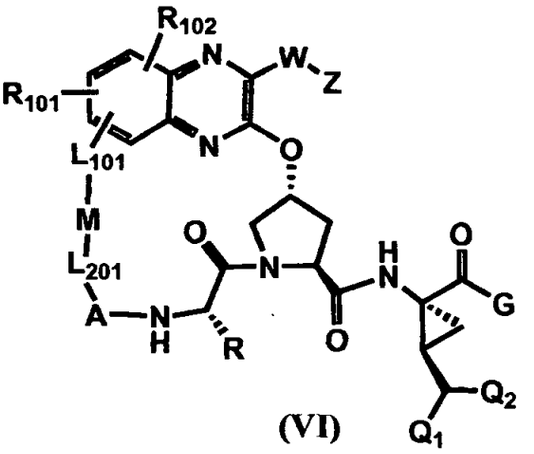
(IV)

or a pharmaceutically acceptable salt, ester or prodrug thereof, where R, R', A, L_{201}, M, L_{101}, Z_{101}, W_{101}, X, Y, R_{101}, R_{102}, W, Z and G are as previously defined in claim 1.

5. The compound of claim 1, wherein the compound is of Formula V or VI:



(V)

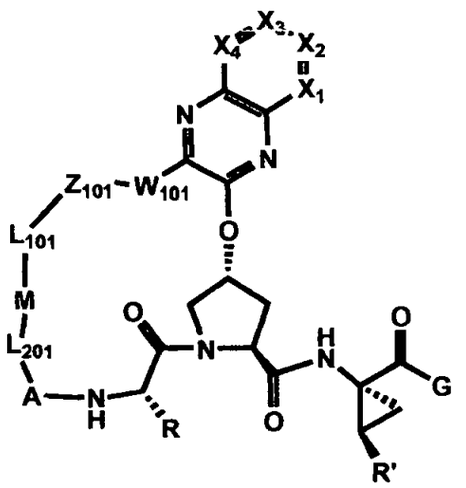


(VI)

or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein Q_1 and Q_2 are each independently selected from F, Cl and Br, and R, A, L_{201}, M, L_{101}, Z_{101}, W_{101}, X, Y, R_{101}, R_{102}, W, Z and G are as previously defined in claim 1.

a.

6. The compound of claim 1, wherein the compound is of Formula VII:



(VII)

or a pharmaceutically acceptable salt, ester or prodrug thereof, where X_1-X_4 are independently selected from -CR_5 and N, wherein:

R_5 is independently selected from:

i. hydrogen; halogen; -NO_2; -CN; N_3; CF_3;

ii. –M-R_4, M is O, S, NH;

iii. NR_3R_4;

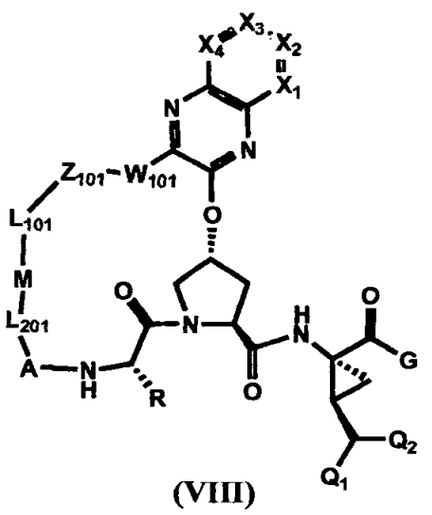
iv. –C_1-C_8 alkyl, –C_2-C_8 alkenyl, or –C_2-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted –C_1-C_8 alkyl, substituted –C_2-C_8 alkenyl, or substituted –C_2-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; –C_3-C_{12} cycloalkyl, or substituted –C_3-C_{12} cycloalkyl; –C_3-C_{12} cycloalkenyl, or substituted –C_3-C_{12} cycloalkenyl;

v. aryl; substituted aryl; heteroaryl; substituted heteroaryl;

vi. heterocycloalkyl or substituted heterocycloalkyl; and

R_3, R_4, R, R', A, L_{201}, M, L_{101}, Z_{101}, W_{101} and G are as previously defined in claim 1.

7. The compound of claim 1, wherein the compound is of Formula VIII:



(VIII)

or a pharmaceutically acceptable salt, ester or prodrug thereof, where X_1-X_4 are independently selected from -CR_5 and N, wherein:

R_5 is independently selected from:

i. hydrogen; halogen; -NO_2; -CN; N_3; CF_3;

ii. –M-R_4, M is O, S, NH;

iii. NR_3R_4;

iv. –C_1-C_8 alkyl, –C_2-C_8 alkenyl, or –C_2-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted –C_1-C_8 alkyl, substituted –C_2-C_8 alkenyl, or substituted –C_2-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; –C_3-C_{12} cycloalkyl, or substituted –C_3-C_{12} cycloalkyl; –C_3-C_{12} cycloalkenyl, or substituted –C_3-C_{12} cycloalkenyl;

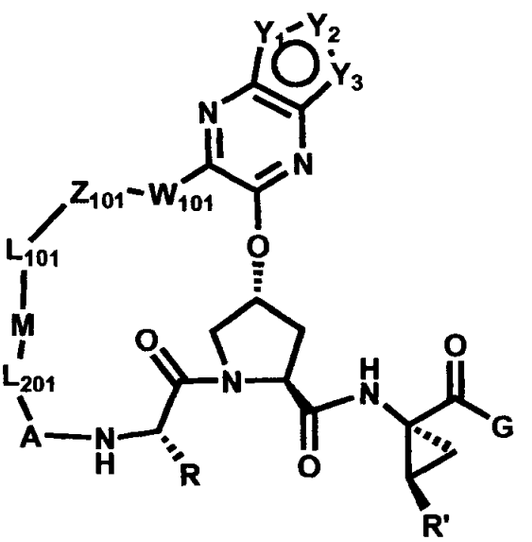
v. aryl; substituted aryl; heteroaryl; substituted heteroaryl;

vi. heterocycloalkyl or substituted heterocycloalkyl;

Q_1 and Q_2 are each independently selected from F, Cl and Br; and

R_3, R_4, R, A, L_{201}, M, L_{101}, Z_{101}, W_{101} and G are as previously defined in claim 1.

8. The compound of claim 1, wherein the compound is of Formula IX:



(IX)

or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

Y_1-Y_3 are independently selected from CR_5, N, NR_5, S and O;

R_5 is independently selected from:

i. hydrogen; halogen; -NO_2; -CN; N_3; CF_3;

ii. –M-R_4, M is O, S, NH;

iii. NR_3R_4;

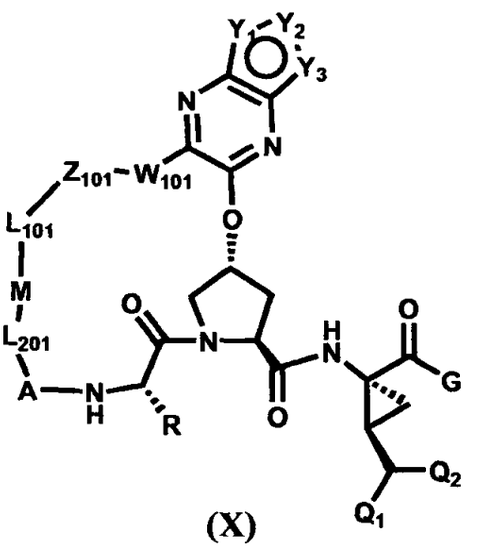
iv. –C_1-C_8 alkyl, –C_2-C_8 alkenyl, or –C_2-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted –C_1-C_8 alkyl, substituted –C_2-C_8 alkenyl, or substituted –C_2-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; –C_3-C_{12} cycloalkyl, or substituted –C_3-C_{12} cycloalkyl; –C_3-C_{12} cycloalkenyl, or substituted –C_3-C_{12} cycloalkenyl;

v. aryl; substituted aryl; heteroaryl; substituted heteroaryl;

vi. heterocycloalkyl or substituted heterocycloalkyl; and

R_3, R_4, R, R', A, L_{201}, M, L_{101}, Z_{101}, W_{101} and G are as previously defined in claim 1.

9. The compound of claim 1, wherein the compound is of Formula X:



(X)

or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

Y_1, Y_2 and Y_3 are independently selected from CR_5, N, NR_5, S and O;

R_5 is independently selected from:

i. hydrogen; halogen; -NO_2; -CN; N_3; CF_3;

ii. –M-R_4, M is O, S, NH;

iii. NR_3R_4;

iv. $-C_1$-C_8 alkyl, $-C_2$-C_8 alkenyl, or $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1$-C_8 alkyl, substituted $-C_2$-C_8 alkenyl, or substituted $-C_2$-C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3$-C_{12} cycloalkyl, or substituted $-C_3$-C_{12} cycloalkyl; $-C_3$-C_{12} cycloalkenyl, or substituted $-C_3$-C_{12} cycloalkenyl;

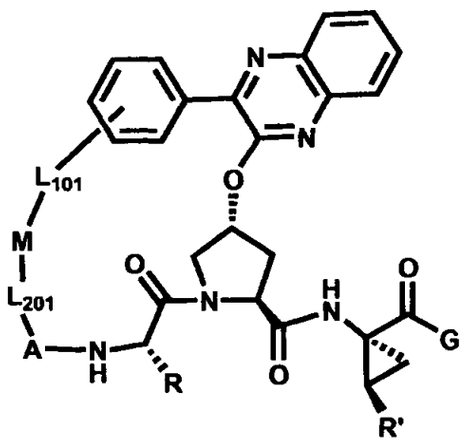
v. aryl; substituted aryl; heteroaryl; substituted heteroaryl;

vi. heterocycloalkyl or substituted heterocycloalkyl;

Q_1 and Q_2 are each independently fluorine, chlorine or bromine; and

R_3, R_4, R, A, L_{201}, M, L_{101}, Z_{101}, W_{101} and G are as previously defined in claim 1.

10. The compound of claim 1, wherein the compound is of Formula XI:

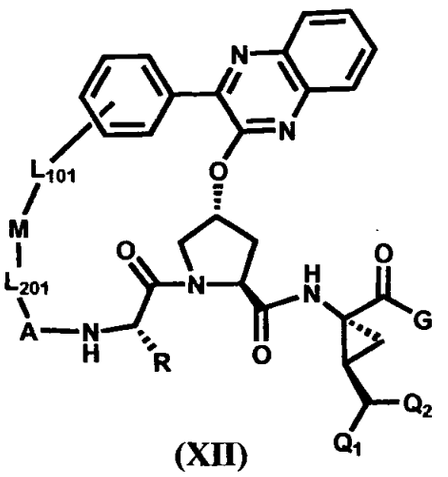


(XI)

or a pharmaceutically acceptable salt, ester or prodrug thereof,where R, R', A, L_{201}, M, L_{101} and G are as previously defined in claim 1.

11. The compound of claim 1, wherein the compound is of Formula XII:

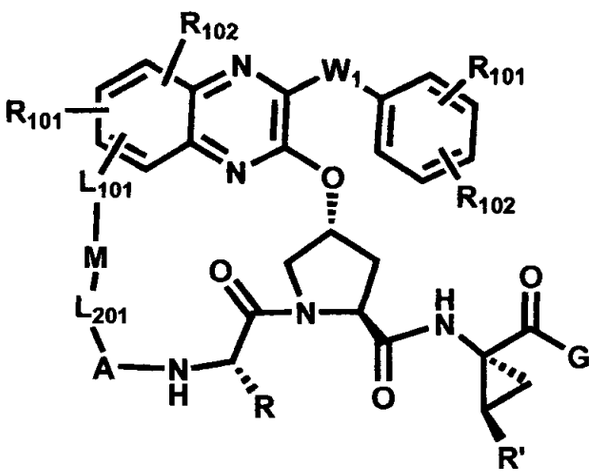
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(XII)

or a pharmaceutically acceptable salt, ester or prodrug thereof,where Q_1 and Q_2 are independently fluorine, chlorine or bromine and R, A, L_{201}, M, L_{101} and G are as previously defined in claim 1.

12. The compound of claim 1, wherein the compound is of Formula XIII:



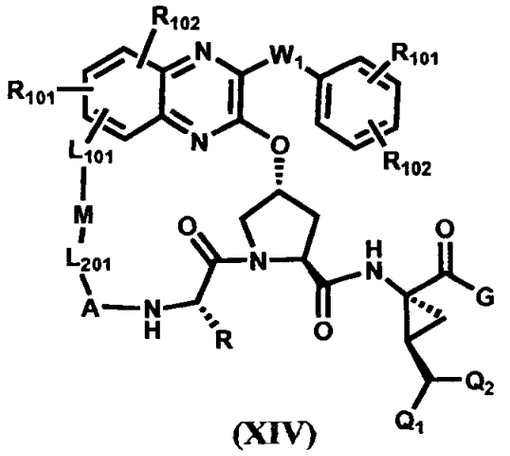
(XIII)

or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein

W_1 is absent or selected from C_1-C_4 alkylene, C_2-C_4 alkenylene, and C_2-C_4 alkynylene; and

R, R', A, L_{201}, M, L_{101} , R_{101}, R_{102} and G are as previously defined in claim 1.

13. The compound of claim 1, wherein the compound is of Formula XIV:



(XIV)

or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein

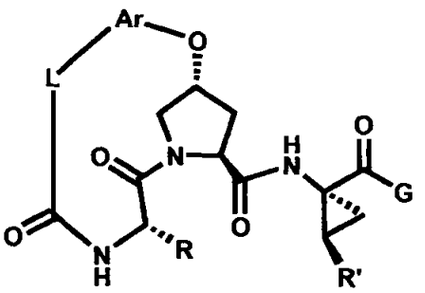
W_1 is absent or selected from C_1-C_4 alkylene, C_2-C_4 alkenylene, and C_2-C_4 alkynylene;

Q_1 and Q_2 are independently fluorine, chlorine or bromine; and

R, A, L_{201}, M, L_{101}, R_{101}, R_{102} and G are as previously defined in claim 1.

14. A compound according to claim 1 as set forth in Table 1 herein.

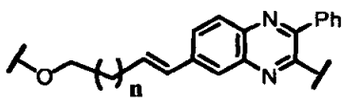
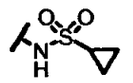
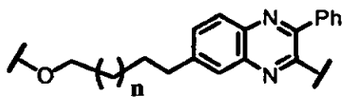
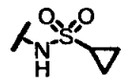
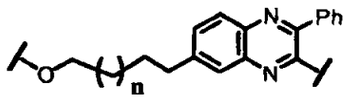
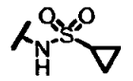
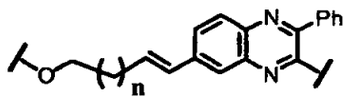
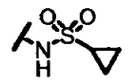
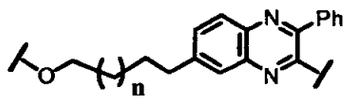
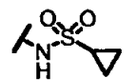
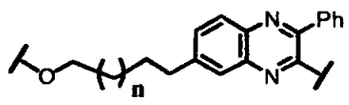
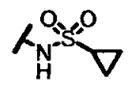
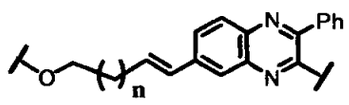
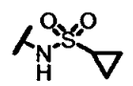
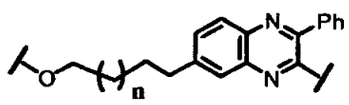
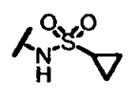
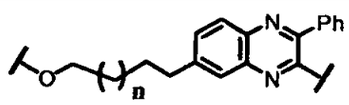
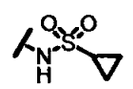
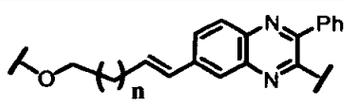
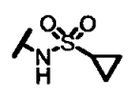
15. A compound according to claim 1 which is selected from compounds of Formula XVI wherein R, L-Ar, R' and G are delineated for each example in Table 2:



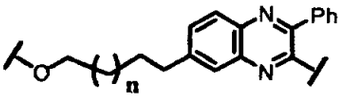
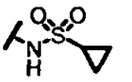
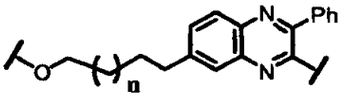
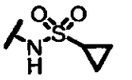
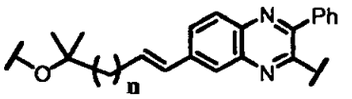
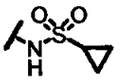
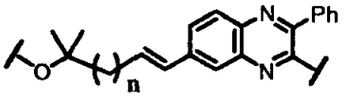
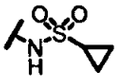
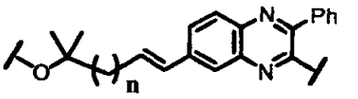
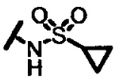
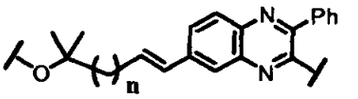
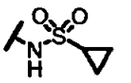
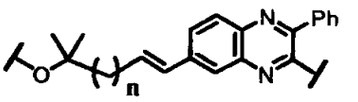
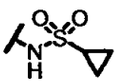
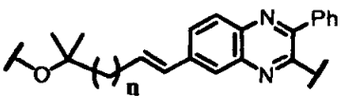
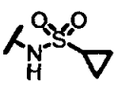
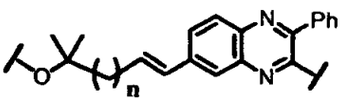
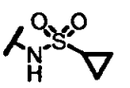
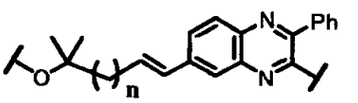
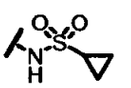
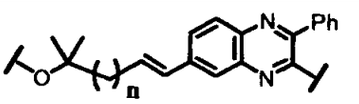
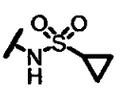
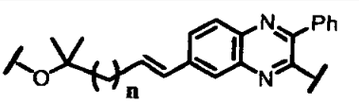
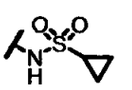
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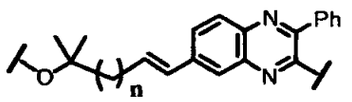
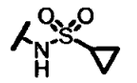
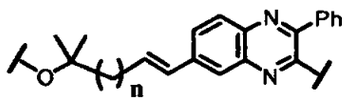
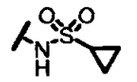
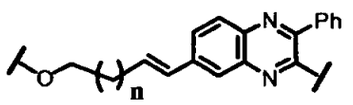
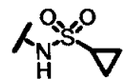
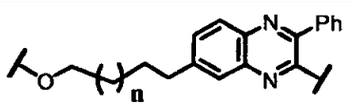
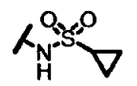
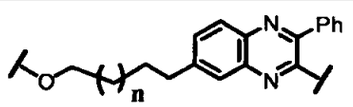
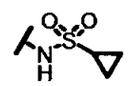
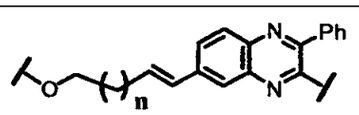
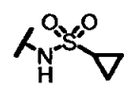
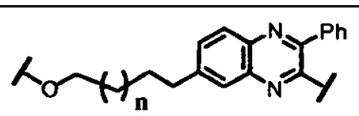
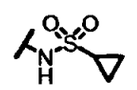
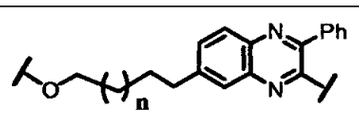
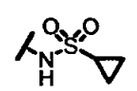
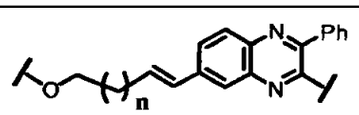
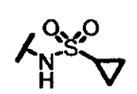
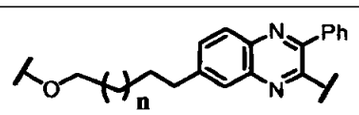
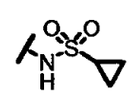
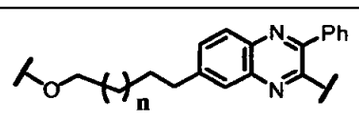
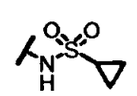
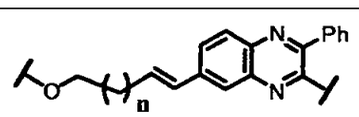
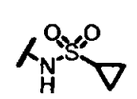
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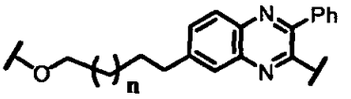
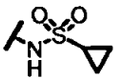
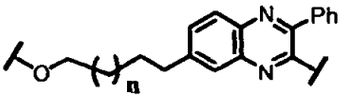
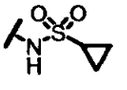
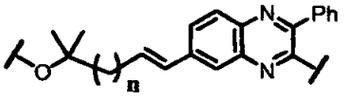
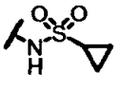
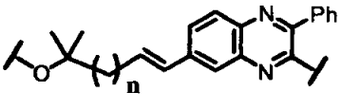
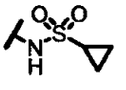
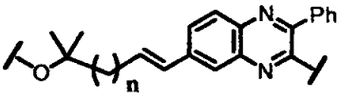
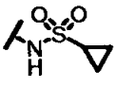
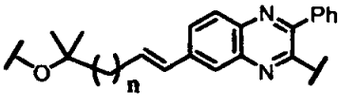
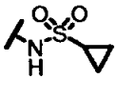
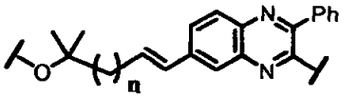
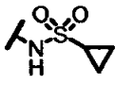
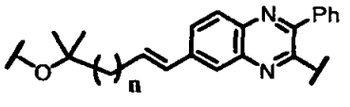
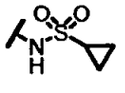
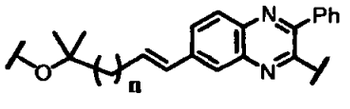
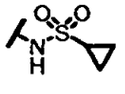
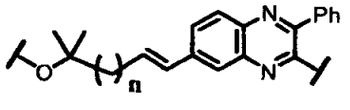
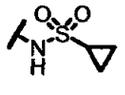
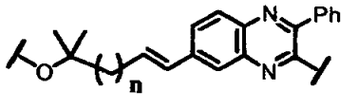
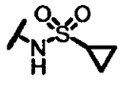
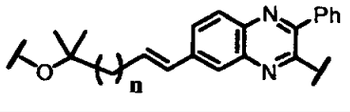
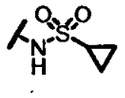
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1507.			4		
1508.			4		
1509.			4		
1510.			3		
1511.			3		
1512.			3		
1513.			2		
1514.			2		
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1516.			1		

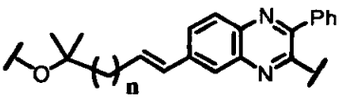
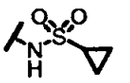
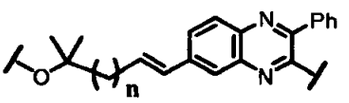
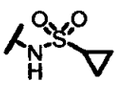
000245

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1518.			1		
1519.			4		
1520.			4		
1521.			4		
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1528.			1		

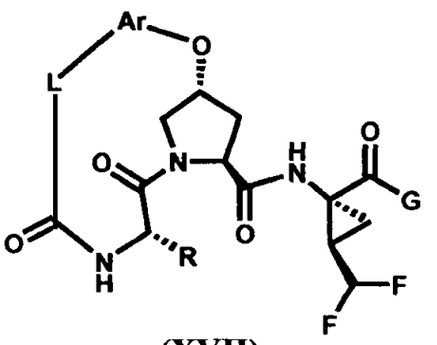
000246

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1536.			3		
1537.			2		
1538.			2		
1539.			2		
1540.			1		

1541.			1		
1542.			1		
1543.			4		
1544.			4		
1545.			4		
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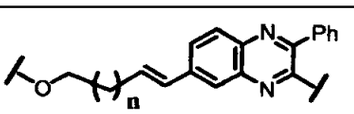
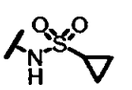
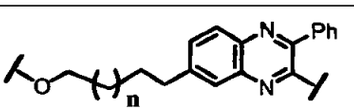
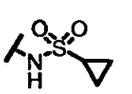
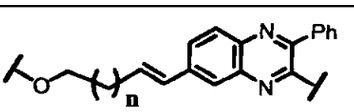
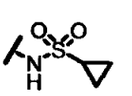
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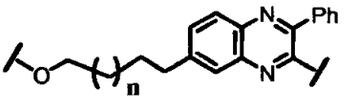
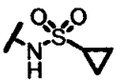
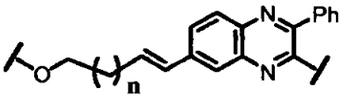
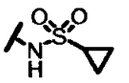
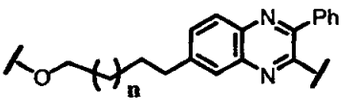
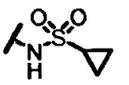
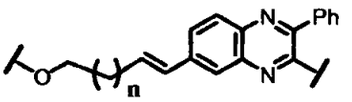
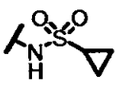
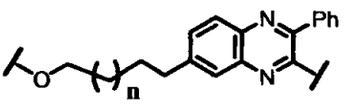
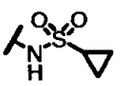
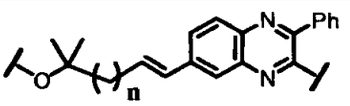
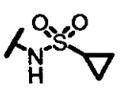
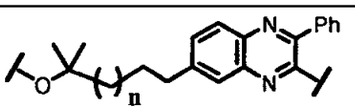
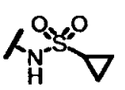
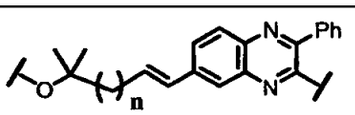
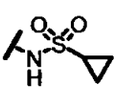
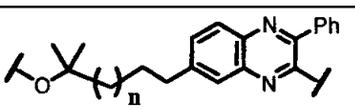
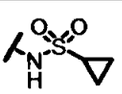
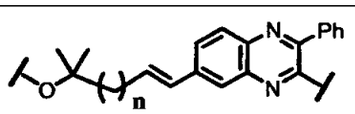
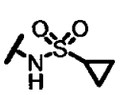
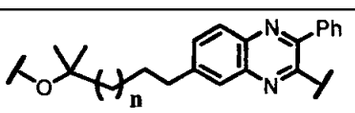
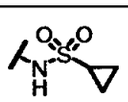
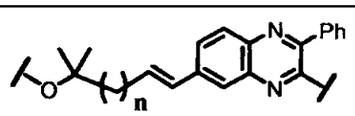
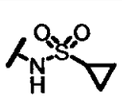
16. A compound according to claim 1 which is selected from compounds of Formula XVII wherein R, L-Ar, and G are delineated for each example in Table 3:

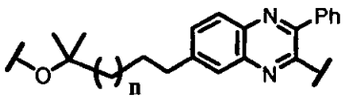
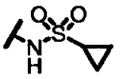
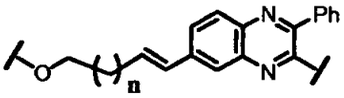
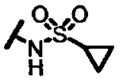
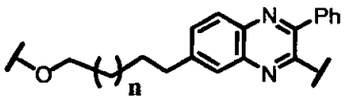
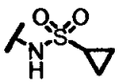
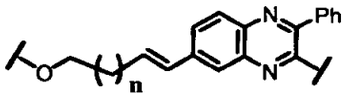
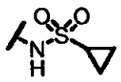
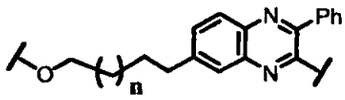
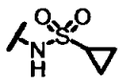
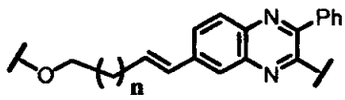
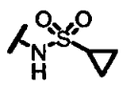
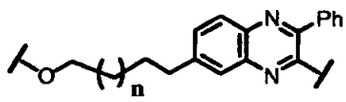
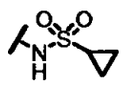
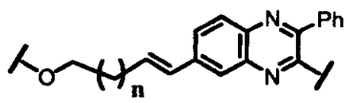
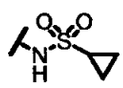
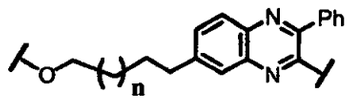
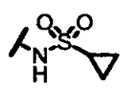
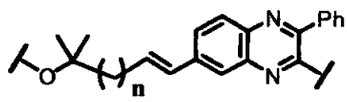
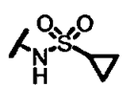
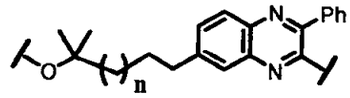
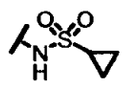
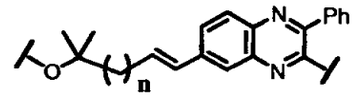
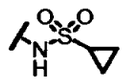
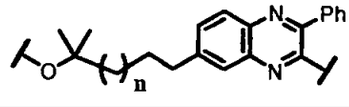
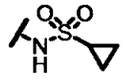


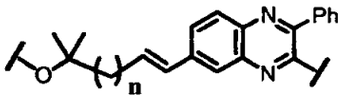
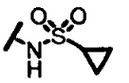
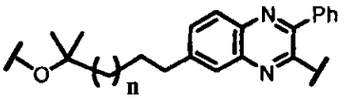
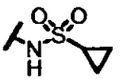
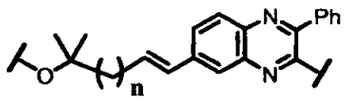
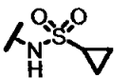
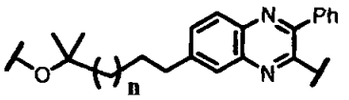
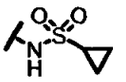
(XVII)

TABLE 3

Example#	R	L-Ar	n	G
1555.			4	
1556.			4	
1557.			3	

1558.			3	
1559.			2	
1560.			2	
1561.			1	
1562.			1	
1563.			4	
1564.			4	
1565.			3	
1566.			3	
1567.			2	
1568.			2	
1569.			1	

1570.			1	
1571.			4	
1572.			4	
1573.			3	
1574.			3	
1575.			2	
1576.			2	
1577.			1	
1578.			1	
1579.			4	
1580.			4	
1581.			3	
1582.			3	

1583.			2	
1584.			2	
1585.			1	
1586.			1	

17. A pharmaceutical composition comprising an inhibitory amount of a compound according to claim 1 or a pharmaceutically acceptable salt, ester, or prodrug thereof, in combination with a pharmaceutically acceptable carrier or excipient.

18. A method of treating a viral infection in a subject, comprising administering to the subject an inhibitory amount of a pharmaceutical composition according to claim 17.

19. The method according to claim 18, wherein the viral infection is hepatitis C virus.

20. A method of inhibiting the replication of hepatitis C virus, the method comprising supplying a hepatitis C viral NS3 protease inhibitory amount of the pharmaceutical composition of claim 17.

21. The method of claim 18 further comprising administering concurrently an additional anti-hepatitis C virus agent.

22. The method of claim 19, wherein said additional anti-hepatitis C virus agent is selected from the group consisting of □-interferon, □-interferon, ribavarin, and adamantine.

23. The method of claim 20, wherein said additional anti-hepatitis C virus agent is an inhibitor of hepatitis C virus helicase, polymerase, metalloprotease, or IRES.

24. The pharmaceutical composition of claim 17, further comprising another anti-HCV agent.

25. The pharmaceutical composition of claim 17, further comprising an agent selected from interferon, ribavirin, amantadine, another HCV protease inhibitor, an HCV polymerase inhibitor, an HCV helicase inhibitor, or an internal ribosome entry site inhibitor.

26. The pharmaceutical composition of claim 17, further comprising pegylated interferon.

27. The pharmaceutical composition of claim 17, further comprising another anti-viral, anti-bacterial, anti-fungal or anti-cancer agent, or an immune modulator.

28. The composition of claim 17, further comprising a cytochrome P450 monooxygenase inhibitor or a pharmaceutically acceptable salt thereof.

29. The composition of claim 28, wherein the cytochrome P450 monoxygenase inhibitor is ritonavir.

30. A method of co-adminstering to a patient in need of anti-hepatitis C viral treatment comprising a cytochrome P450 monooxygenase inhibitor or a pharmaceutically acceptable salt thereof and a compound as set forth in claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

000253

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/60; A61K 31/495 (2009.01)
USPC - 514/234.8, 248-249
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/234.8, 248-249

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/228.2, 252.1, 255.05-255.06, 311; 528/332; 540/552; 544/353 (text search - see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB) and Google Web/Patent/Scholar
Search terms: quinoxaline, benzopyrazine, hepatitis, HCV, ritonavir, cytochrome, p450, pegylated, interferon, macrocycle, tethered

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/0106559 A1 (Wang et al.) 3 June 2004 (03.06.2004) para [0004], [0009]-[0018], [0020]-[0022], [0025]-[0026], [0042], [0193]	1-30
Y	US 2007/0060510 A1 (Nakajima et al.) 15 March 2007 (15.03.2007) para [0011]-[0012]	1-30
Y	US 2007/0054842 A1 (Blatt et al.) 8 March 2007 (08.03.2007) para [0616]	28-30

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 January 2009 (28.01.2009)	03 MAR 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

000254

COMPUESTOS QUE CONTIENEN QUINOXALINA COMO INHIBIDORES DEL VIRUS DE LA HEPATITIS C

SOLICITUDES RELACIONADAS

Esta solicitud invoca el beneficio de la solicitud provisional de los EE.UU. número 60/987.958 presentada el 14 de Noviembre del 2007 y la solicitud provisional de los EE.UU. número 61/025.458 presentada el 1° de Febrero del 2008. Los contenidos de las solicitudes anteriores se incorporan a la presente a modo de referencia.

CAMPO TÉCNICO

La presente invención se relaciona con nuevos compuestos inhibidores de proteasa del virus de la hepatitis C (VHC) que tienen actividad antiviral contra VHC y que son útiles en el tratamiento de infecciones por VHC. Más particularmente, la invención se relaciona con compuestos que contienen quinoxalina, composiciones que contienen dichos compuestos y métodos para usar los mismos, y también procesos para obtener dichos compuestos.

ANTECEDENTES DE LA INVENCIÓN

El VHC es la principal causa de hepatitis no A, no B y es un grave y creciente problema de la salud pública, tanto en el mundo desarrollado como en el mundo en desarrollo. Se estima que el virus infecta a más de 200 millones de personas en todo el mundo, lo que sobrepasa el número de individuos que están infectados con el virus de inmunodeficiencia humana (VIH) en aproximadamente cinco veces. Los pacientes infectados con VHC, debido al alto porcentaje de individuos afectados por infecciones crónicas, tienen un elevado riesgo de desarrollar cirrosis hepática, carcinoma hepatocelular subsiguiente y enfermedad terminal del hígado. El VHC es la causa de

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mayor prevalencia de cáncer hepatocelular y de pacientes que requieren transplante de hígado en el mundo occidental.

Hay obstáculos considerables para el desarrollo de terapéuticas anti-VHC, entre las que se incluye, pero sin carácter taxativo, la persistencia del virus, la diversidad genética del virus durante la replicación en el huésped, la alta tasa de incidencia de mutantes del virus que desarrollan resistencia a las drogas, y la carencia de sistemas de cultivo infecciosos reproducibles y de modelos animales pequeños para la replicación y patogénesis del VHC. En la mayoría de los casos, dado el curso moderado de la infección y la compleja biología del hígado, se debe tener un gran cuidado con las drogas antivirales, las cuales pueden tener significativos efectos colaterales.

Actualmente hay sólo dos terapias aprobadas disponibles para la infección por VHC. El régimen de tratamiento original por lo general involucra un tratamiento de entre 3 y 12 meses con interferón alfa (IFN-α) intravenoso, mientras que un nuevo tratamiento de segunda generación aprobado involucra un co-tratamiento con IFN-α y con el análogo de nucleósido antiviral general ribavirina. Ambos tratamientos sufren de efectos colaterales relacionados con el interferón así como de baja eficacia contra las infecciones por VHC. Existe una necesidad de desarrollar agentes antivirales eficaces para el tratamiento de la infección por VHC debido a la poca tolerancia y a la decepcionante eficacia de las terapias existentes.

En una población de pacientes en donde la mayoría de los individuos están infectados en forma crónica y asintomática, y en donde no se conocen los pronósticos, una droga eficaz preferentemente debería poseer una cantidad de efectos colaterales significativamente menor que los tratamientos que se encuentran disponibles actualmente. La proteína no estructural-3 de hepatitis C (NS3) es una enzima

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proteolítica que se requiere para el procesamiento de la poliproteína viral y en consecuencia para la replicación viral. A pesar del inmenso número de variantes virales asociadas con la infección por VHC, el sitio activo de la proteasa NS3 permanece altamente conservado, lo que hace de su inhibición un modo de intervención atractivo. Estudios recientes en el tratamiento de VIH con inhibidores de proteasa apoyan el concepto de que la inhibición de NS3 es un blanco fundamental en la batalla contra el VHC.

El VHC es un virus a ARN de tipo *flaviridae*. El genoma del VHC se encuentra envuelto y contiene una molécula de ARN de cadena simple compuesta por alrededor de 9600 pares de bases. La misma codifica para un polipéptido que comprende aproximadamente 3010 aminoácidos.

La poliproteína de VHC se procesa mediante peptidasa viral y del huésped en 10 péptidos discretos que sirven para una variedad de funciones. Hay tres proteínas estructurales, C, E1 y E2. La proteína P7 es de función desconocida y comprende una secuencia altamente variable. Hay seis proteínas no estructurales. NS2 es una metaloproteinasa dependiente de zinc que funciona en conjunto con una porción de la proteína NS3. La NS3 incorpora dos funciones catalíticas (aparte de su asociación con NS2): una serina proteasa en su extremo N-terminal, que requiere de NS4A como cofactor, y una función helicasa dependiente de ATP-asa en el extremo carboxilo. NS4A es un factor fuertemente asociado, pero no en forma covalente, a la serina proteasa.

La proteasa NS3-NS4A es responsable de clivar cuatro sitios de la poliproteína viral. El clivado de NS3-NS4A es autocatalítico, y ocurre en cis. Las otras tres hidrólisis, las de NS4A-NS4B, NS4B-NS5A y NS5A-NS5B ocurren todas en trans. NS3 es una serina proteasa que se clasifica estructuralmente como una proteasa similar a

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quimiotripsina. Mientras que la serina proteasa NS posee actividad catalítica por si misma, la enzima proteasa de VHC no es una enzima eficiente en términos de la catálisis del clivado de poliproteína. Se ha demostrado que se requiere una región hidrofóbica central de la proteína NS4A para su potenciación. La formación del complejo de la proteína NS3 con NS4A parece necesaria para los eventos de procesamiento, lo que potencia la eficacia proteolítica en todos los sitios.

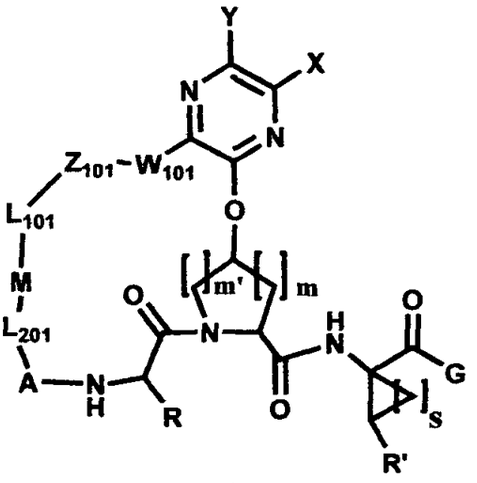
Una estrategia general para el desarrollo de agentes antivirales es inactivar las enzimas codificadas por el virus, incluyendo la NS3, que son esenciales para la replicación del virus. Los esfuerzos actuales dirigidos hacia el descubrimiento de inhibidores de la proteasa NS3 han sido comentados por S. Tan, A. Pause, Y. Shi, N. Sonenberg, Hepatitis C Therapeutics: Current Status and Emerging Strategies (Terapéuticas para hepatitis C: Estado actual y estrategias emergentes, *Nature Rev. Drug Discov.* 1, 867-881 (2002).

SÍNTESIS DE LA INVENCIÓN

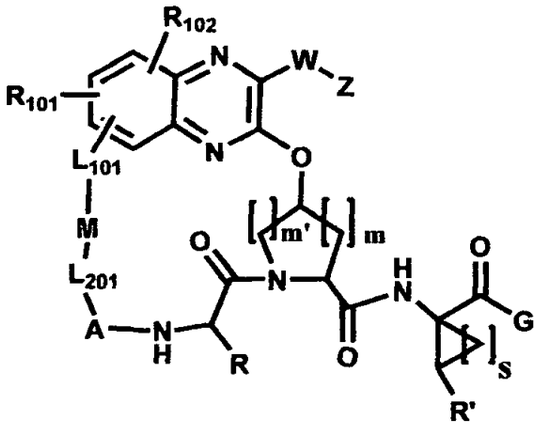
La presente invención se relaciona con compuestos que contienen quinoxalina y sales, ésteres o prodrogas de los mismos, aceptables para uso farmacéutico y métodos para usarlos para el tratamiento de infecciones de hepatitis C en un sujeto que necesita dicha terapia. Los compuestos de la presente invención interfieren con el ciclo de vida del virus de la hepatitis C y también son útiles como agentes antivirales. La presente invención se relaciona además con composiciones farmacéuticas que comprenden los compuestos mencionados anteriormente y sus sales, ésteres o prodrogas, para administrar a un sujeto que sufre de infección por VHC. La presente invención presenta además composiciones farmacéuticas que comprenden un compuesto de la presente invención (o una sal, éster o prodroga del mismo, aceptable para uso farmacéutico) y otro agente anti-VHC, tal como interferón (por ejemplo alfa-

interferón, beta-interferón, interferón consenso, interferón tratado con PEG, o interferón conjugado con albúmina u otro conjugado), ribavirina, amantadina, otro inhibidor de proteasa del VHC, o un inhibidor de la polimerasa del VHC, de la helicasa o del sitio interno de entrada al ribosoma. La invención también se relaciona con métodos para tratar una infección por VHC al sujeto por medio de la administración de una composición de la presente invención. La presente invención también se relaciona con composiciones farmacéuticas que comprenden los compuestos de la presente invención, o sus sales, ésteres o prodrogas, aceptables para uso farmacéutico, en combinación con un vehículo o excipiente aceptable para uso farmacéutico.

En una realización de la presente invención se revelan compuestos representados por las Fórmulas I o II, o sus sales aceptables para uso farmacéutico, ésteres, o prodrogas del mismo:



(I)



(II)

En donde

A está ausente o se selecciona entre $-(C=O)-$, $-S(O)_2$, $-C=N-OR_1$ o $-C(=N-CN)$;

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L_{201} está ausente o se selecciona entre -C_1-C_8 alquileno, –C_2-C_8 alquenileno, o –C_2-C_8 alquinileno cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C_1-C_8 alquileno sustituido, –C_2-C_8 alquenileno sustituido, o –C_2-C_8 alquinileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquileno, o–C_3-C_{12} cicloalquileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquenileno, o–C_3-C_{12} cicloalquenileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N;

M está ausente o se selecciona entre O, S, SO, SO_2 o NR_1; en donde R_1 se selecciona en cada oportunidad entre el grupo formado por:

(i) hidrógeno;

(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(iii) heterocicloalquilo o heterocicloalquilo sustituido;

(iv) –C_1-C_8 alquilo, –C_2-C_8 alquenilo, o –C_2-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C_1-C_8 alquilo sustituido, –C_2-C_8 alquenilo sustituido, o –C_2-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquilo, o–C_3-C_{12} cicloalquilo sustituido; –C_3-C_{12} cicloalquenilo, o–C_3-C_{12} cicloalquenilo sustituido;

L_{101} está ausente o se selecciona entre -C_1-C_8 alquileno, –C_2-C_8 alquenileno, o –C_2-C_8 alquinileno cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C_1-C_8 alquileno sustituido, –C_2-C_8 alquenileno sustituido, o –C_2-C_8 alquinileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquileno, o–C_3-C_{12} cicloalquileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12}

cicloalquenileno, o–C_3-C_{12} cicloalquenileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N;

Z_{101} está ausente o se selecciona entre arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

W_{101} está ausente o se selecciona entre –O–, –S–, –NR_1-, -C(O)- o -C(O)NR_1-;

X y Y se toman juntos con el átomo de carbono al cual se encuentran unidos para formar una porción carbocíclico o una porción heterocíclico. La porción carbocíclico o heterocíclico se puede seleccionar entre arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, heterocíclico, o heterocíclico sustituido; o X y Y juntos pueden formar un grupo C_2- C_8-alquileno o un grupo C_2-C_8-heteroalquileno.

R_{101} y R_{102}se seleccionan en forma independiente entre el grupo formado por:

(i) hidrógeno, halógeno, CN, CF_3, N_3, NO_2, OR_1, SR_1, SO_2R_2, –NHS(O)$_2$–R_2, -NH(SO_2)NR_3R_4, NR_3R_4, CO_2R_1, COR_1, $CONR_1R_2$, N(R_1)COR_2;

(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(iii) heterocicloalquilo o heterocicloalquilo sustituido;

(iv) –C_1-C_8 alquilo, –C_2-C_8 alquenilo, o –C_2-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C_1-C_8 alquilo sustituido, –C_2-C_8 alquenilo sustituido, o –C_2-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquilo, o–C_3-C_{12} cicloalquilo sustituido; –C_3-C_{12} cicloalquenilo, o–C_3-C_{12} cicloalquenilo sustituido;

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R y R' se seleccionan en forma independiente entre sí entre el grupo formado por:

(i) $-C_1$-C_8 alquilo, $-C_2$-C_8 alquenilo, o $-C_2$-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; $-C_1$-C_8 alquilo sustituido, $-C_2$-C_8 alquenilo sustituido, o $-C_2$-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; $-C_3$-C_{12} cicloalquilo, o $-C_3$-C_{12} cicloalquilo sustituido; $-C_4$-C_{12} alquilcicloalquilo, o $-C_4$-C_{12} alquilcicloalquilo sustituido; $-C_3$-C_{12} cicloalquenilo, o $-C_3$-C_{12} cicloalquenilo sustituido; $-C_4$-C_{12} alquilcicloalquenilo, o $-C_4$-C_{12} alquilcicloalquenilo sustituido;

(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(iii) heterocicloalquilo o heterocicloalquilo sustituido;

(iv) hidrógeno; deuterio;

o R' es C_1-C_8-alquilo sustituido con uno o más átomos de halógeno, preferentemente uno o más átomos de flúor, cloro o bromo. Preferentemente, R' es $-CHQ_1Q_2$, donde Q_1 y Q_2 se seleccionan en forma independiente entre halógeno; preferentemente F, Cl y Br;

G se selecciona entre –OH, $-NHS(O)_2-R_2$, $-NH(SO_2)NR_3R_4$, y NR_3R_4;

R_2 se selecciona entre :

(i) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido

(ii) heterocicloalquilo; heterocicloalquilo sustituido;

(iii) $-C_1$-C_8 alquilo, $-C_2$-C_8 alquenilo, o $-C_2$-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N, $-C_1$-C_8 alquilo sustituido, $-C_2$-C_8 alquenilo sustituido, o $-C_2$-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; $-C_3$-

C_{12} cicloalquilo, o–C_3-C_{12} cicloalquilo sustituido; –C_3-C_{12} cicloalquenilo, o –C_3-C_{12} cicloalquenilo sustituido; heterocíclico; heterocíclico sustituido;

R_3 y R_4 se seleccionan en forma independiente entre:

(i) hidrógeno;

(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(iii) heterocicloalquilo o heterocicloalquilo sustituido;

(iv) –C_1-C_8 alquilo, –C_2-C_8 alquenilo, o –C_2-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C_1-C_8 alquilo sustituido, –C_2-C_8 alquenilo sustituido, o –C_2-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquilo, o –C_3-C_{12} cicloalquilo sustituido; –C_3-C_{12} cicloalquenilo, o –C_3-C_{12} cicloalquenilo sustituido; heterocíclico, o heterocíclico sustituido;

como alternativa, R_3 y R_4 se toman juntos con el nitrógeno al cual se encuentran unidos para formar un heterocíclico o heterocíclico sustituido;

Z se selecciona entre los grupos que consisten de:

(i) hidrógeno;

(ii) CN;

(iii) N_3;

(iv) halógeno;

(v) –NH-N=CHR_1;

(vi) arilo, arilo sustituido;

(vii) heteroarilo, heteroarilo sustituido;

(viii) $-C_3-C_{12}$ cicloalquilo, $-C_3-C_{12}$ cicloalquilo sustituido, heterocicloalquilo, heterocicloalquilo sustituido;

(ix) $-C_1-C_6$ alquilo con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N, opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

(x) $-C_2-C_6$ alquenilo con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N, opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

(xi) $-C_2-C_6$ alquinilo con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N, opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

W se encuentra ausente, o se selecciona entre alquileno, alquenileno, alquinileno, –O–, –S–, $-NR_1-$, $-C(O)NR_1-$, o -C(O)-;

m es 0, 1, 2 o 3; preferentemente 1;

m' es 0, 1, 2 o 3; preferentemente 1; y

s es 1, 2, 3 o 4; preferentemente 1.

En un subconjunto de los compuestos de Fórmulas I y II:

M está ausente o se selecciona entre O o NR_1;

Z_{101} es arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

W_{101} está ausente, o se selecciona entre –O–, –S–, –NH-, -N(Me)-, -C(O)NH-, o -C(O)N(Me)-;

X e Y se toman junto con los átomos de carbono a los cuales están unidos para formar una unidad cíclica que se selecciona entre arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo o heterociclo sustituido;

R_{101} y R_{102} se seleccionan de forma independiente del grupo formado por:

(i) hidrógeno, halógeno, CN, CF_3, NO_2, OR_1, SR_1, $-NHS(O)_2-R_2$, $-NH(SO_2)NR_3R_4$, NR_3R_4, CO_2R_1, COR_1, $CONR_1R_2$, $N(R_1)COR_2$;

(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(iii) heterocicloalquilo o heterocicloalquilo sustituido;

(iv) $-C_1$-C_8 alquilo, $-C_2$-C_8 alquenilo, o $-C_2$-C_8 alquinilo cada uno conteniendo 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; $-C_1$-C_8 alquilo sustituido, $-C_2$-C_8 alquenilo sustituido, o $-C_2$-C_8 alquinilo sustituido cada uno conteniendo 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; $-C_3$-C_{12} cicloalquilo, o $-C_3$-C_{12} cicloalquilo sustituido; $-C_3$-C_{12} cicloalquenilo, o $-C_3$-C_{12} cicloalquenilo sustituido ;

R_3 y R_4 se seleccionan en forma independiente entre:

(i) hidrógeno;

(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(iii) heterocicloalquilo o heterocicloalquilo sustituido;

(iv) $-C_1$-C_8 alquilo, $-C_2$-C_8 alquenilo, o $-C_2$-C_8 alquinilo cada uno conteniendo 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; $-C_1$-C_8 alquilo sustituido, $-C_2$-C_8 alquenilo sustituido, o $-C_2$-C_8 alquinilo sustituido cada uno conteniendo 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; $-C_3$-C_{12} cicloalquilo, o $-C_3$-C_{12} cicloalquilo

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sustituido; $-C_3-C_{12}$ cicloalquenilo, o $-C_3-C_{12}$ cicloalquenilo sustituido; heterociclo heterociclo sustituido;

W está ausente, o se selecciona entre alquileno, alquenileno, alquinileno, –O–, –S–, –NH-, -N(Me)-, -C(O)NH-, o -C(O)N(Me)-;

m = 0, 1, o 2;

m' = 1 o 2; y

s es 1.

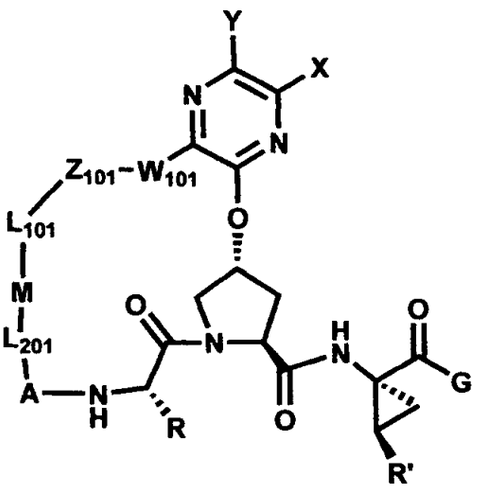
En otra realización la presente invención presenta composiciones farmacéuticas que comprenden un compuesto, o una sal, éster o prodroga del mismo, aceptable para uso farmacéutico. En aún otra realización de la presente invención se revelan composiciones farmacéuticas que comprenden una cantidad eficaz para terapia de un compuesto de la invención o una sal, éster o prodroga del mismo, aceptable para uso farmacéutico, en combinación con un vehículo o excipiente aceptable para uso farmacéutico. En aún otra realización de la invención se presentan métodos para tratar una infección por hepatitis C en un sujeto que necesite dicho tratamiento con dichas composiciones farmacéuticas.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

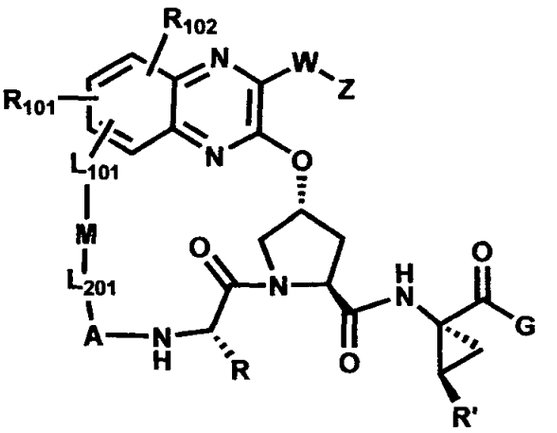
Una primera realización de la invención es un compuesto representado por la fórmula I o la fórmula II tal como se describió anteriormente, o una sal, éster o prodroga del mismo, aceptable para uso farmacéutico, sólo o en combinación con un vehículo o excipiente aceptable para uso farmacéutico.

Otras realizaciones de la invención son compuestos representados por Fórmula III o IV:

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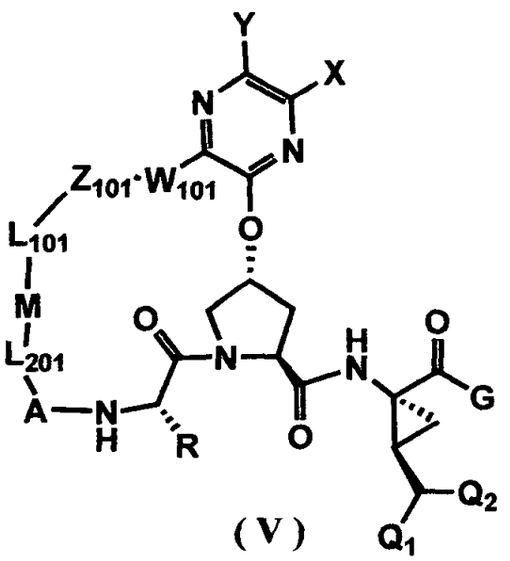
(III)



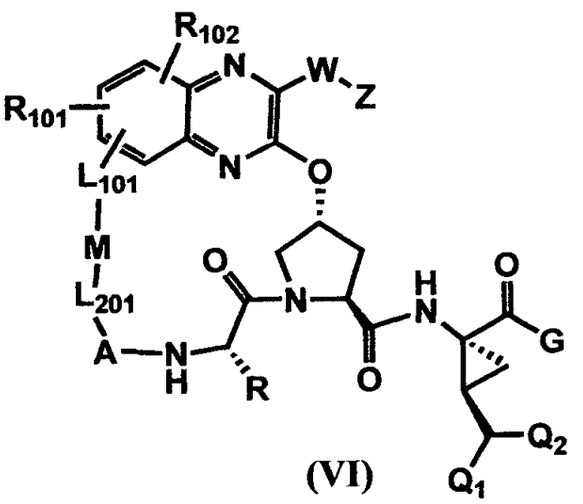
(IV)

o una sal aceptable para uso farmacéutico, éster o prodroga del mismo, solo o en combinación con un vehículo o excipiente aceptable para uso farmacéutico, donde R, R', A, L_{201}, M, L_{101}, Z_{101}, W_{101}, X, Y, R_{101}, R_{102}, W, Z, y G son como se define precedentemente.

Otras realizaciones de la invención son compuestos representados por la Fórmula V o VI:



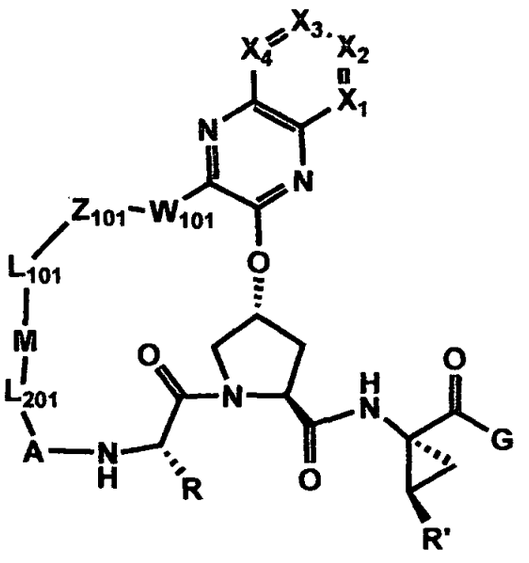
(V)



(VI)

o una sal aceptable para uso farmacéutico, éster o prodroga del mismo, solo o en combinación con un vehículo o excipiente aceptable para uso farmacéutico, donde Q_1 y Q_2 son en forma independiente flúor, cloro o bromo, y donde R, A, L_{201}, M, L_{101}, Z_{101}, W_{101}, X, Y, R_{101}, R_{102}, W, Z, y G son como se define precedentemente. En realizaciones particularmente preferidas, Q_1 y Q_2 son ambos flúor.

Otra realización de la invención es un compuesto representado por la Fórmula VII:



(VII)

o una sal aceptable para uso farmacéutico, éster o prodroga del mismo, solo o en combinación con un vehículo o excipiente aceptable para uso farmacéutico, donde X_1-X_4se seleccionan en forma independiente entre $-CR_5$ y N, en donde R_5 se selecciona en forma independiente entre:

(i) hidrógeno; halógeno; $-NO_2$; -CN; N_3; CF_3;

(ii) $-M-R_4$, M es O, S, NH;

(iii) NR_3R_4;

(iv) $-C_1$-C_8 alquilo, $-C_2$-C_8 alquenilo, o $-C_2$-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; $-C_1$-C_8 alquilo sustituido, $-C_2$-C_8 alquenilo sustituido, o $-C_2$-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; $-C_3$-C_{12} cicloalquilo, o $-C_3$-C_{12} cicloalquilo sustituido; $-C_3$-C_{12} cicloalquenilo, o $-C_3$-C_{12} cicloalquenilo sustituido;

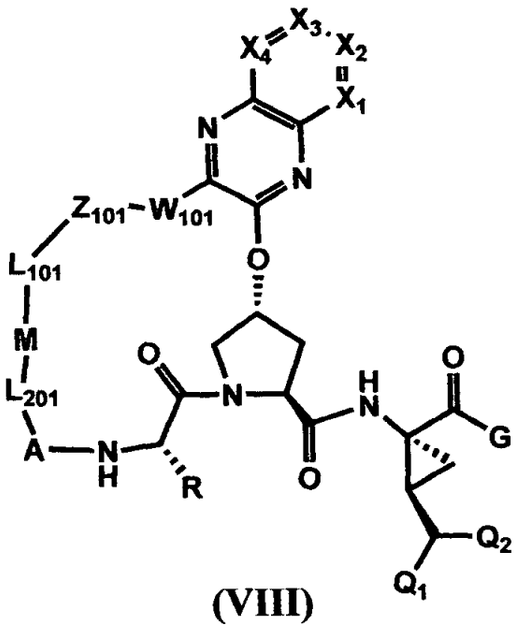
(v) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(vi) heterocicloalquilo o heterocicloalquilo sustituido;

000269

donde R_3, R_4, R, R', A, L_{201}, M, L_{101}, Z_{101}, W_{101} y G son como se define precedentemente.

Otra realización de la invención es un compuesto representado por Fórmula VIII:

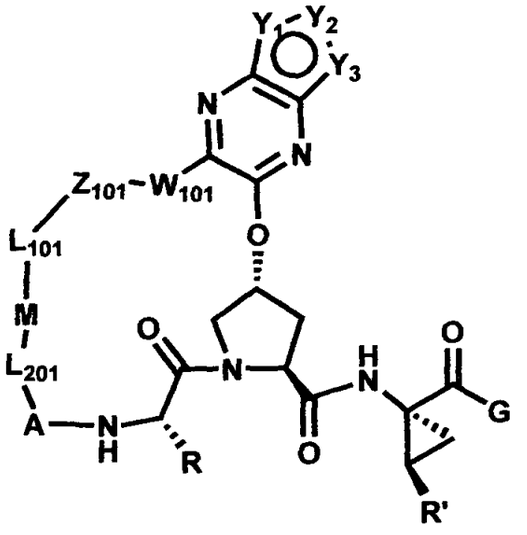


(VIII)

o una sal aceptable para uso farmacéutico, éster o prodroga del mismo, solo o en combinación con un vehículo o excipiente aceptable para uso farmacéutico, en donde X_1-X_4 son como se define para la Fórmula VII, y R, A, Q_1, Q_2, L_{201}, M, L_{101}, Z_{101}, W_{101} y G son como se define precedentemente.

Otra realización de la invención es un compuesto representado por Fórmula IX:

000270

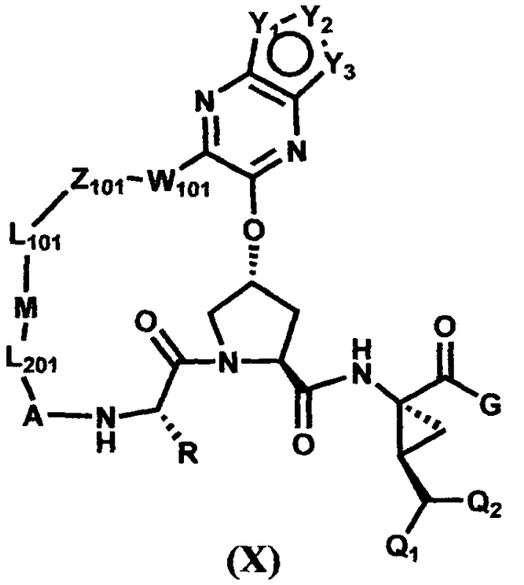


(IX)

o una sal aceptable para uso farmacéutico, éster o prodroga del mismo, solo o en combinación con un vehículo o excipiente aceptable para uso farmacéutico, donde Y_1-Y_3 se seleccionan en forma independiente entre CR_5, N, NR_5, S y O; donde R_5, R, R', A, L_{201}, M, L_{101}, Z_{101}, W_{101} y G son como se define precedentemente.

Otra realización de la invención es un compuesto representado por Fórmula X:

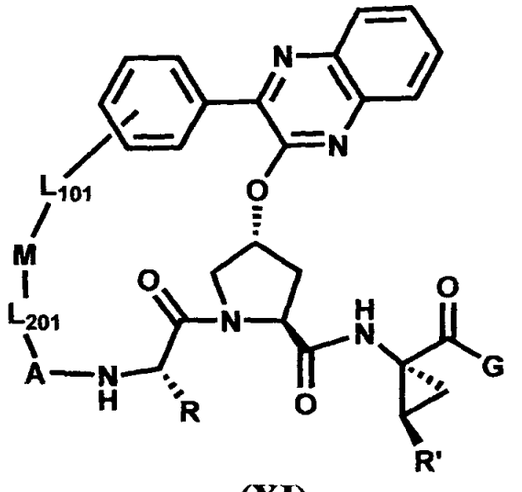
000271



(X)

una sal aceptable para uso farmacéutico, éster o prodroga del mismo, solo o en combinación con un vehículo o excipiente aceptable para uso farmacéutico, donde Y_1-Y_3 son como se define para Fórmula IX, y R, Q_1, Q_2, A, L_{201}, M, L_{101}, Z_{101}, W_{101} y G son como se define precedentemente.

Otra realización de la invención es un compuesto representado por Fórmula XI:

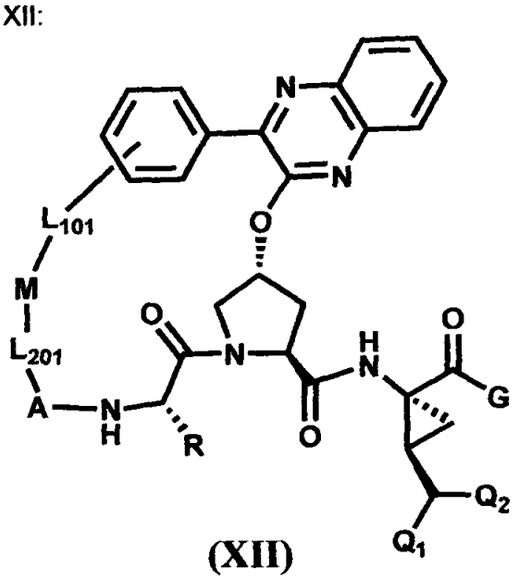


(XI)

000272

o una sal aceptable para uso farmacéutico, éster o prodroga del mismo, solo o en combinación con un vehículo o excipiente aceptable para uso farmacéutico, donde R, R', A, L_{201}, M, L_{101} y G son como se define precedentemente.

Otra realización de la invención es un compuesto representado por Fórmula XII:

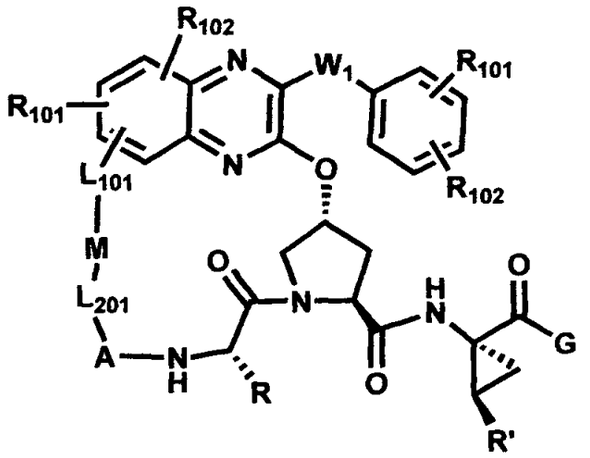


(XII)

una sal aceptable para uso farmacéutico, éster o prodroga del mismo, solo o en combinación con un vehículo o excipiente aceptable para uso farmacéutico, donde R, Q_1, Q_2, A, L_{201}, M, L_{101} y G son como se define precedentemente.

Otra realización de la invención es un compuesto representado por Fórmula XIII:

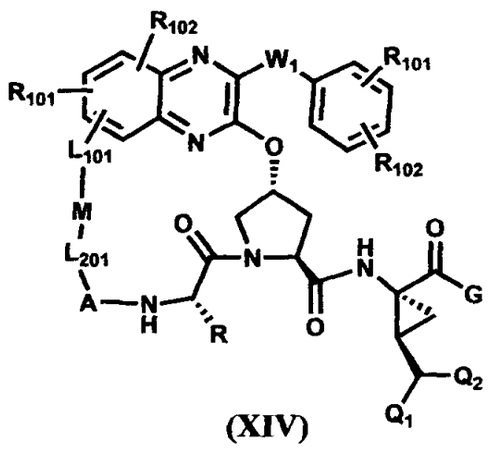
000273



(XIII)

o una sal aceptable para uso farmacéutico, éster o prodroga del mismo, solo o en combinación con un vehículo o excipiente aceptable para uso farmacéutico, donde W_1 está ausente o se selecciona entre C_1-C_4 alquileno, C_2-C_4 alquenileno, C_2-C_4 alquinileno; donde R, R', A, L_{201}, M, L_{101} , R_{101}, R_{102} y G son como se define precedentemente.

Otra realización de la invención es un compuesto representado por Fórmula XIV:



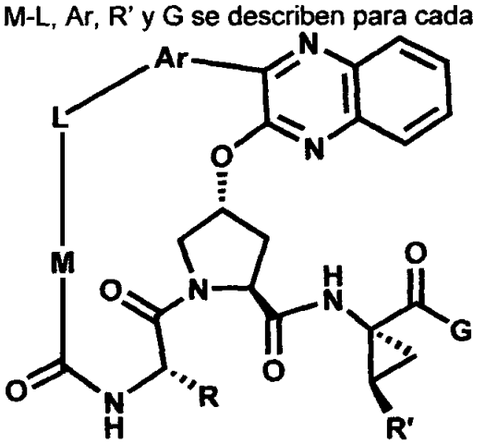
(XIV)

una sal aceptable para uso farmacéutico, éster o prodroga del mismo, solo o en combinación con un vehículo o excipiente aceptable para uso farmacéutico, donde W_1

000274

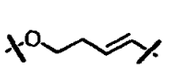
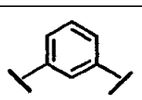
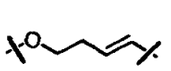
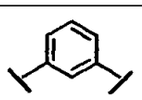
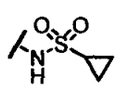
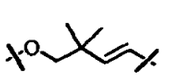
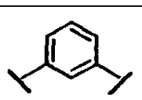
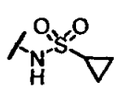
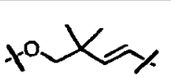
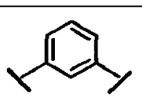
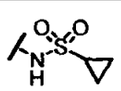
es como se define para la Fórmula XIII, y R, Q_1, Q_2, A, L_{201}, M, L_{101} , R_{101}, R_{102} y G son como se define precedentemente.

Los compuestos representativos de la invención incluyen, pero sin carácter taxativo, los siguientes compuestos (tabla 1) de acuerdo a la fórmula XV en donde R, M-L, Ar, R' y G se describen para cada ejemplo en la tabla 1.

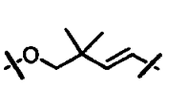
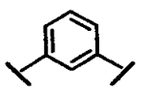
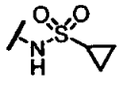
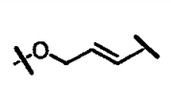
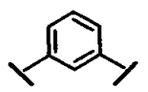
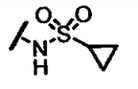
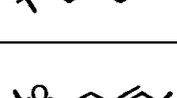
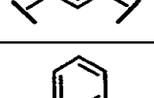
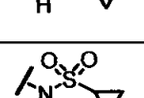
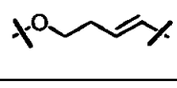
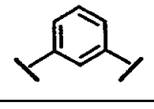
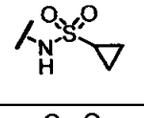
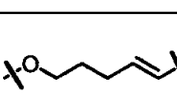
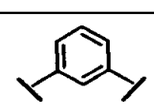
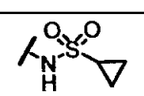
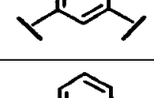
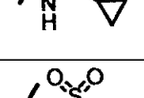
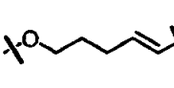
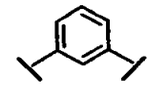
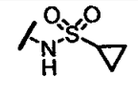
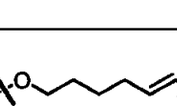
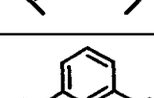
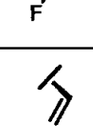
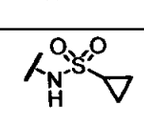


(XV)

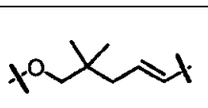
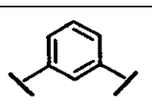
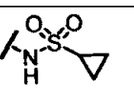
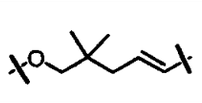
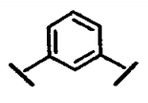
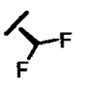
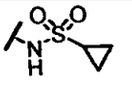
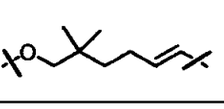
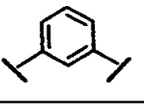
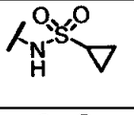
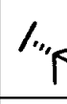
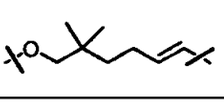
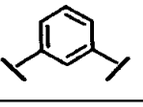
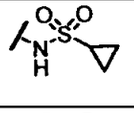
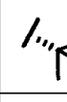
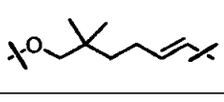
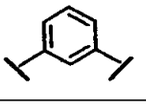
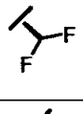
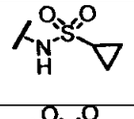
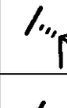
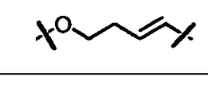
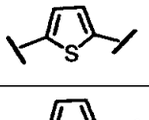
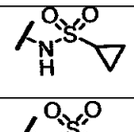
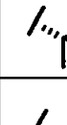
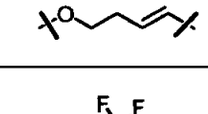
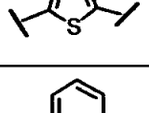
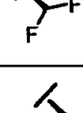
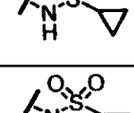
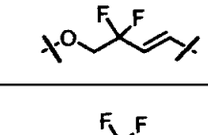
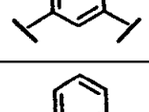
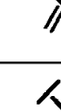
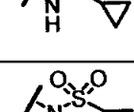
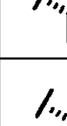
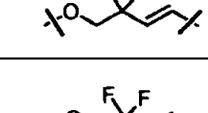
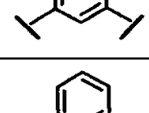
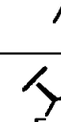
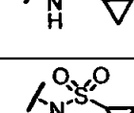
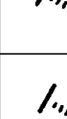
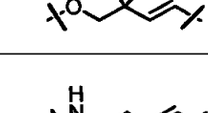
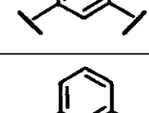
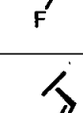
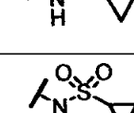
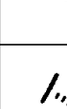
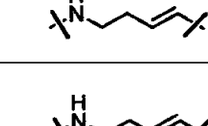
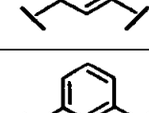
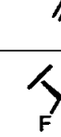
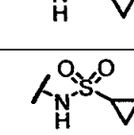
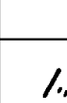
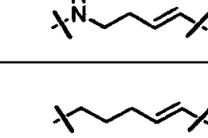
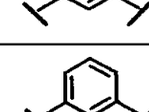
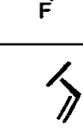
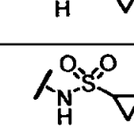
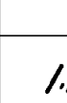
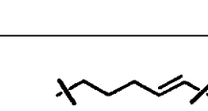
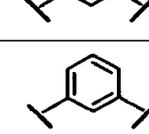
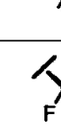
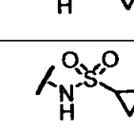
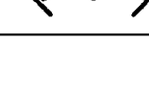
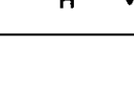
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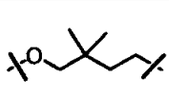
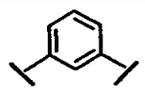
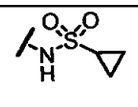
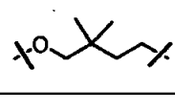
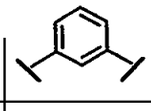
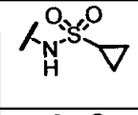
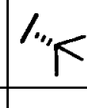
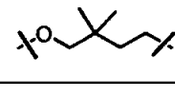
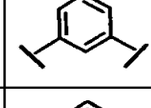
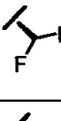
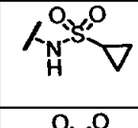
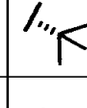
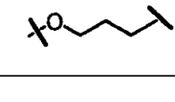
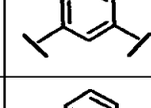
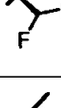
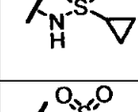
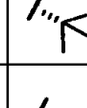
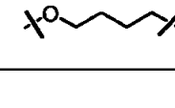
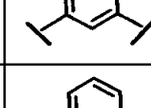
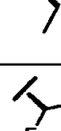
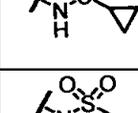
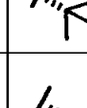
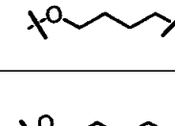
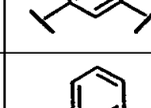
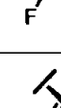
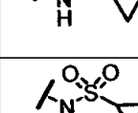
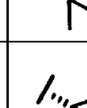
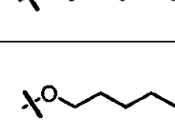
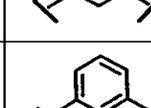
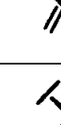
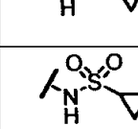
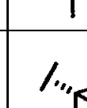
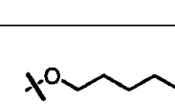
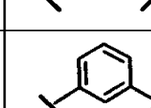
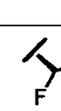
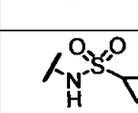
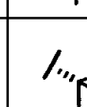
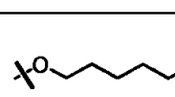
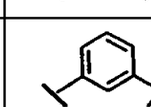
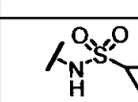
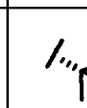
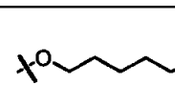
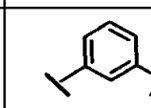
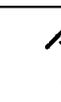
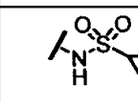
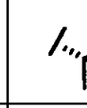
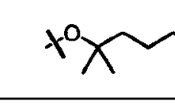
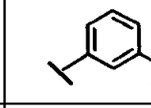
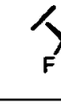
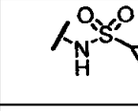
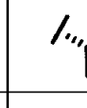
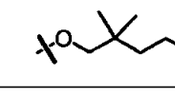
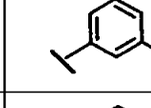
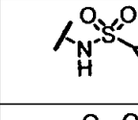
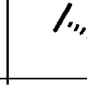
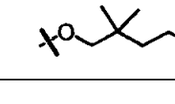
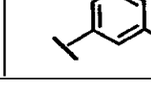
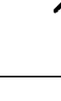
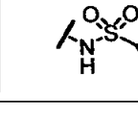
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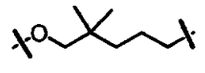
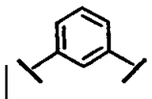
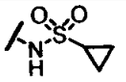
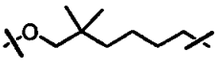
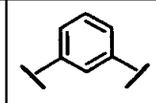
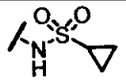
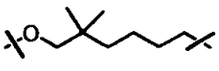
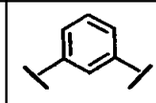
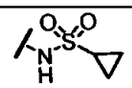
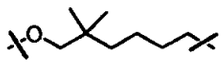
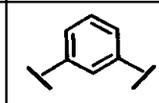
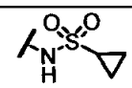
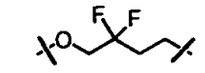
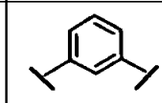
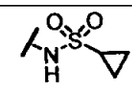
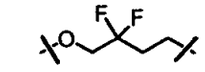
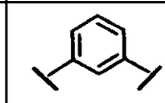
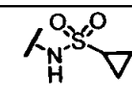
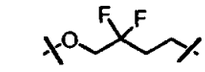
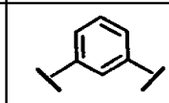
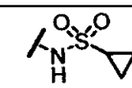
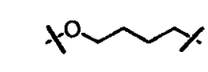
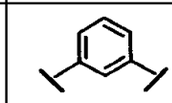
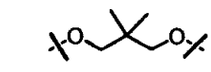
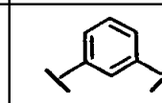
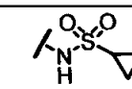
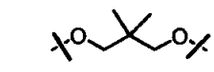
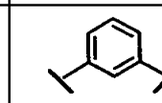
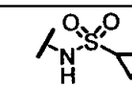
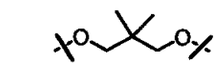
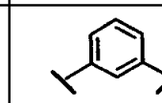
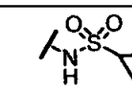
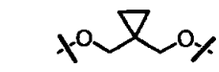
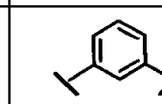
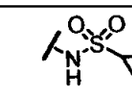
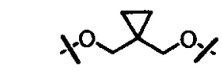
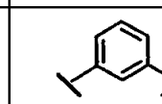
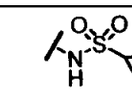
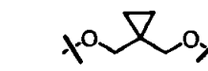
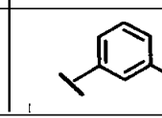
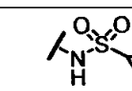
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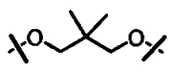
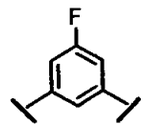
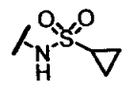
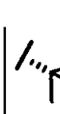
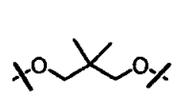
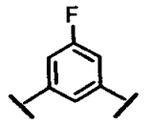
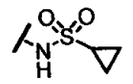
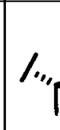
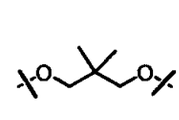
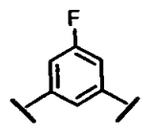
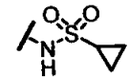
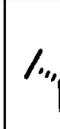
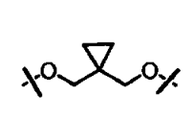
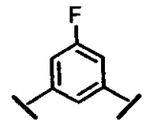
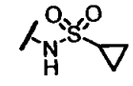
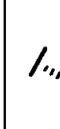
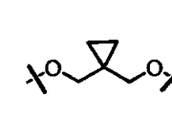
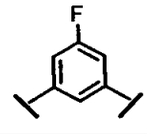
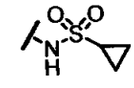
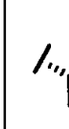
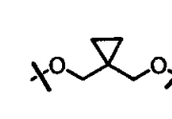
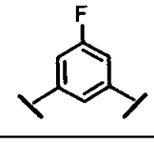
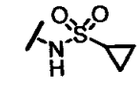
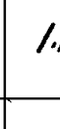
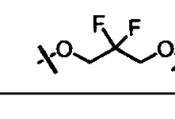
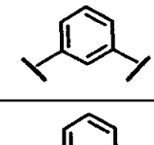
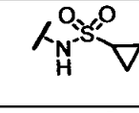
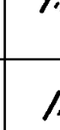
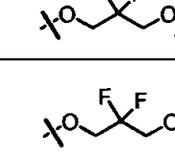
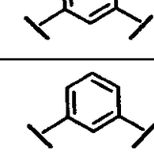
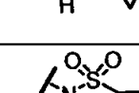
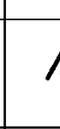
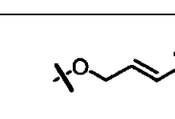
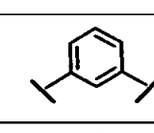
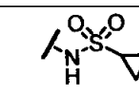
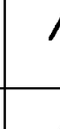
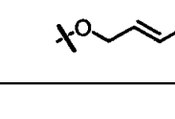
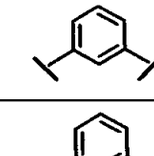
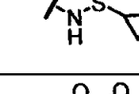
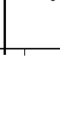
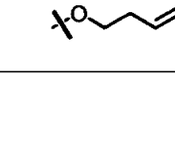
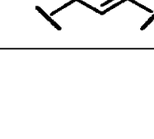
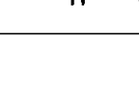
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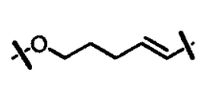
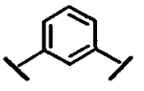
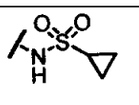
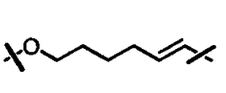
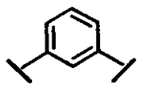
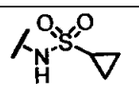
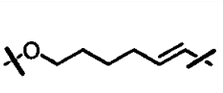
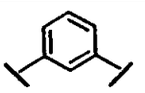
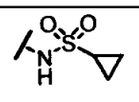
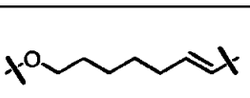
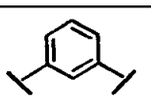
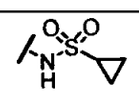
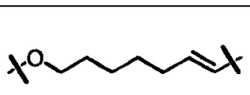
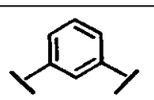
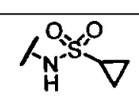
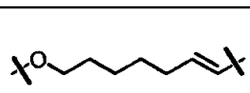
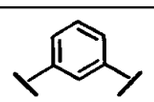
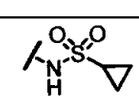
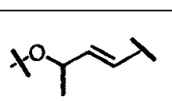
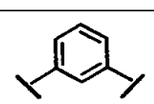
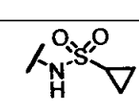
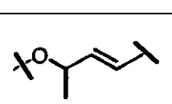
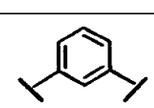
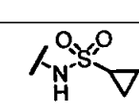
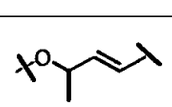
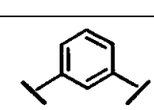
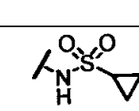
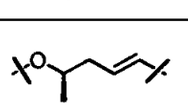
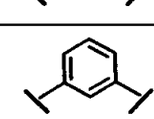
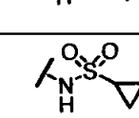
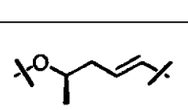
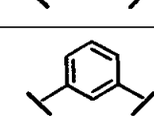
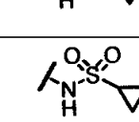
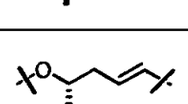
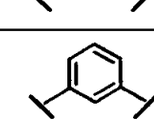
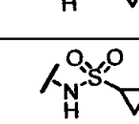
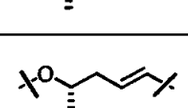
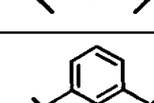
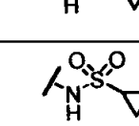
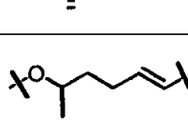
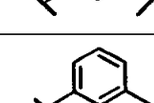
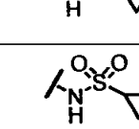
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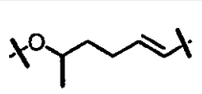
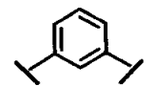
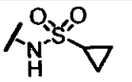
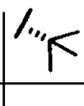
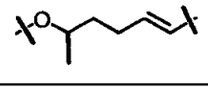
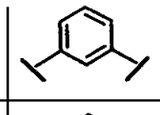
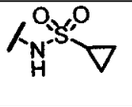
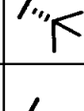
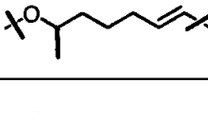
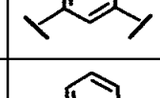
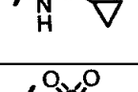
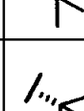
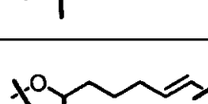
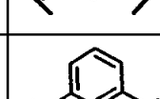
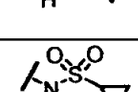
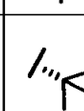
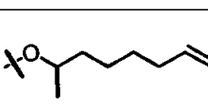
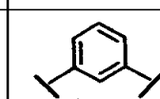
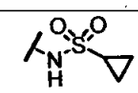
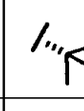
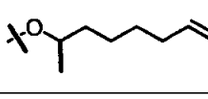
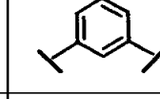
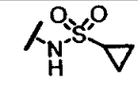
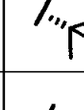
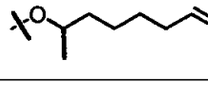
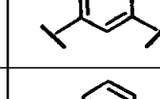
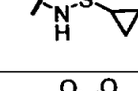
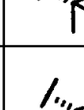
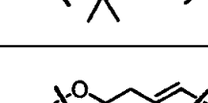
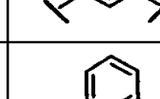
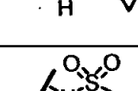
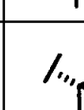
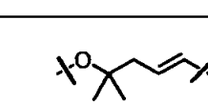
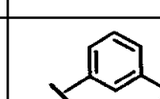
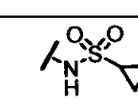
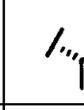
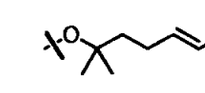
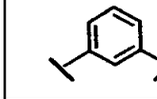
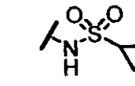
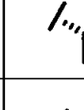
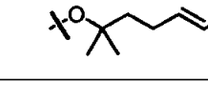
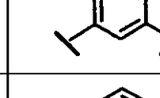
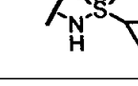
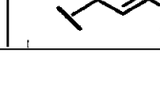
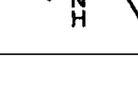
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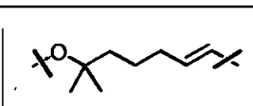
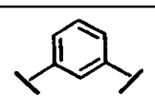
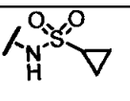
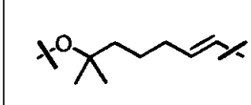
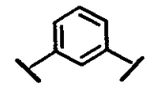
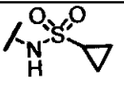
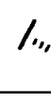
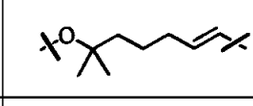
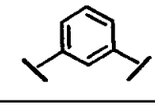
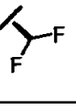
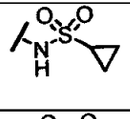
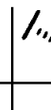
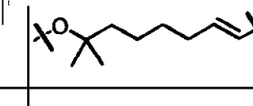
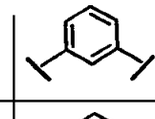
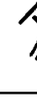
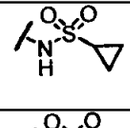
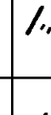
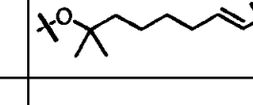
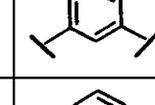
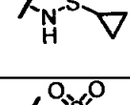
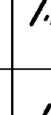
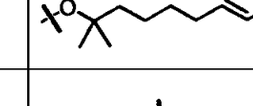
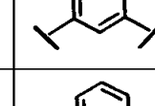
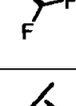
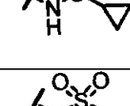
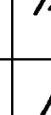
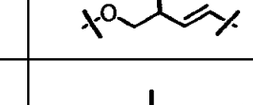
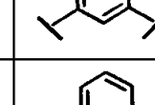
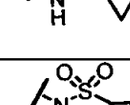
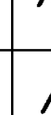
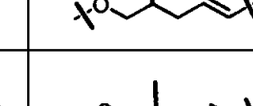
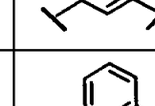
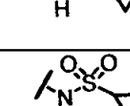
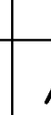
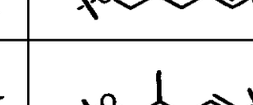
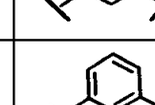
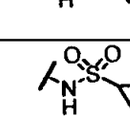
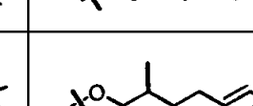
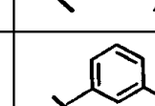
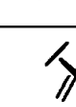
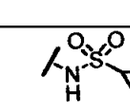
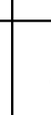
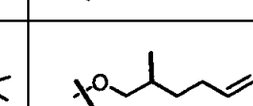
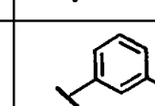
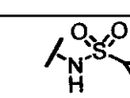
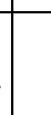
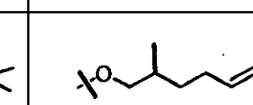
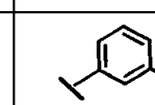
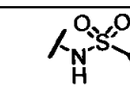
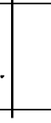
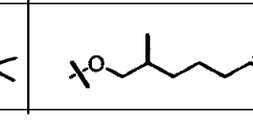
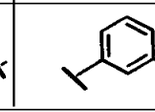
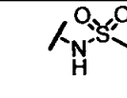
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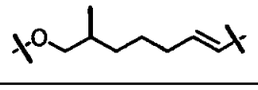
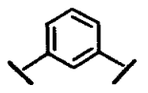
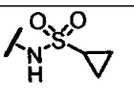
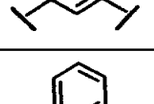
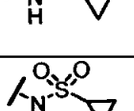
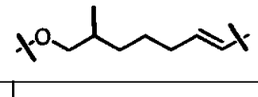
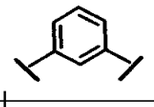
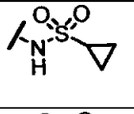
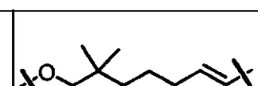
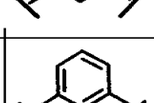
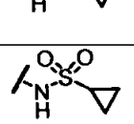
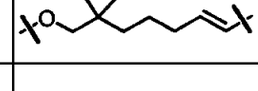
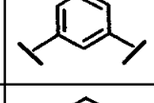
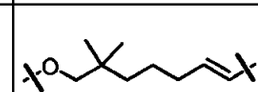
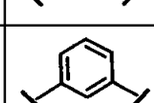
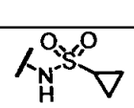
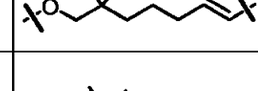
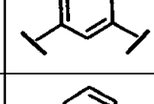
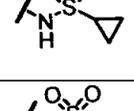
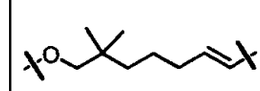
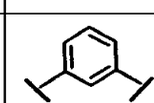
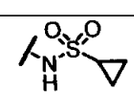
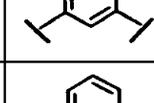
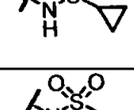
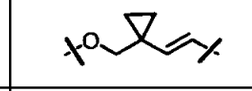
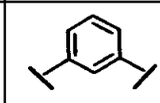
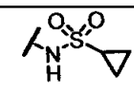
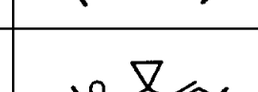
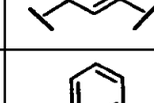
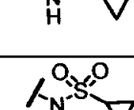
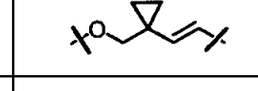
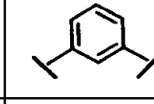
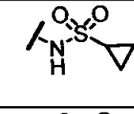
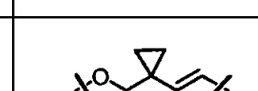
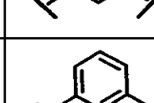
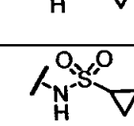
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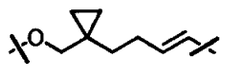
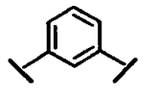
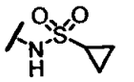
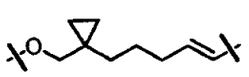
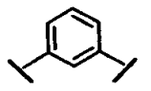
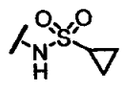
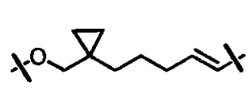
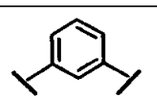
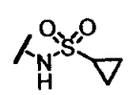
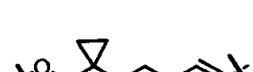
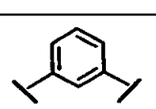
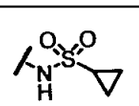
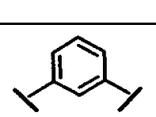
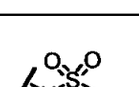
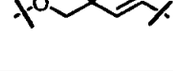
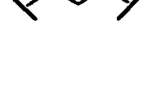
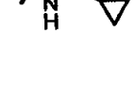
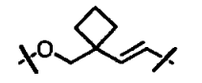
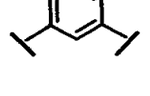
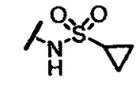
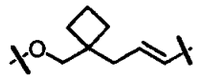
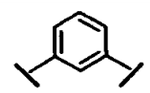
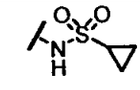
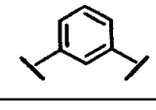
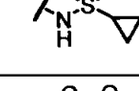
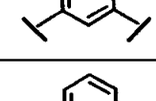
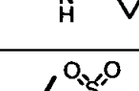
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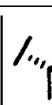
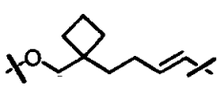
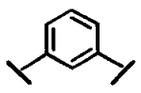
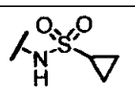
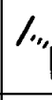
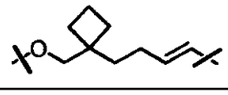
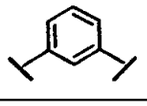
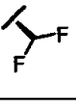
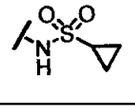
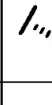
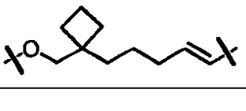
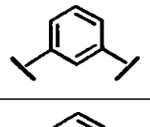
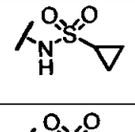
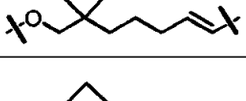
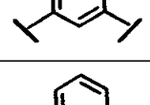
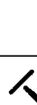
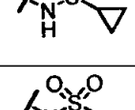
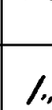
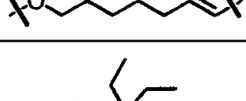
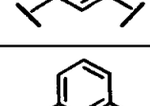
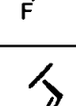
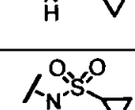
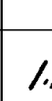
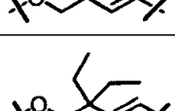
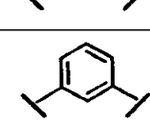
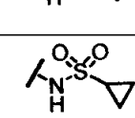
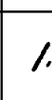
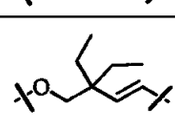
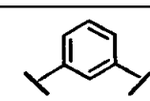
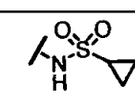
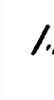
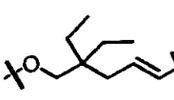
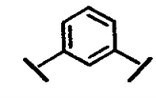
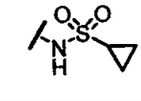
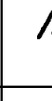
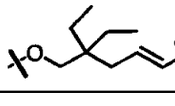
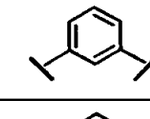
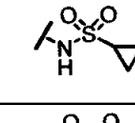
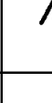
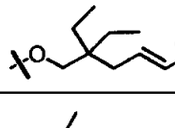
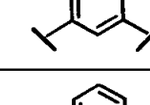
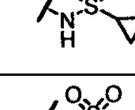
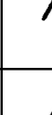
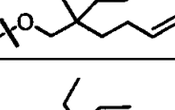
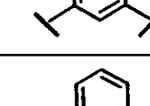
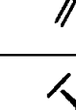
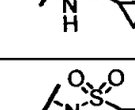
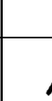
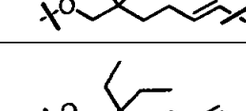
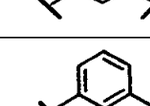
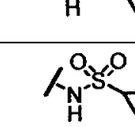
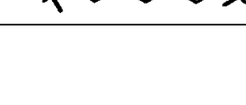
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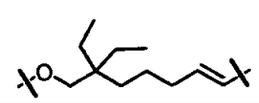
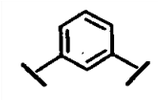
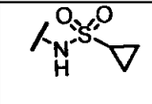
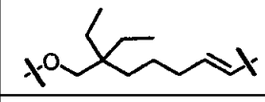
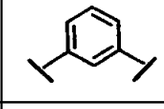
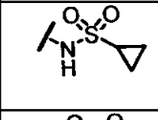
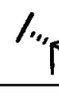
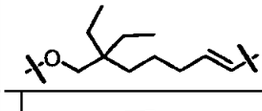
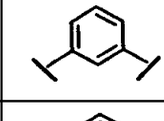
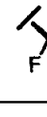
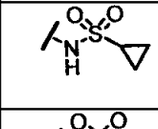
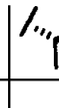
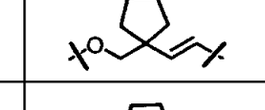
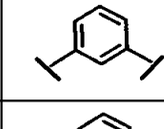
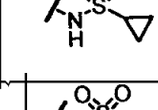
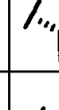
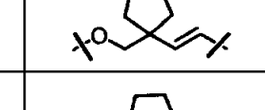
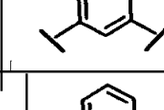
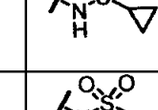
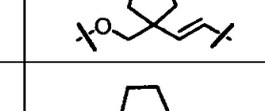
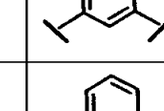
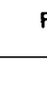
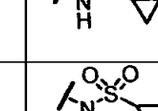
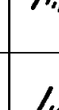
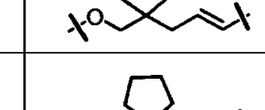
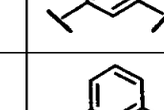
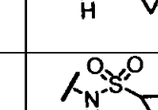
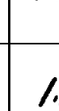
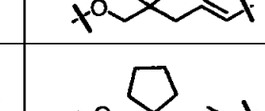
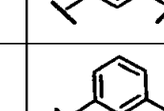
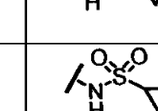
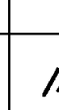
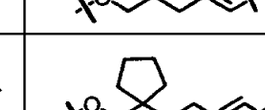
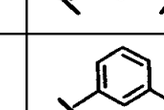
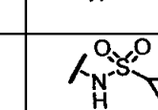
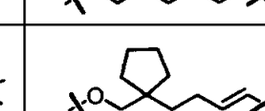
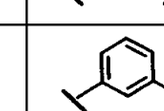
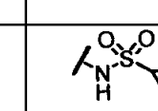
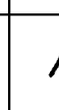
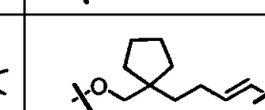
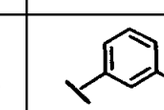
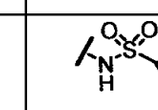
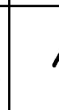
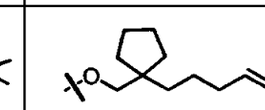
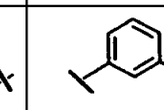
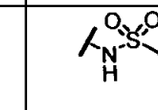
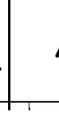
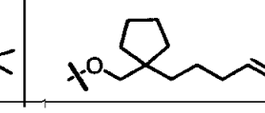
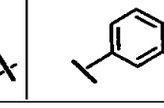
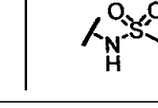
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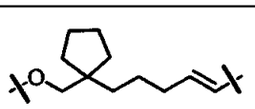
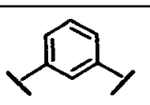
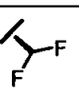
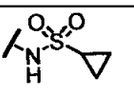
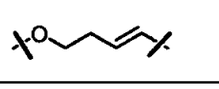
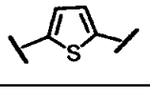
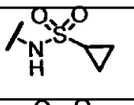
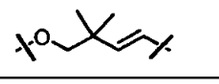
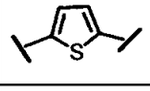
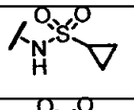
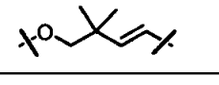
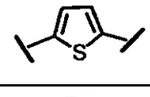
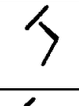
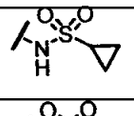
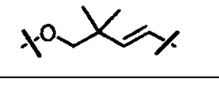
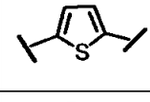
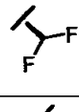
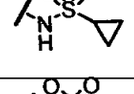
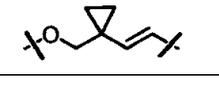
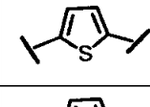
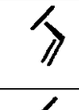
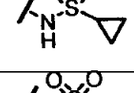
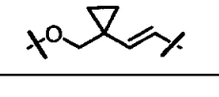
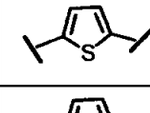
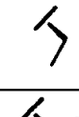
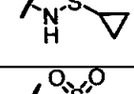
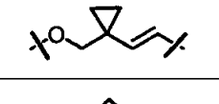
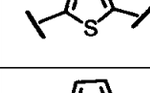
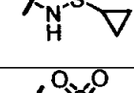
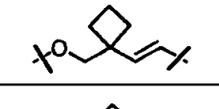
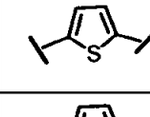
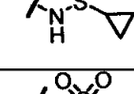
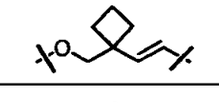
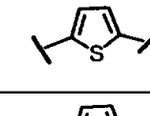
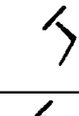
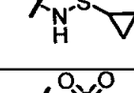
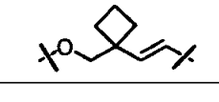
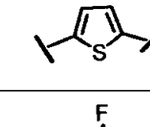
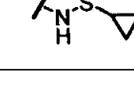
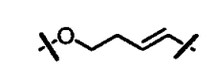
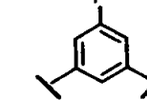
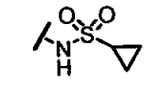
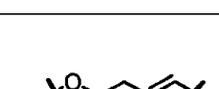
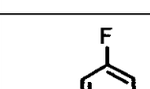
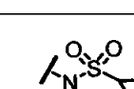
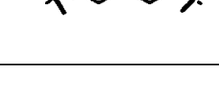
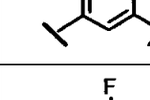
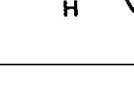
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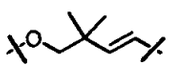
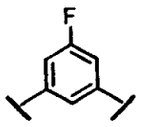
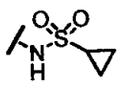
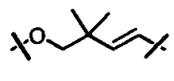
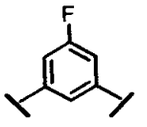
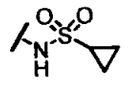
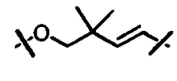
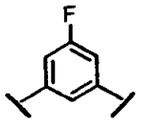
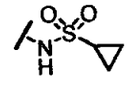
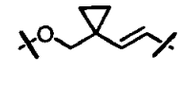
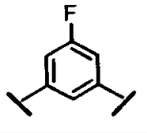
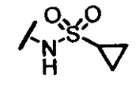
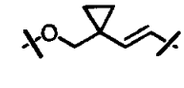
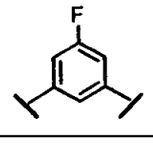
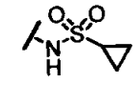
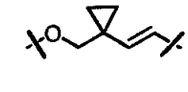
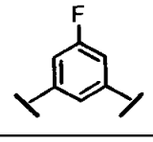
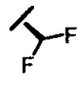
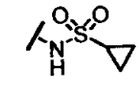
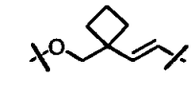
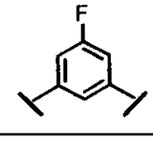
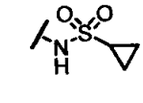
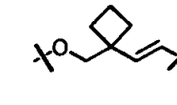
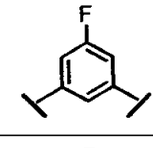
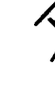
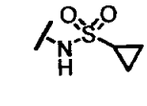
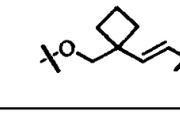
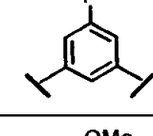
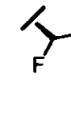
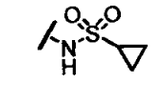
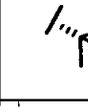
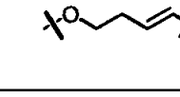
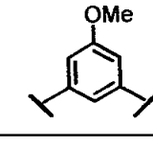
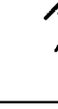
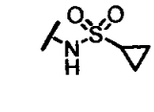
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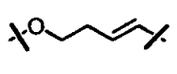
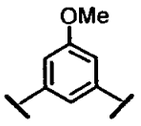
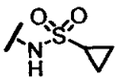
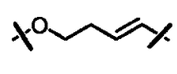
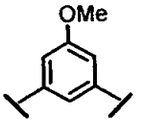
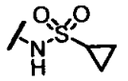
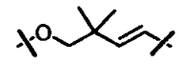
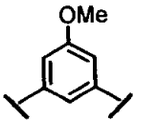
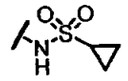
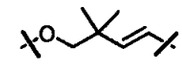
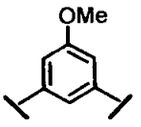
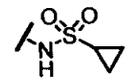
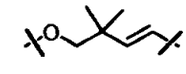
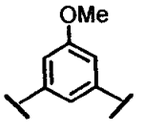
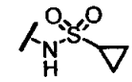
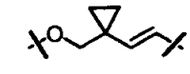
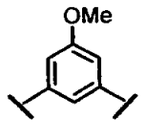
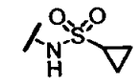
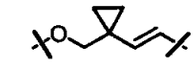
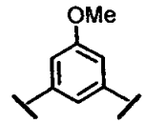
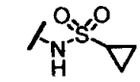
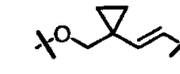
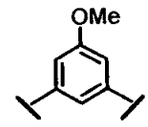
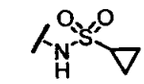
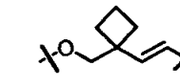
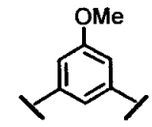
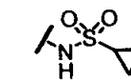
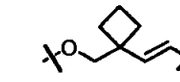
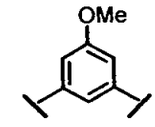
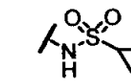
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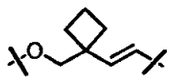
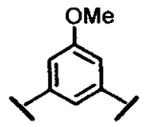
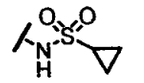
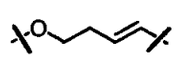
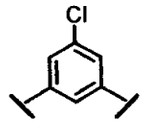
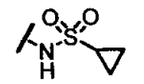
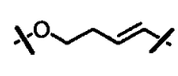
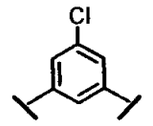
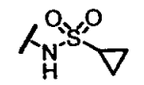
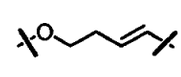
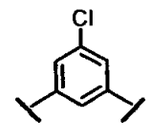
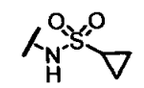
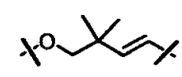
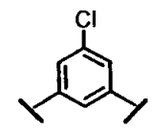
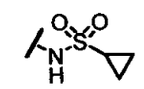
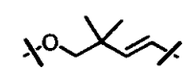
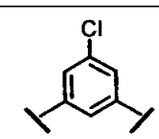
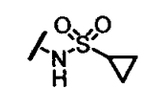
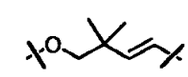
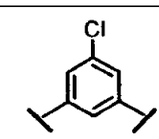
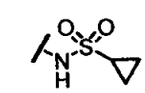
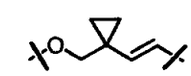
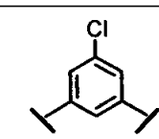
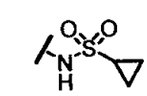
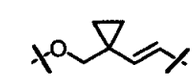
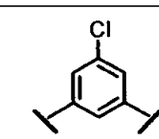
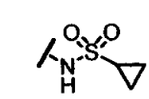
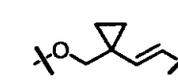
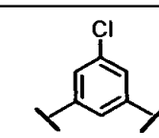
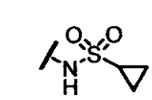
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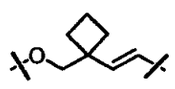
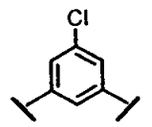
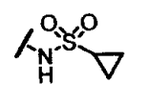
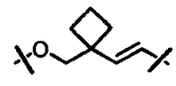
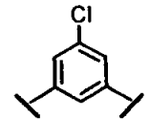
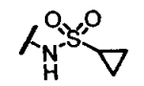
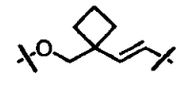
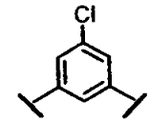
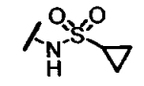
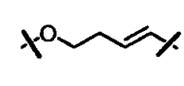
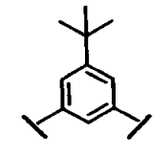
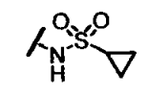
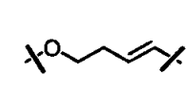
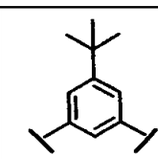
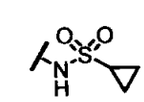
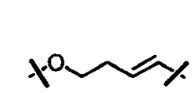
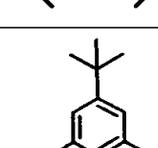
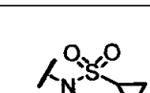
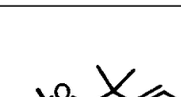
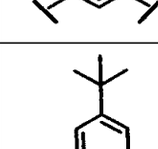
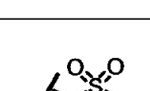
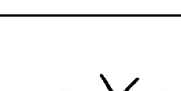
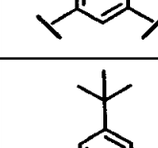
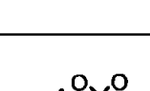
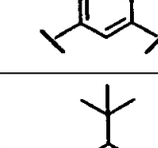
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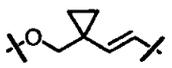
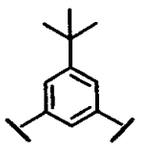
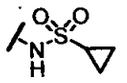
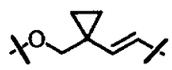
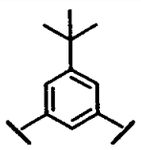
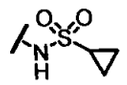
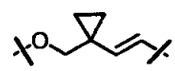
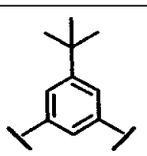
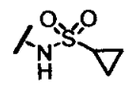
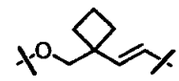
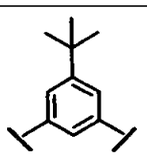
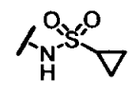
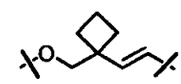
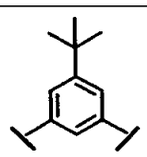
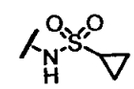
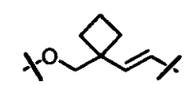
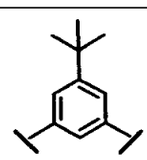
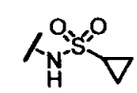
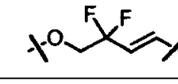
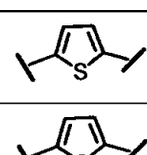
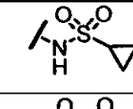
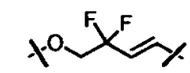
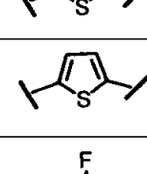
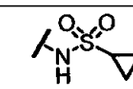
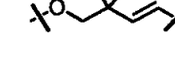
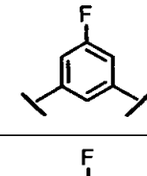
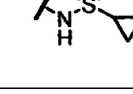
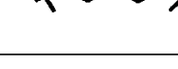
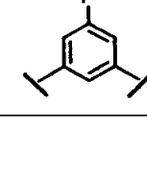
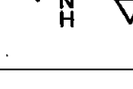
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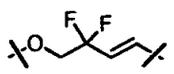
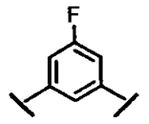
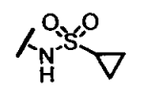
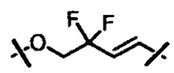
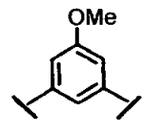
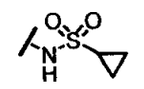
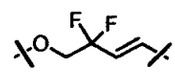
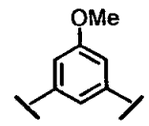
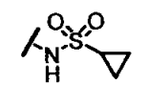
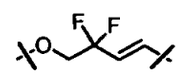
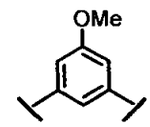
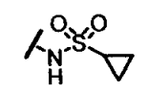
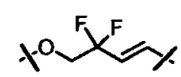
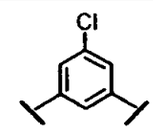
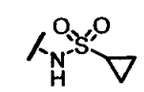
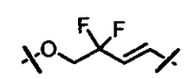
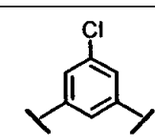
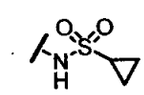
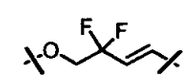
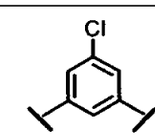
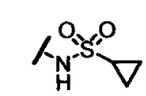
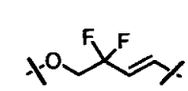
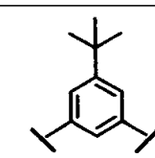
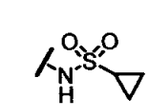
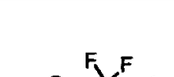
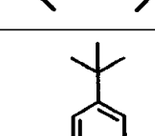
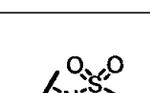
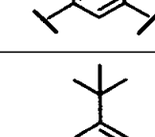
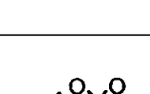
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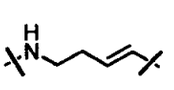
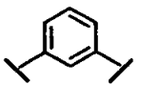
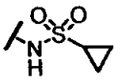
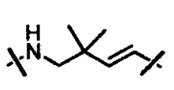
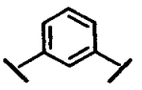
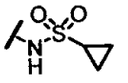
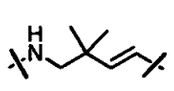
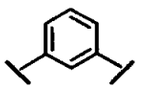
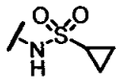
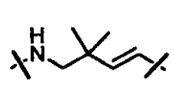
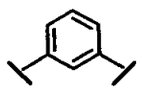
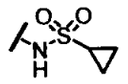
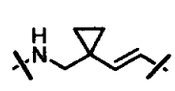
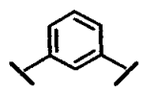
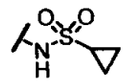
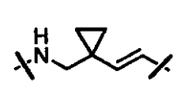
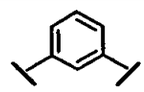
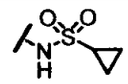
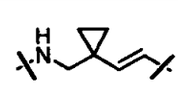
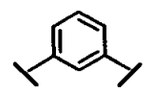
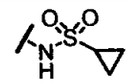
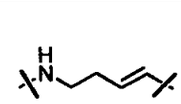
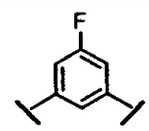
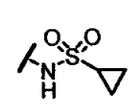
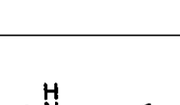
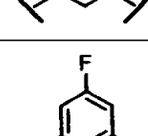
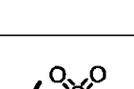
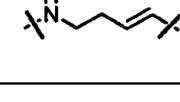
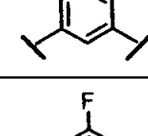
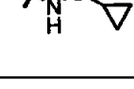
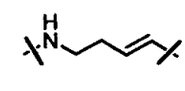
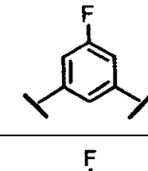
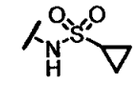
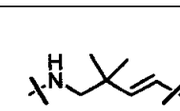
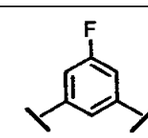
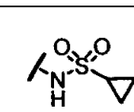
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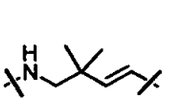
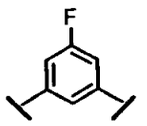
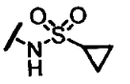
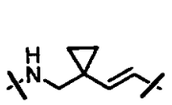
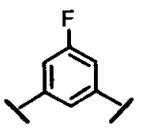
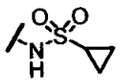
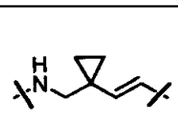
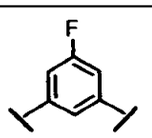
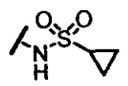
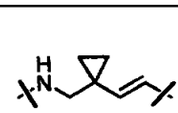
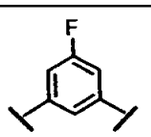
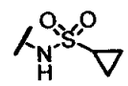
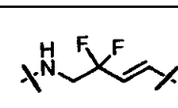
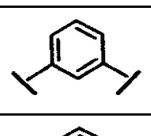
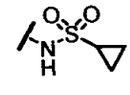
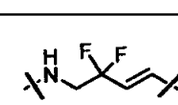
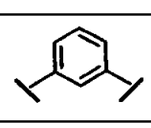
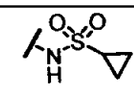
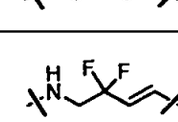
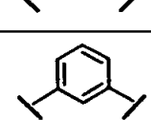
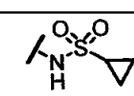
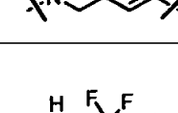
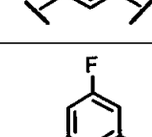
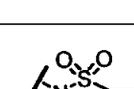
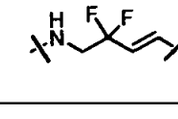
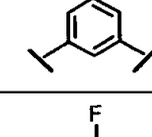
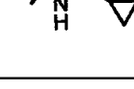
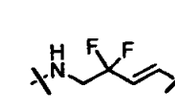
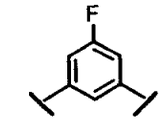
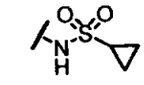
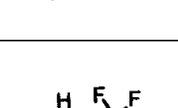
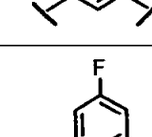
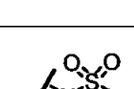
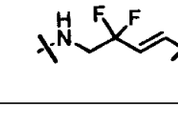
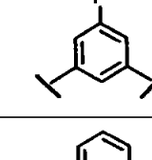
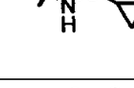
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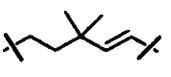
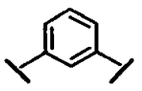
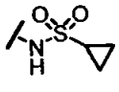
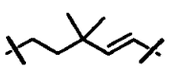
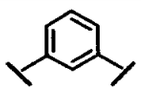
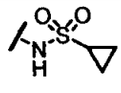
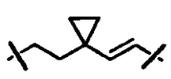
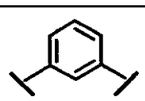
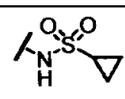
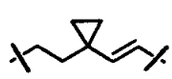
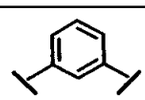
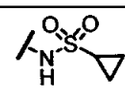
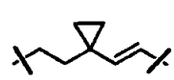
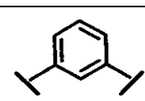
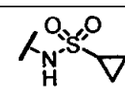
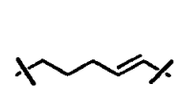
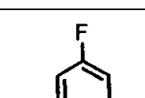
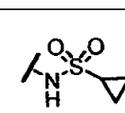
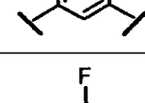
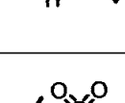
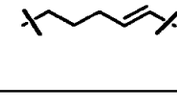
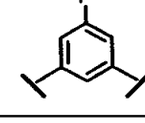
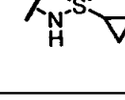
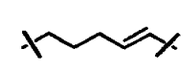
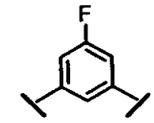
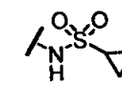
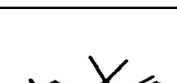
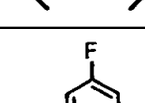
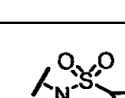
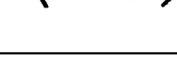
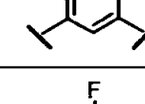
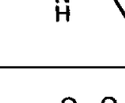
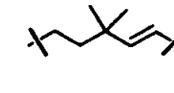
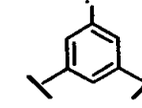
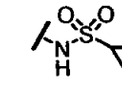
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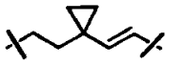
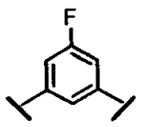
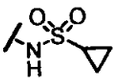
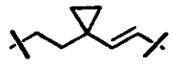
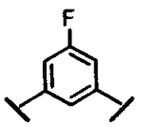
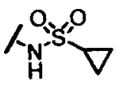
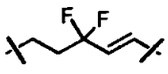
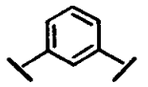
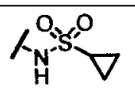
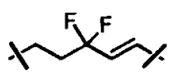
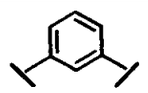
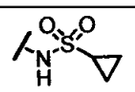
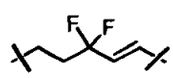
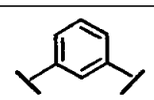
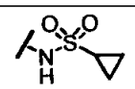
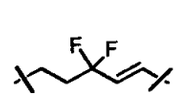
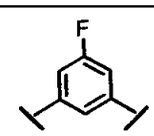
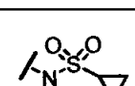
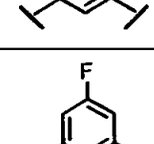
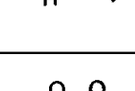
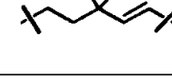
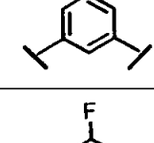
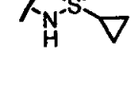
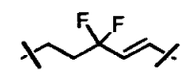
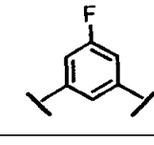
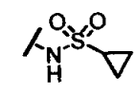
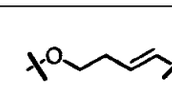
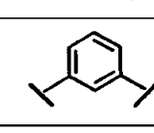
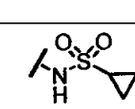
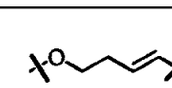
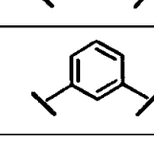
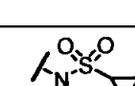
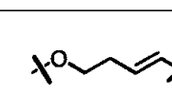
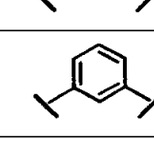
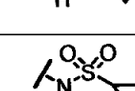
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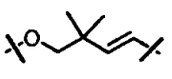
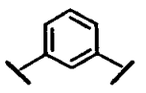
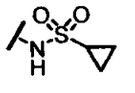
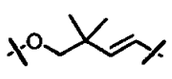
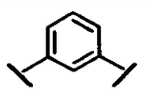
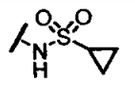
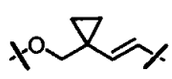
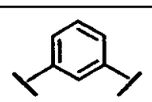
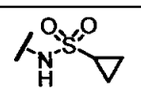
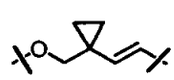
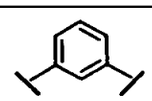
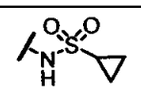
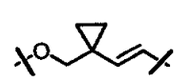
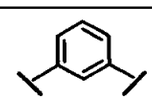
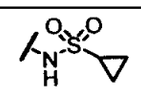
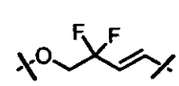
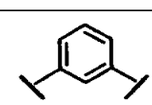
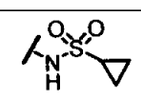
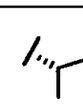
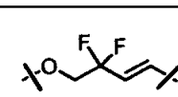
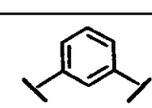
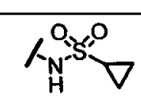
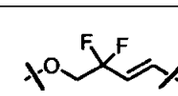
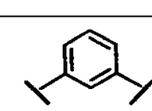
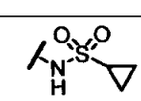
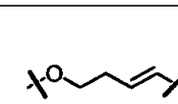
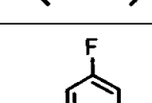
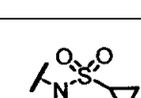
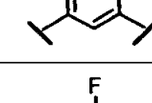
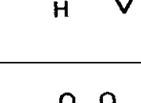
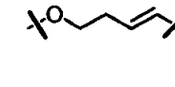
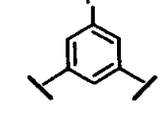
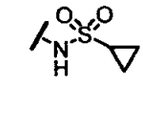
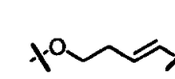
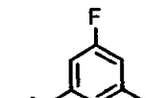
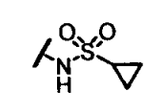
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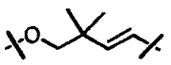
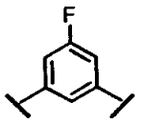
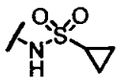
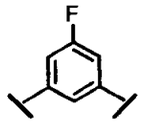
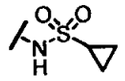
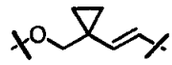
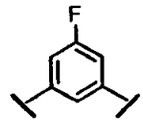
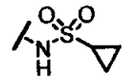
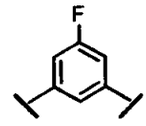
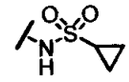
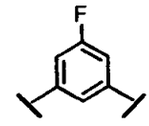
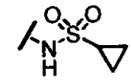
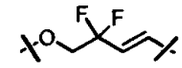
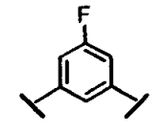
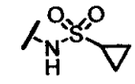
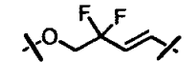
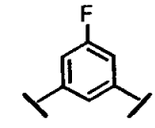
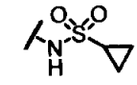
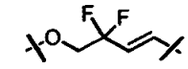
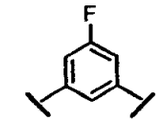
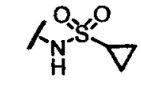
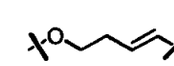
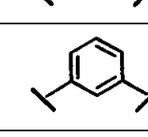
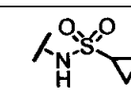
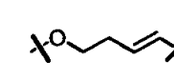
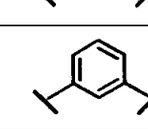
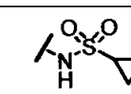
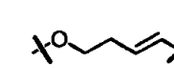
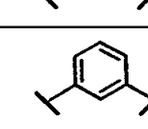
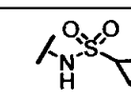
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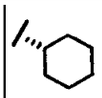
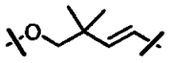
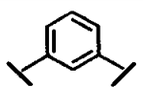
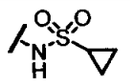
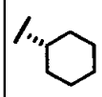
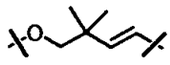
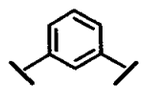
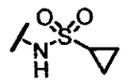
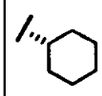
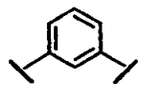
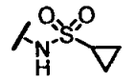
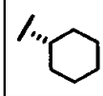
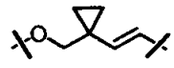
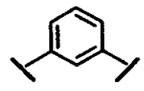
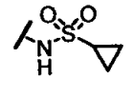
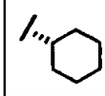
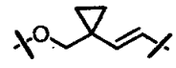
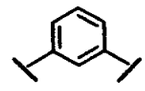
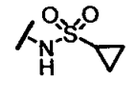
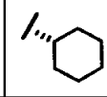
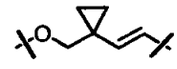
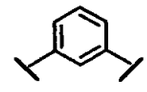
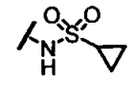
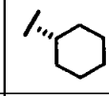
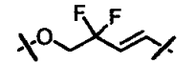
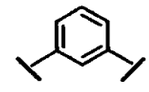
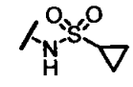
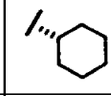
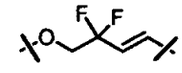
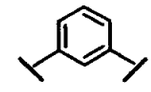
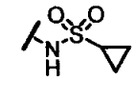
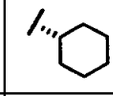
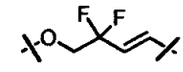
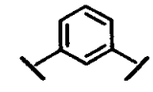
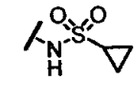
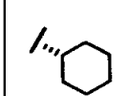
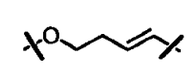
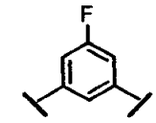
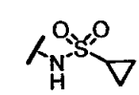
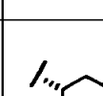
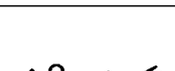
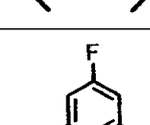
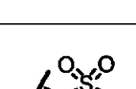
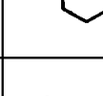
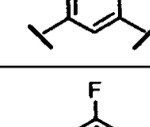
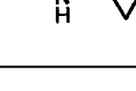
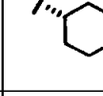
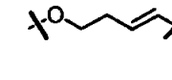
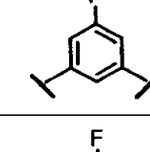
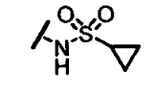
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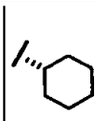
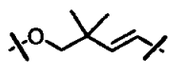
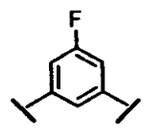
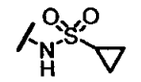
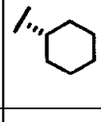
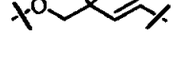
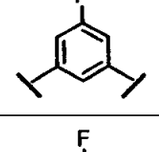
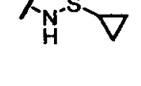
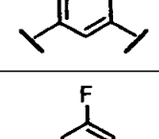
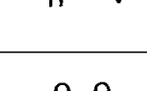
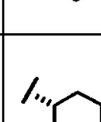
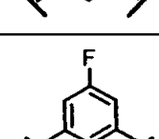
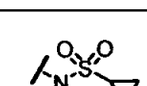
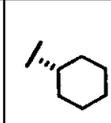
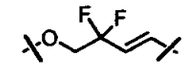
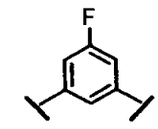
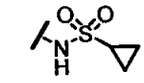
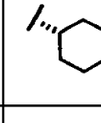
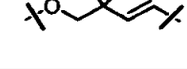
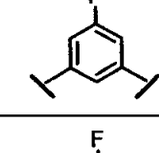
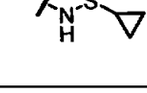
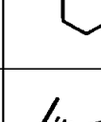
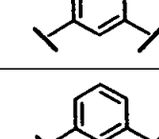
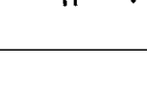
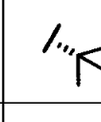
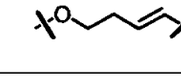
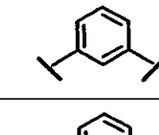
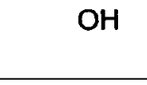
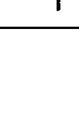
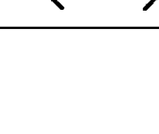
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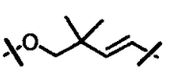
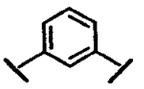
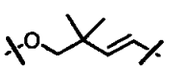
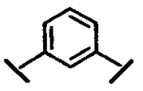
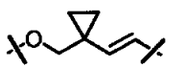
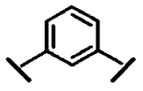
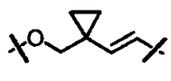
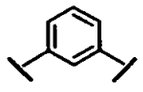
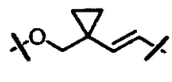
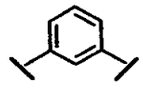
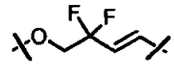
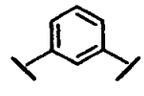
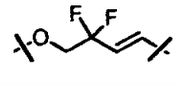
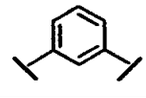
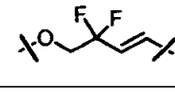
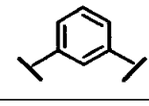
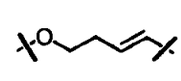
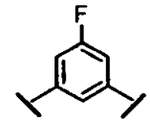
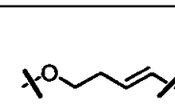
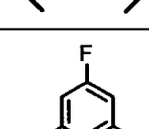
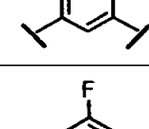
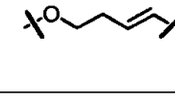
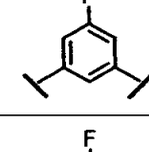
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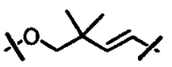
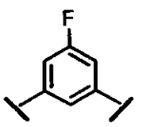
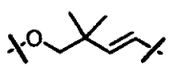
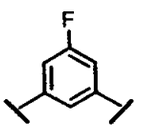
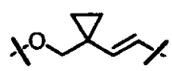
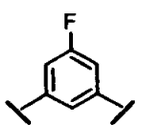
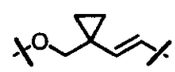
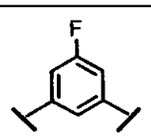
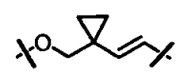
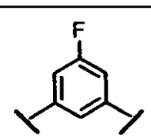
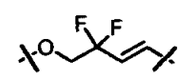
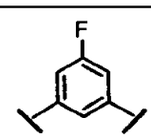
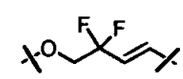
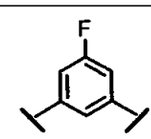
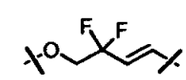
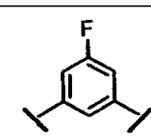
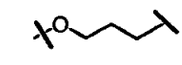
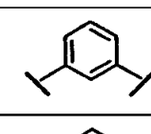
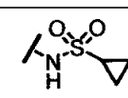
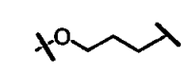
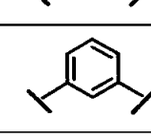
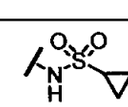
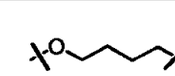
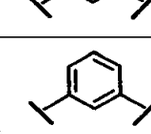
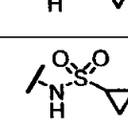
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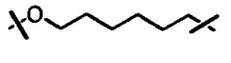
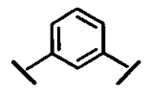
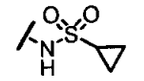
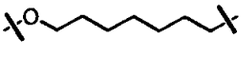
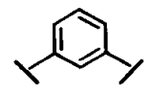
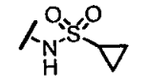
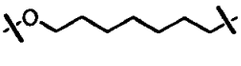
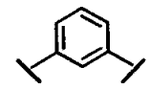
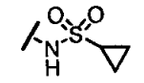
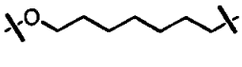
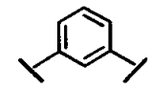
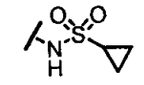
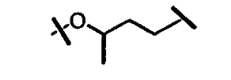
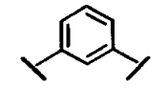
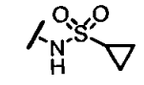
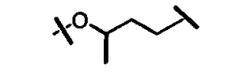
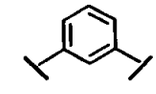
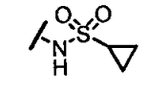
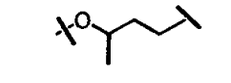
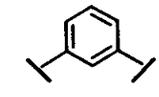
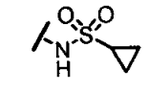
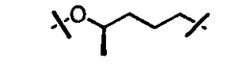
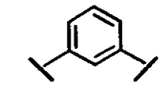
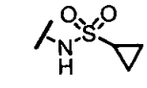
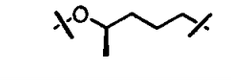
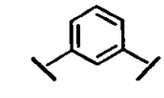
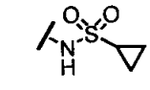
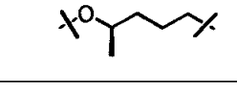
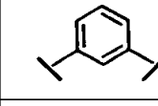
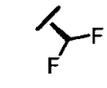
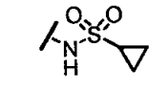
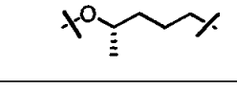
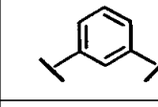
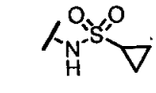
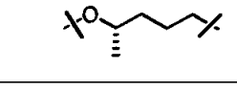
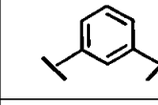
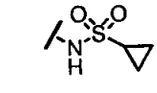
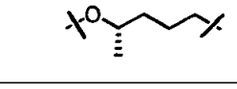
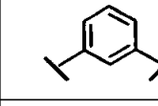
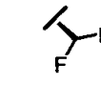
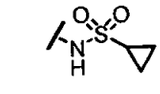
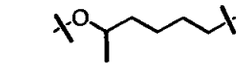
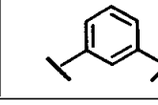
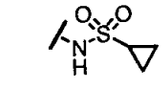
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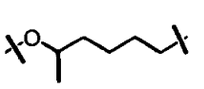
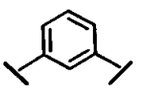
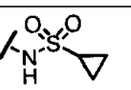
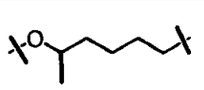
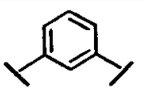
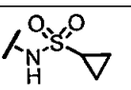
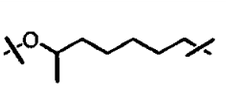
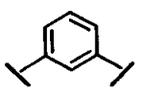
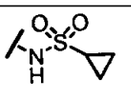
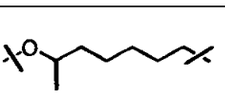
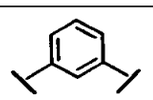
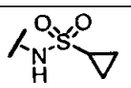
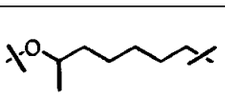
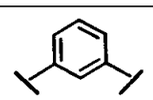
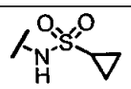
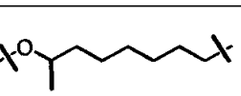
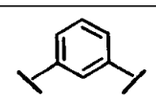
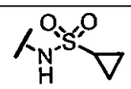
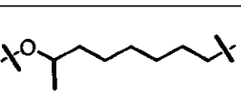
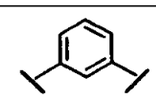
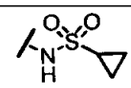
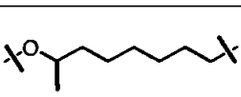
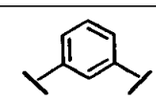
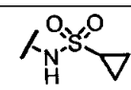
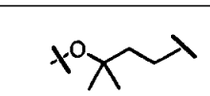
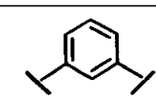
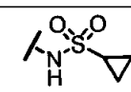
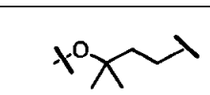
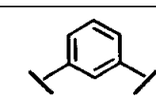
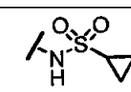
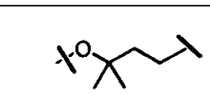
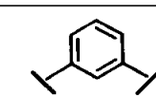
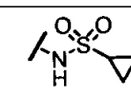
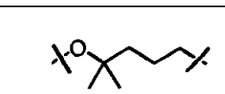
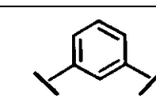
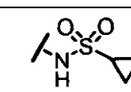
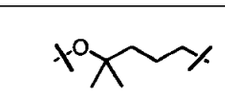
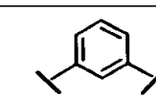
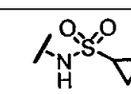
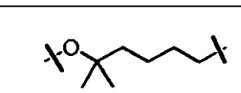
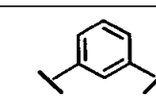
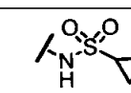
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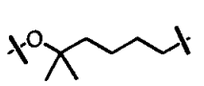
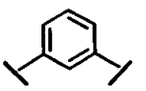
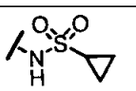
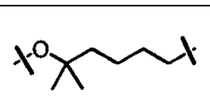
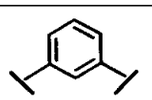
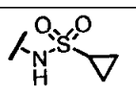
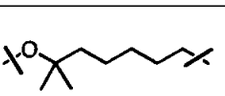
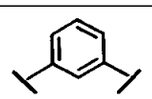
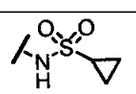
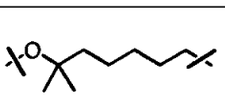
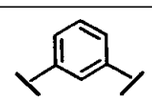
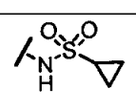
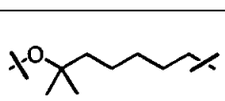
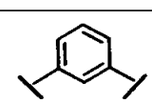
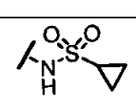
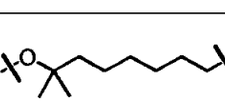
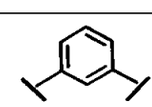
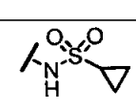
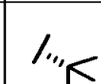
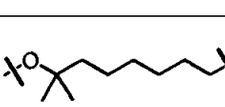
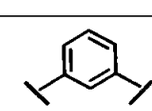
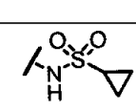
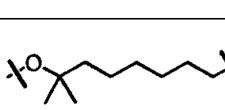
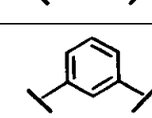
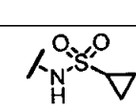
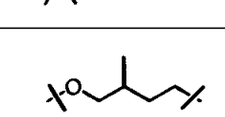
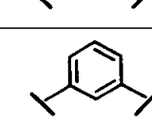
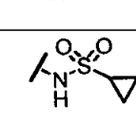
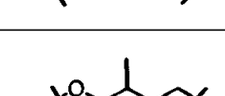
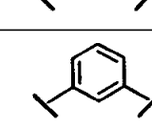
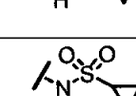
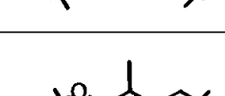
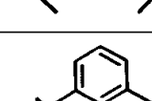
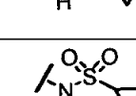
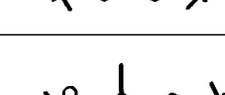
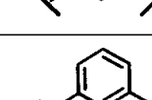
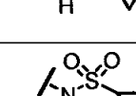
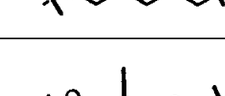
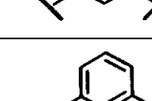
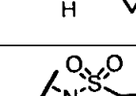
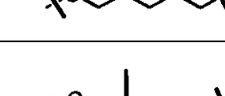
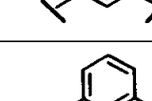
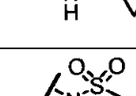
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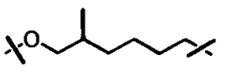
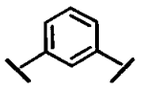
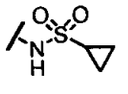
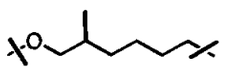
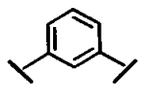
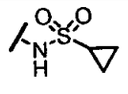
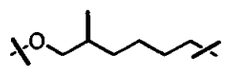
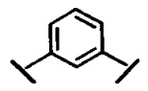
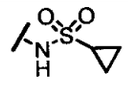
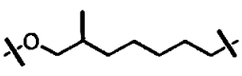
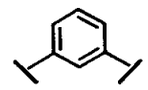
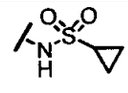
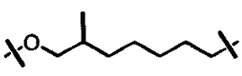
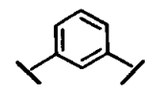
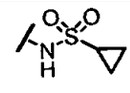
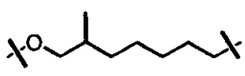
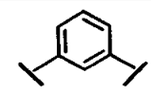
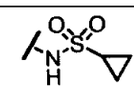
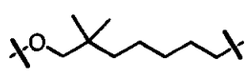
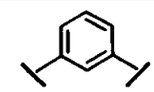
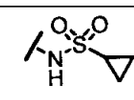
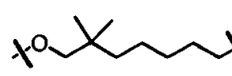
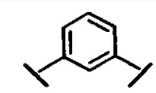
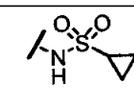
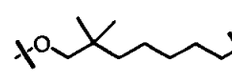
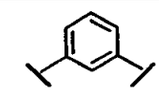
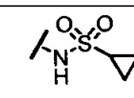
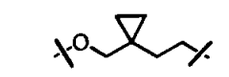
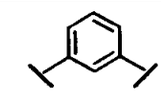
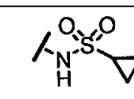
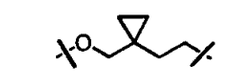
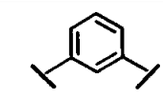
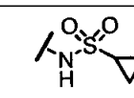
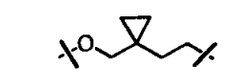
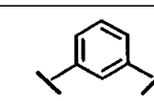
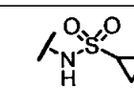
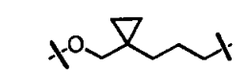
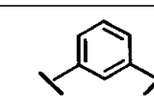
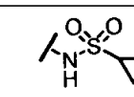
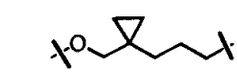
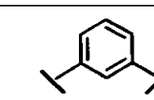
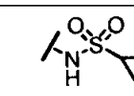
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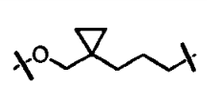
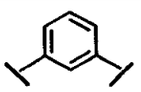
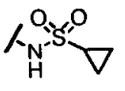
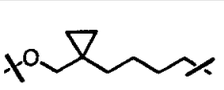
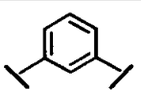
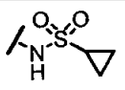
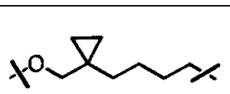
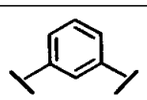
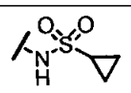
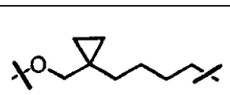
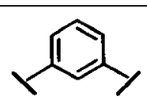
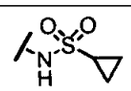
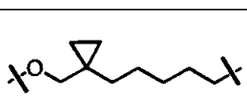
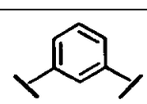
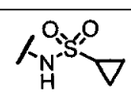
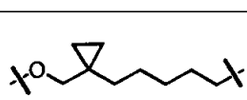
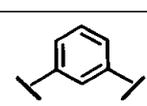
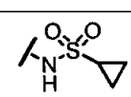
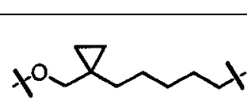
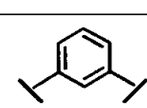
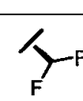
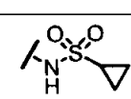
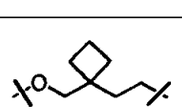
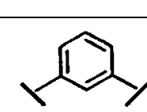
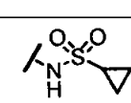
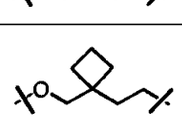
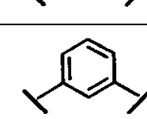
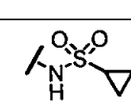
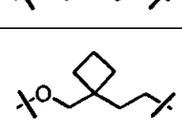
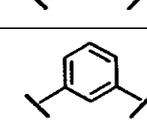
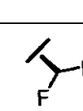
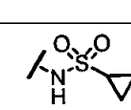
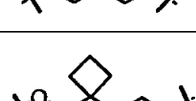
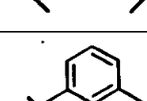
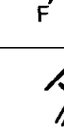
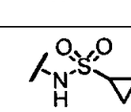
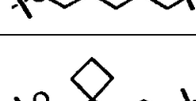
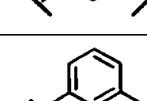
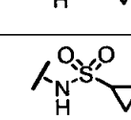
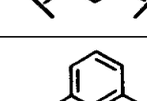
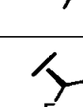
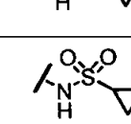
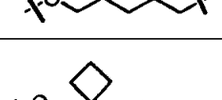
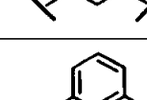
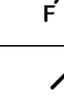
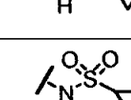
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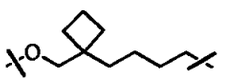
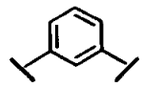
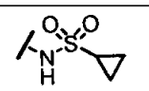
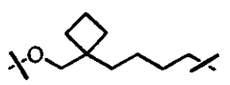
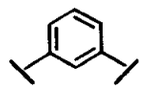
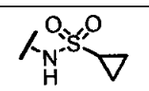
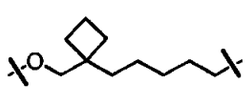
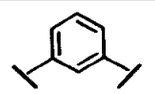
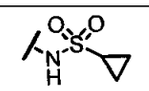
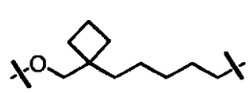
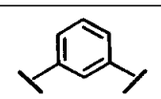
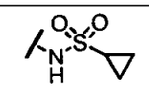
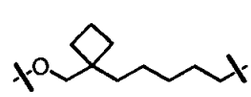
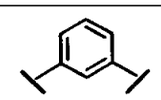
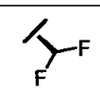
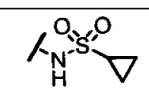
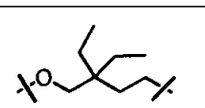
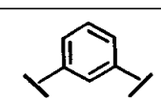
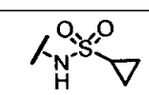
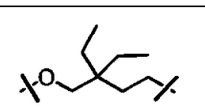
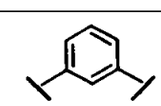
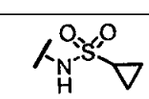
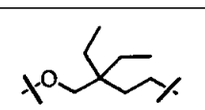
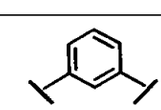
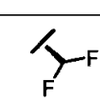
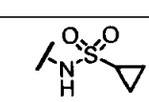
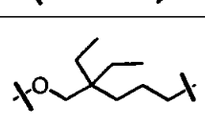
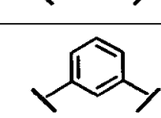
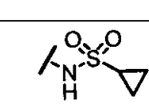
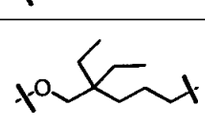
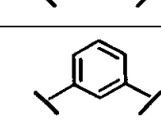
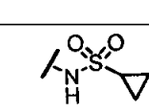
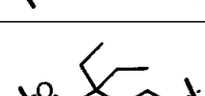
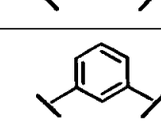
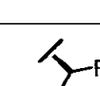
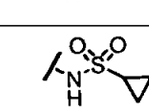
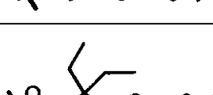
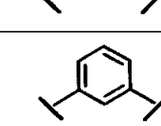
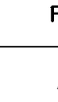
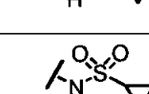
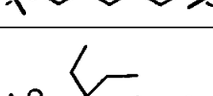
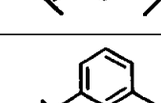
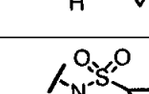
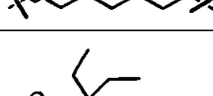
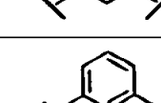
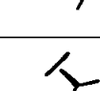
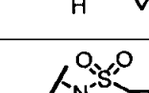
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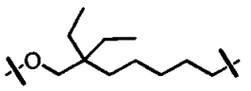
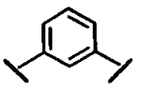
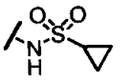
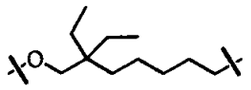
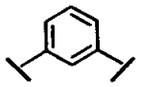
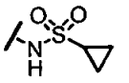
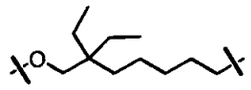
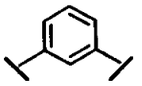
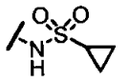
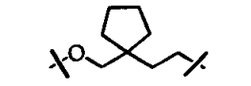
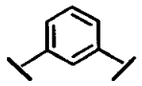
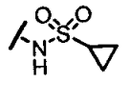
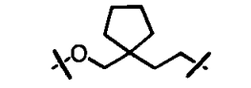
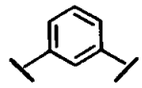
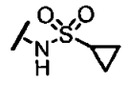
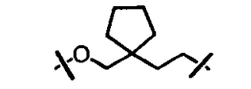
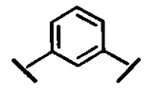
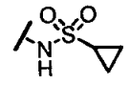
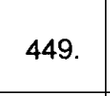
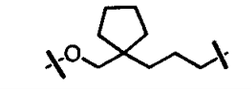
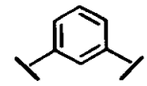
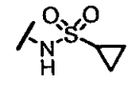
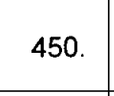
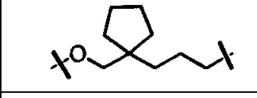
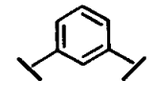
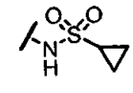
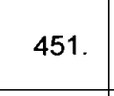
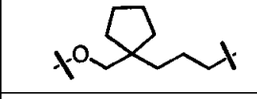
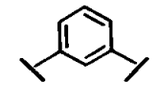
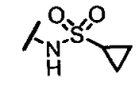
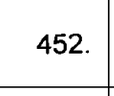
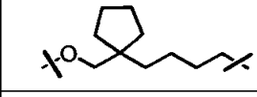
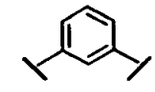
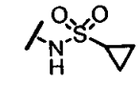
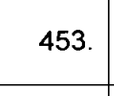
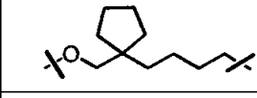
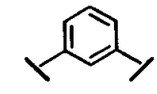
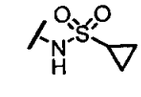
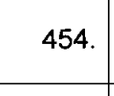
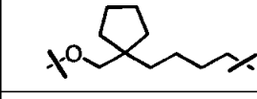
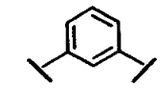
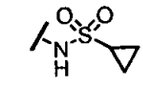
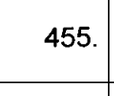
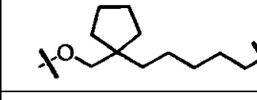
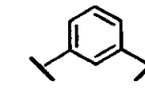
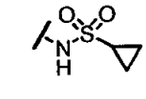
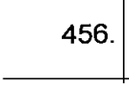
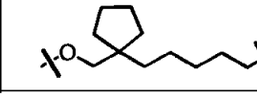
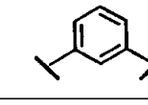
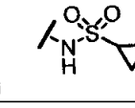
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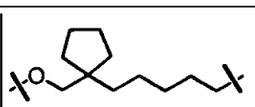
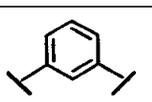
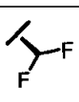
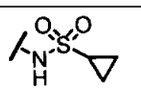
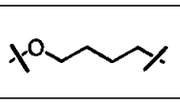
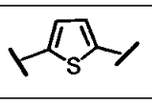
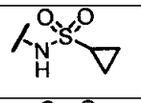
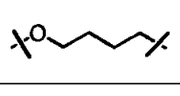
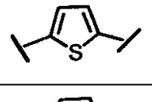
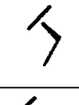
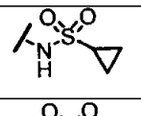
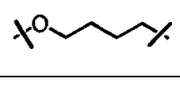
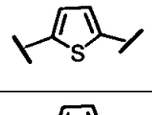
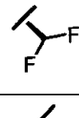
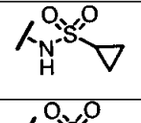
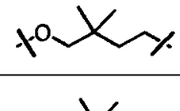
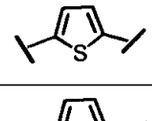
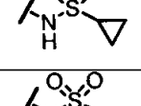
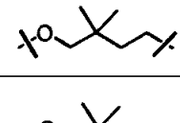
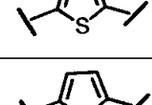
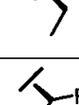
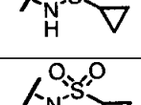
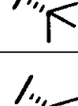
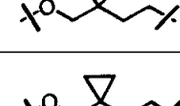
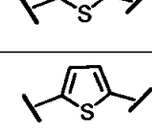
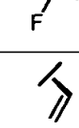
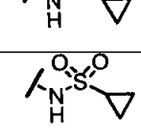
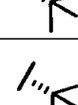
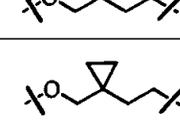
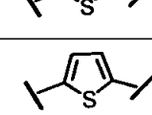
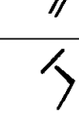
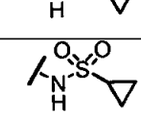
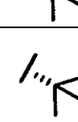
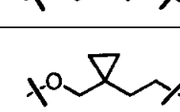
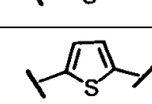
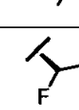
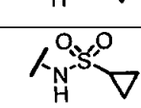
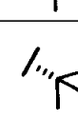
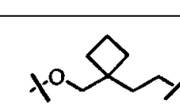
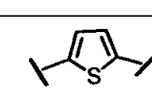
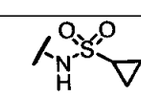
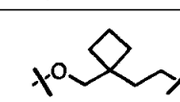
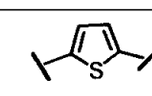
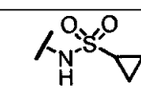
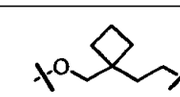
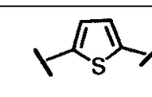
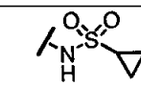
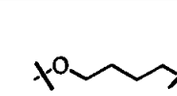
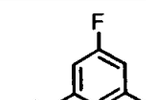
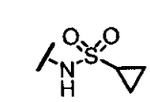
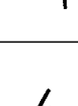
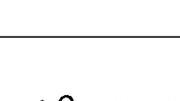
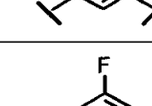
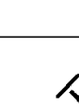
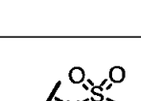
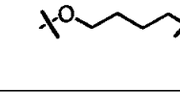
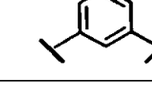
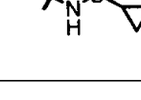
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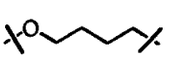
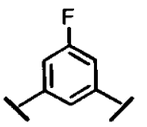
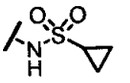
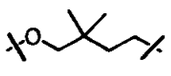
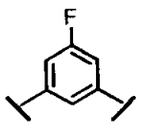
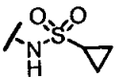
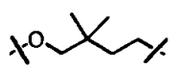
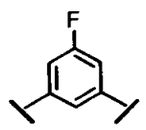
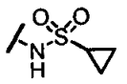
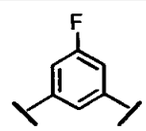
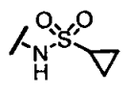
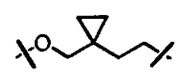
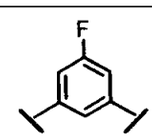
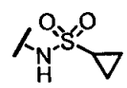
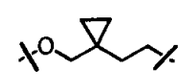
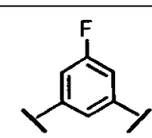
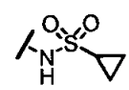
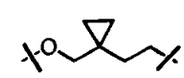
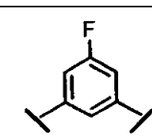
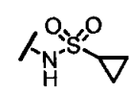
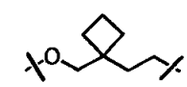
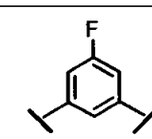
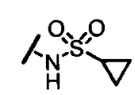
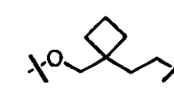
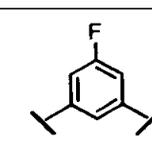
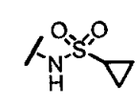
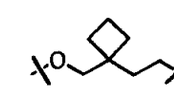
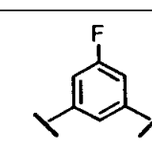
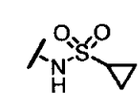
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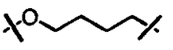
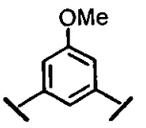
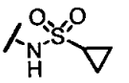
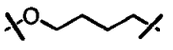
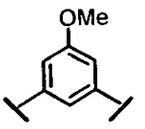
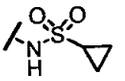
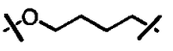
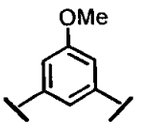
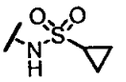
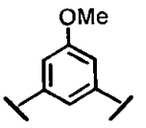
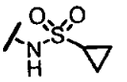
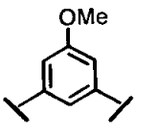
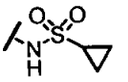
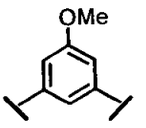
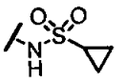
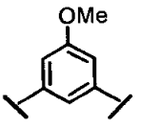
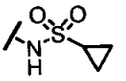
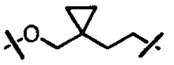
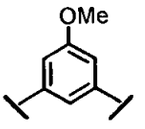
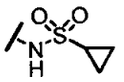
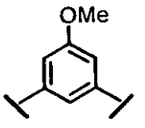
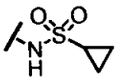
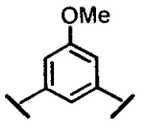
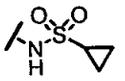
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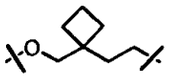
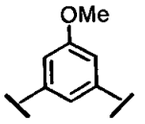
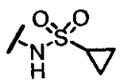
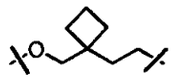
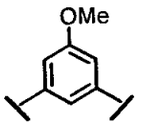
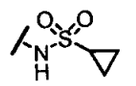
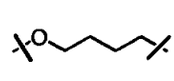
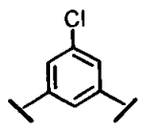
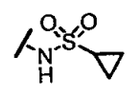
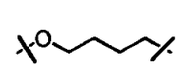
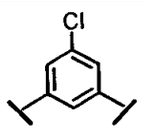
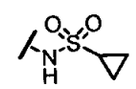
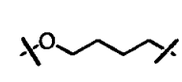
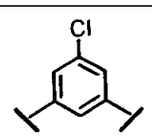
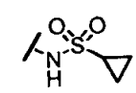
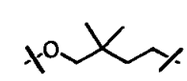
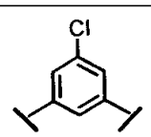
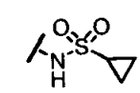
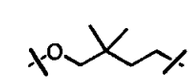
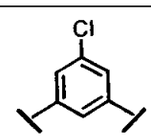
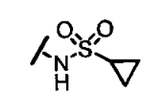
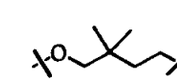
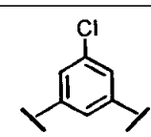
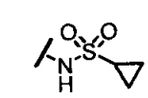
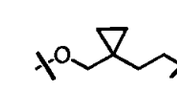
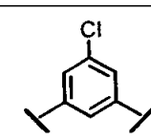
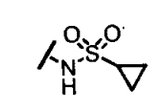
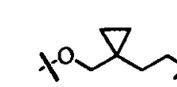
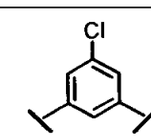
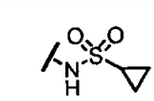
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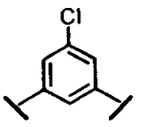
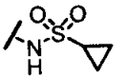
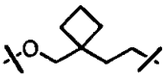
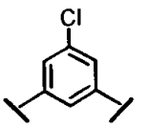
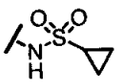
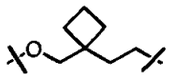
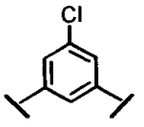
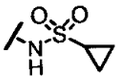
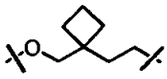
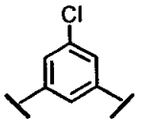
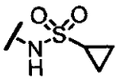
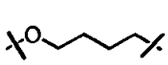
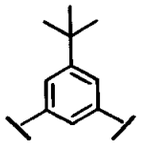
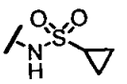
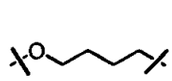
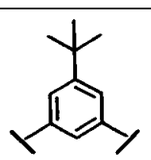
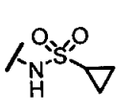
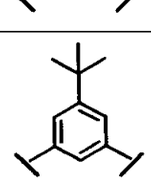
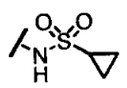
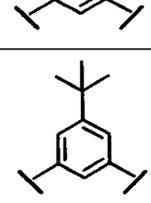
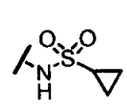
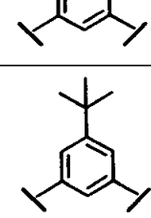
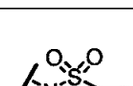
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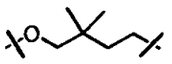
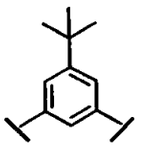
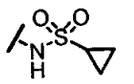
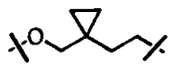
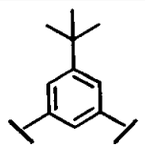
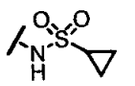
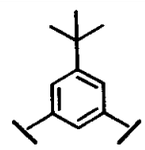
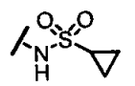
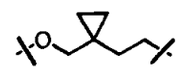
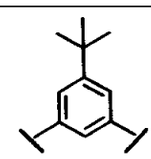
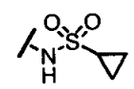
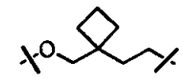
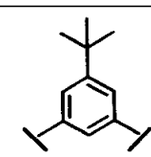
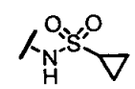
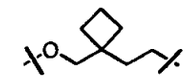
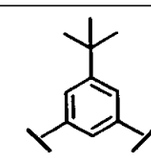
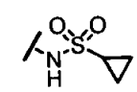
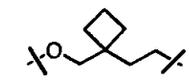
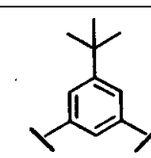
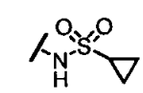
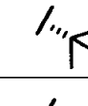
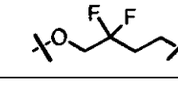
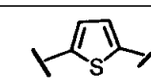
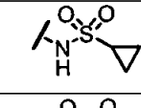
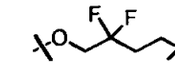
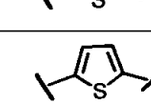
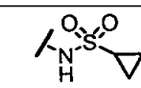
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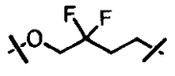
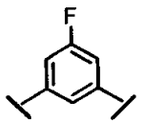
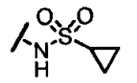
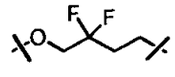
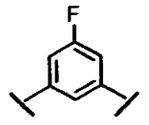
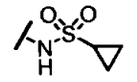
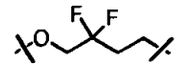
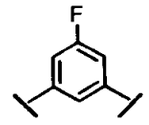
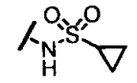
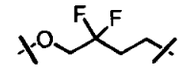
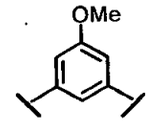
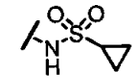
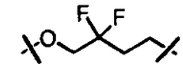
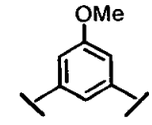
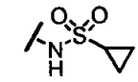
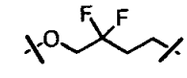
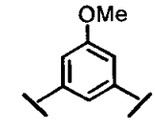
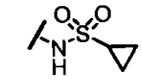
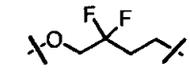
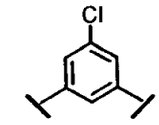
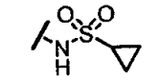
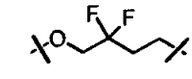
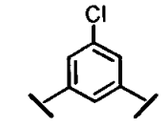
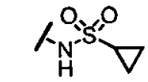
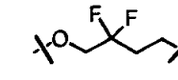
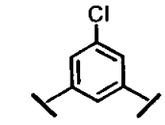
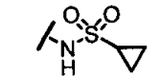
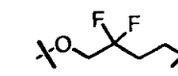
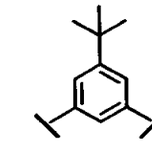
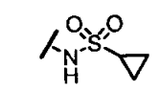
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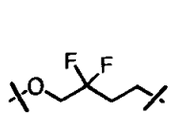
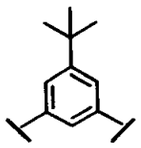
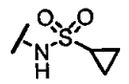
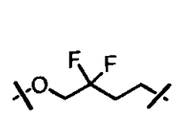
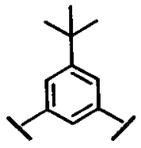
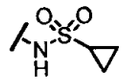
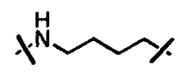
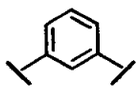
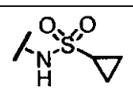
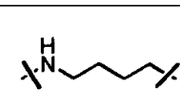
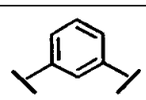
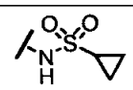
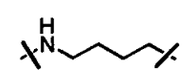
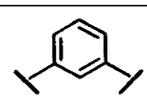
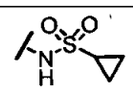
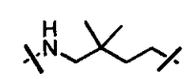
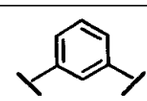
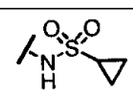
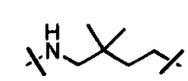
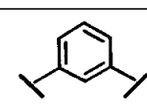
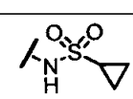
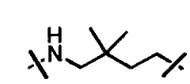
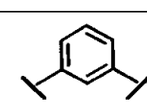
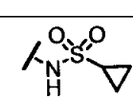
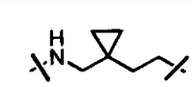
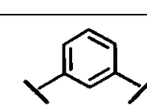
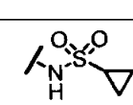
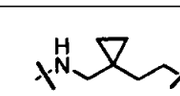
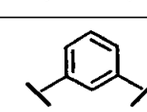
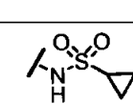
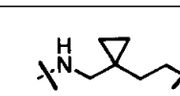
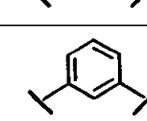
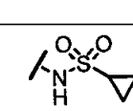
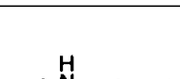
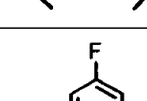
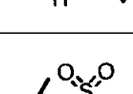
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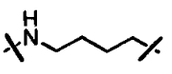
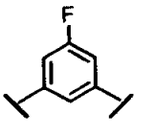
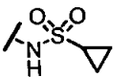
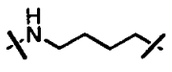
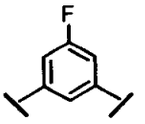
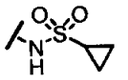
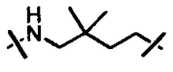
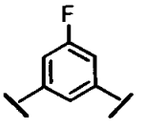
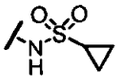
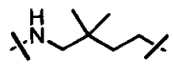
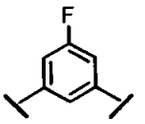
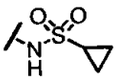
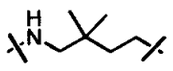
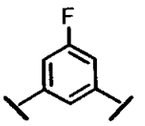
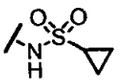
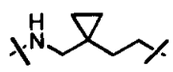
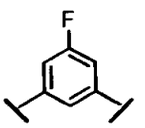
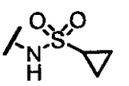
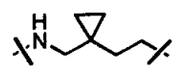
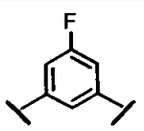
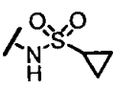
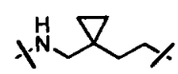
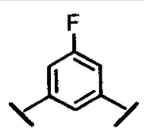
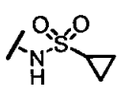
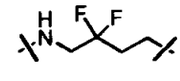
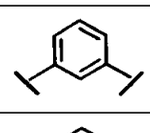
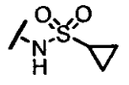
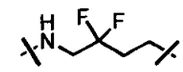
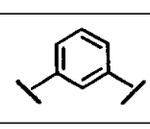
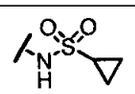
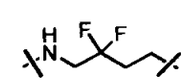
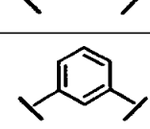
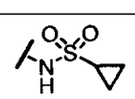
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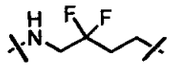
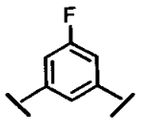
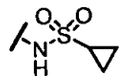
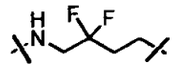
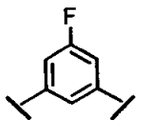
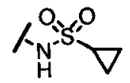
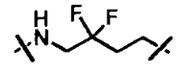
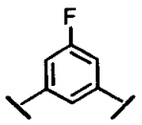
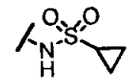
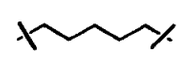
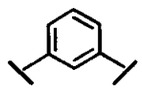
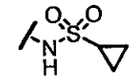
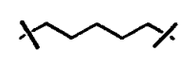
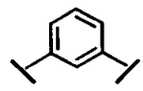
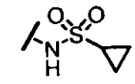
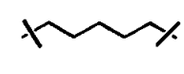
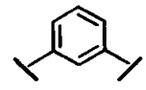
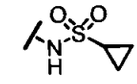
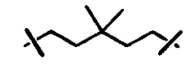
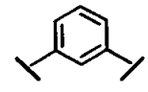
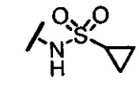
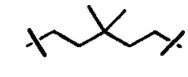
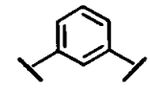
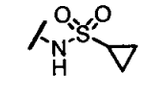
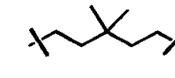
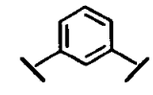
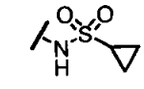
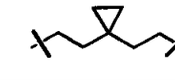
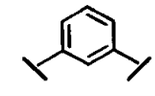
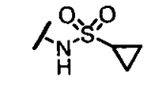
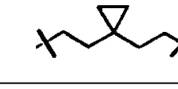
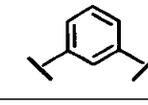
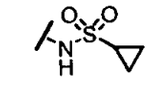
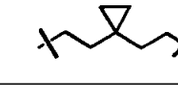
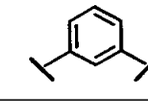
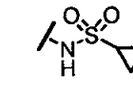
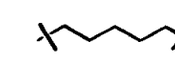
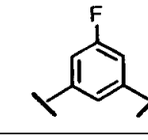
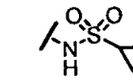
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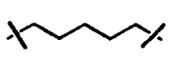
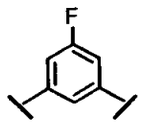
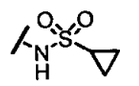
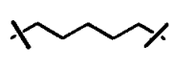
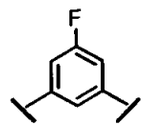
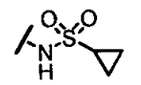
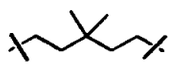
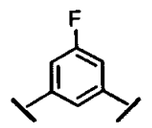
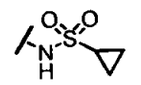
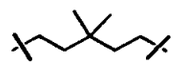
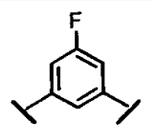
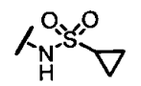
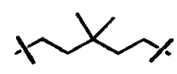
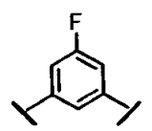
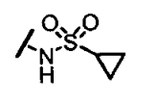
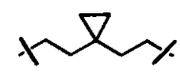
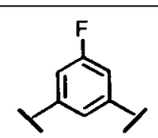
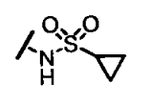
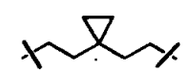
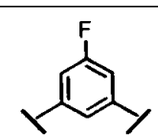
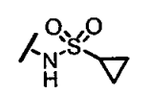
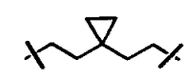
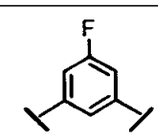
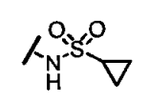
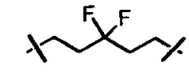
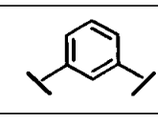
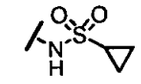
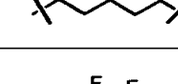
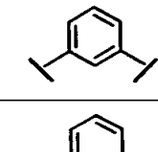
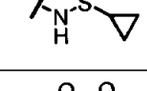
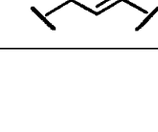
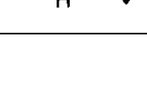
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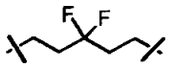
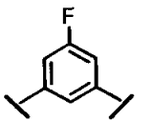
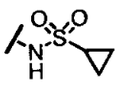
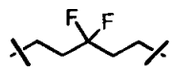
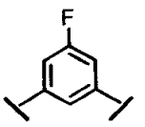
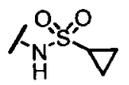
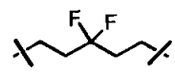
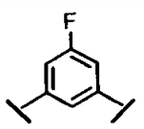
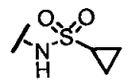
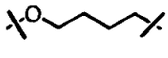
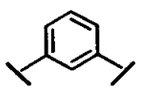
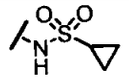
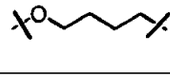
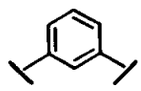
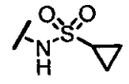
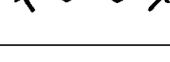
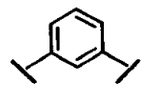
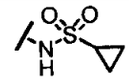
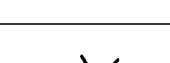
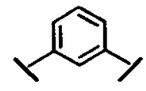
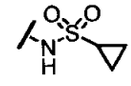
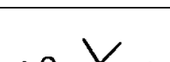
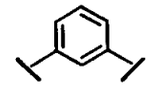
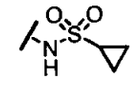
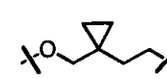
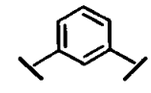
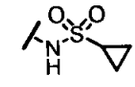
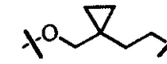
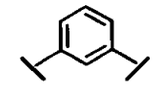
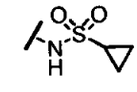
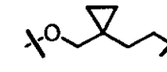
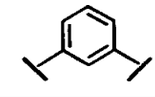
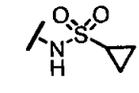
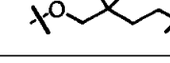
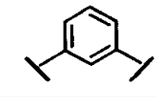
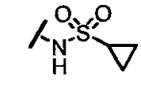
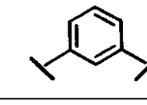
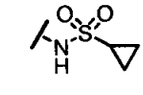
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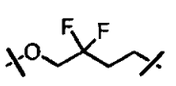
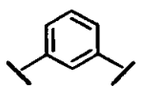
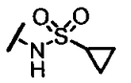
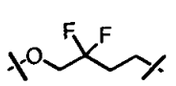
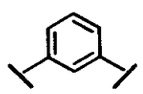
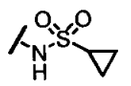
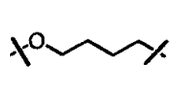
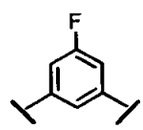
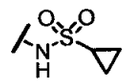
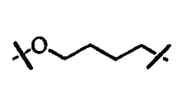
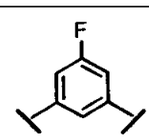
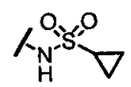
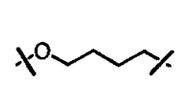
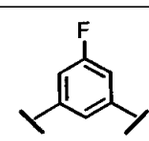
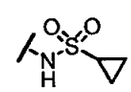
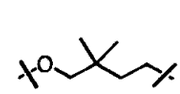
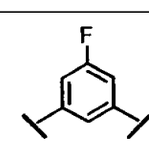
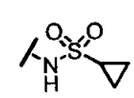
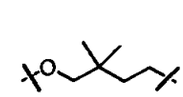
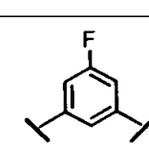
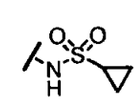
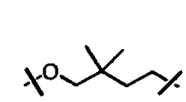
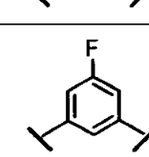
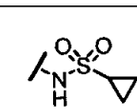
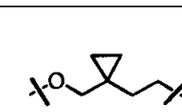
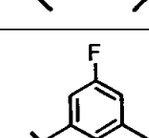
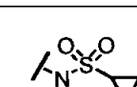
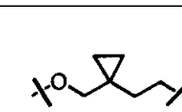
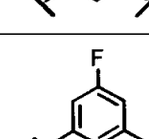
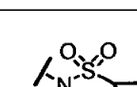
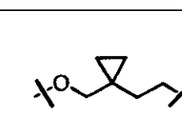
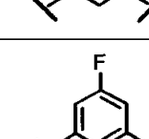
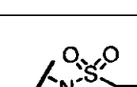
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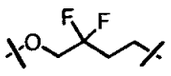
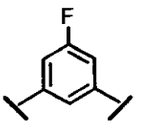
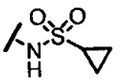
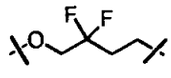
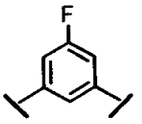
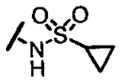
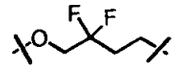
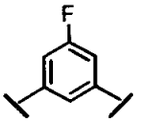
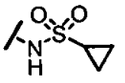
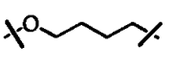
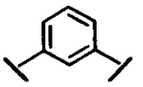
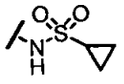
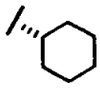
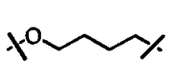
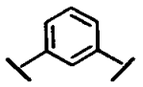
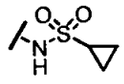
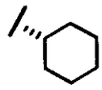
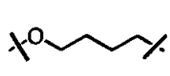
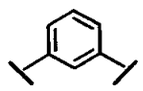
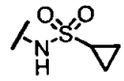
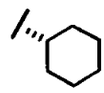
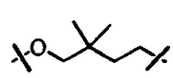
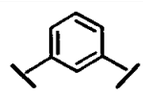
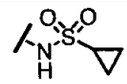
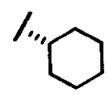
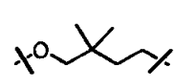
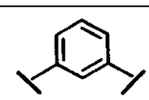
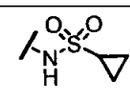
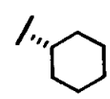
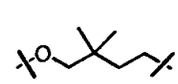
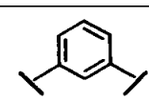
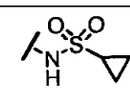
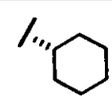
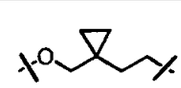
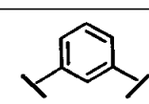
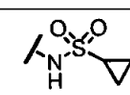
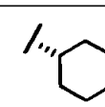
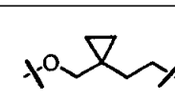
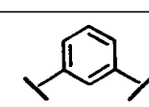
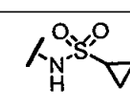
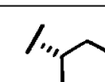
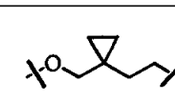
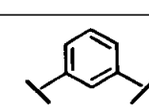
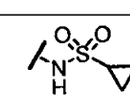
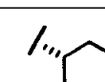
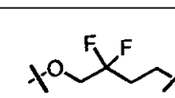
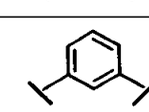
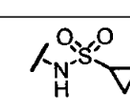
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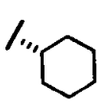
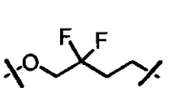
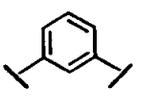
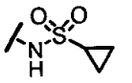
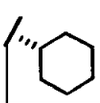
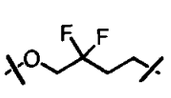
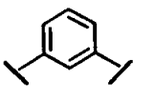
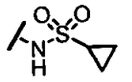
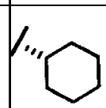
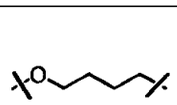
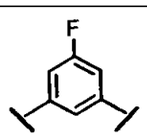
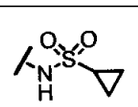
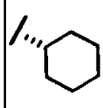
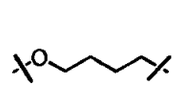
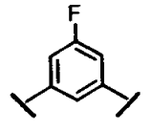
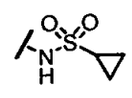
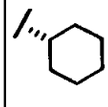
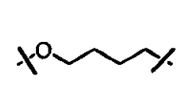
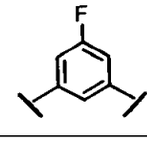
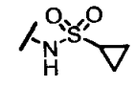
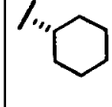
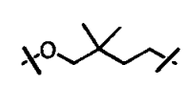
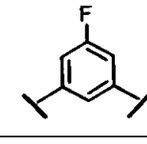
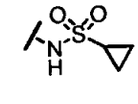
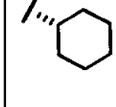
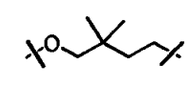
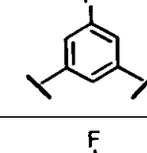
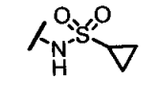
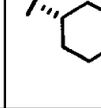
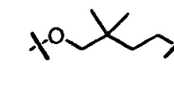
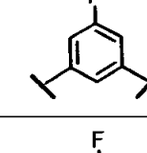
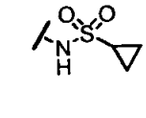
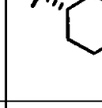
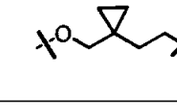
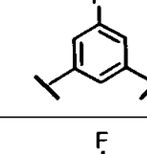
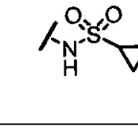
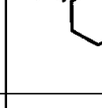
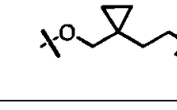
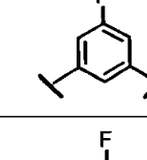
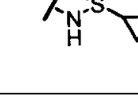
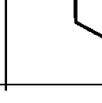
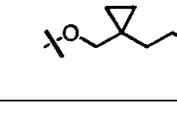
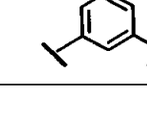
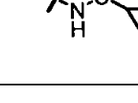
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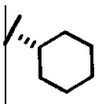
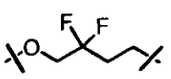
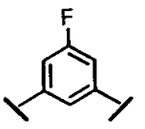
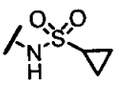
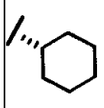
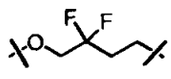
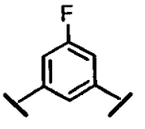
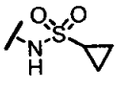
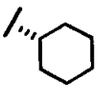
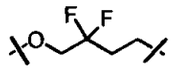
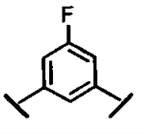
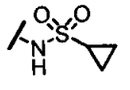
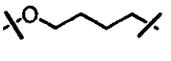
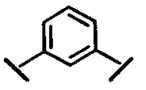
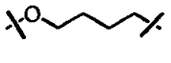
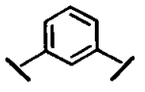
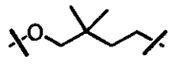
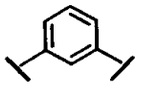
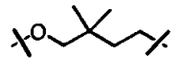
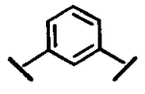
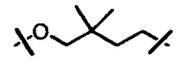
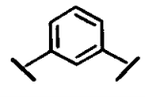
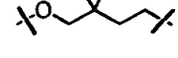
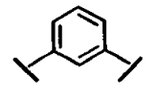
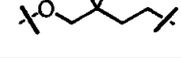
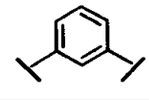
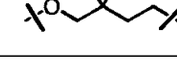
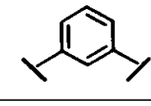
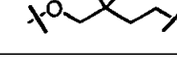
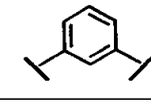
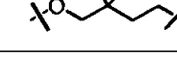
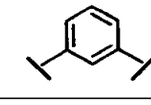
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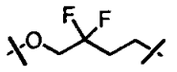
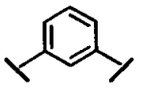
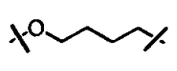
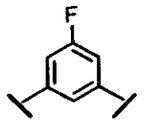
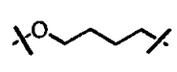
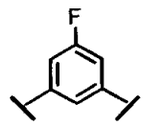
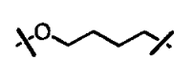
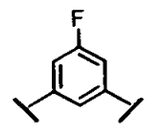
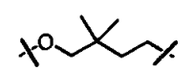
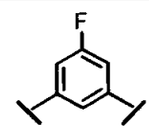
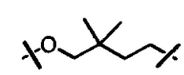
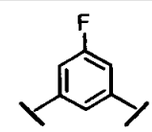
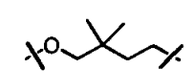
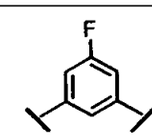
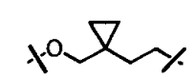
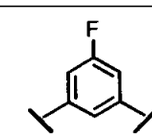
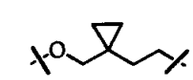
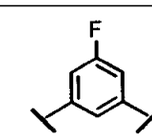
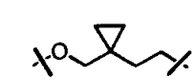
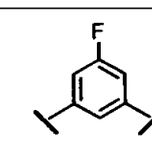
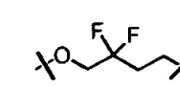
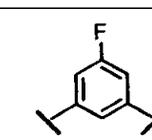
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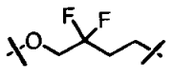
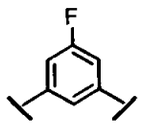
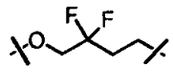
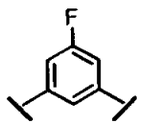
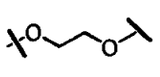
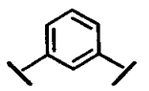
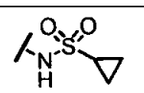
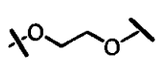
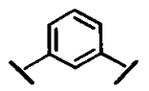
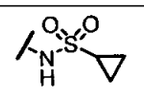
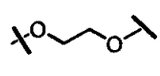
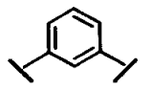
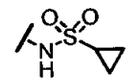
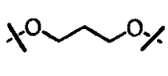
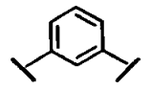
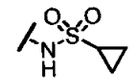
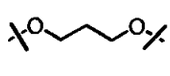
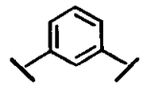
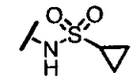
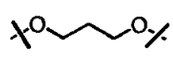
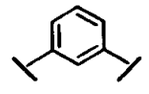
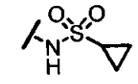
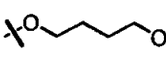
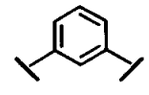
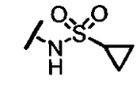
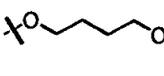
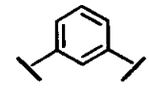
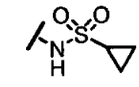
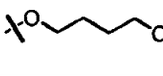
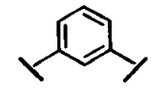
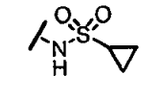
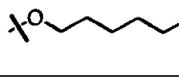
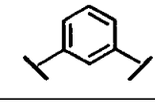
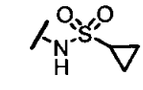
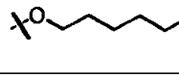
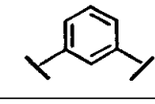
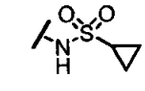
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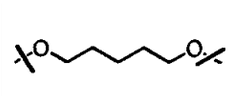
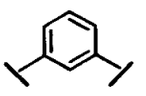
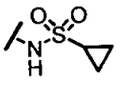
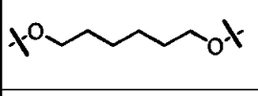
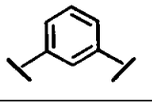
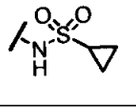
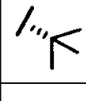
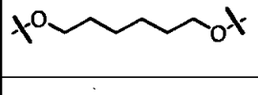
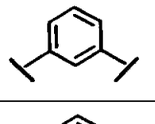
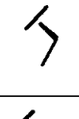
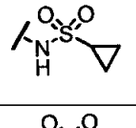
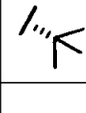
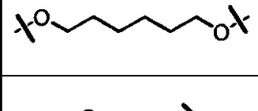
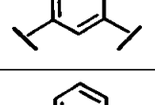
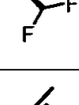
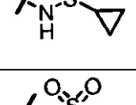
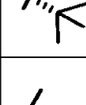
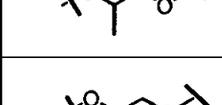
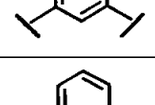
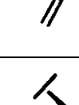
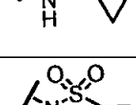
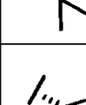
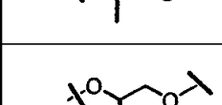
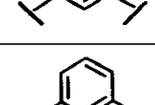
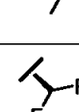
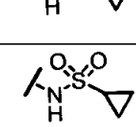
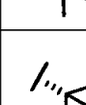
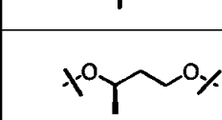
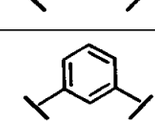
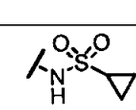
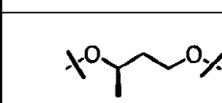
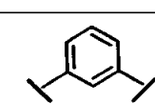
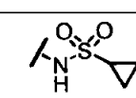
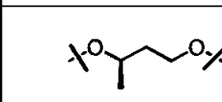
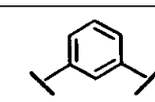
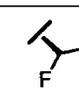
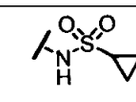
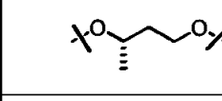
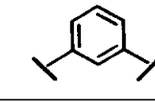
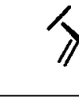
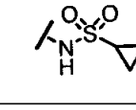
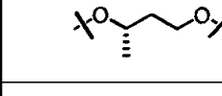
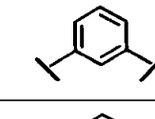
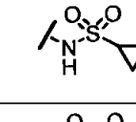
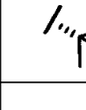
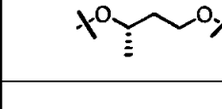
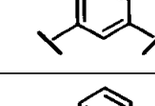
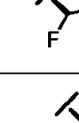
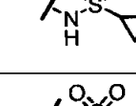
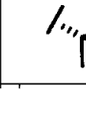
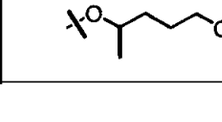
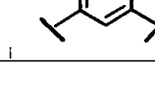
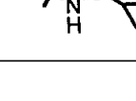
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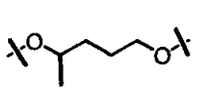
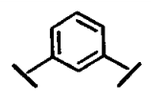
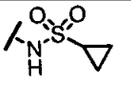
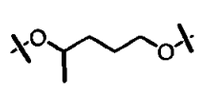
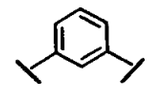
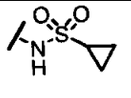
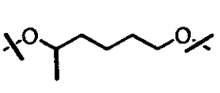
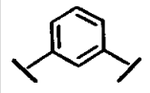
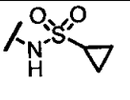
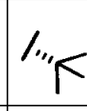
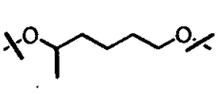
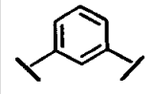
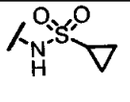
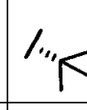
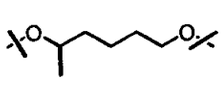
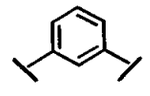
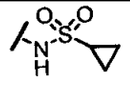
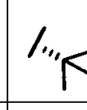
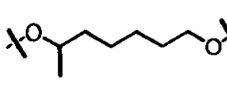
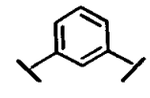
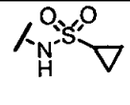
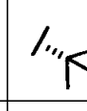
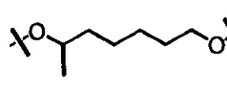
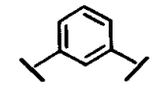
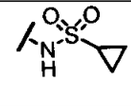
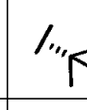
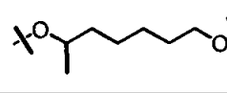
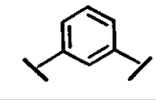
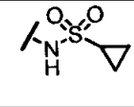
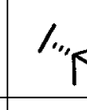
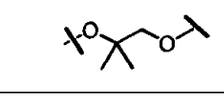
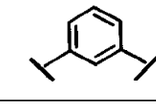
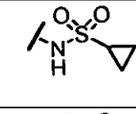
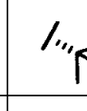
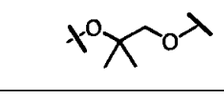
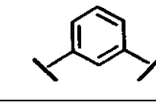
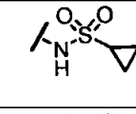
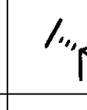
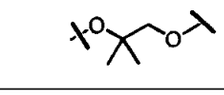
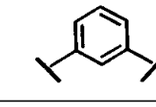
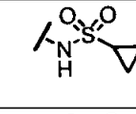
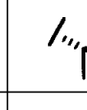
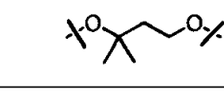
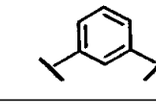
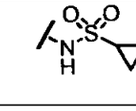
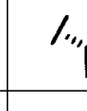
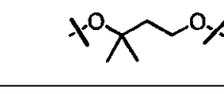
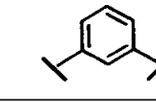
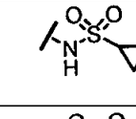
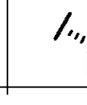
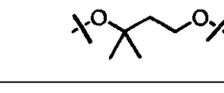
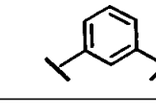
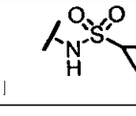
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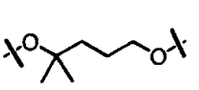
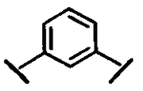
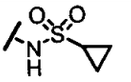
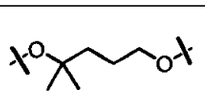
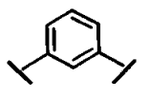
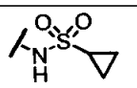
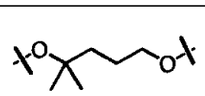
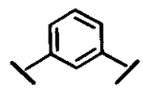
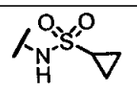
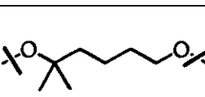
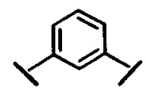
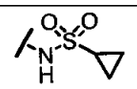
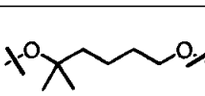
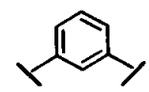
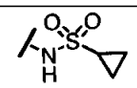
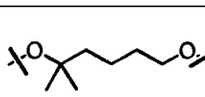
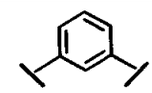
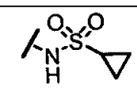
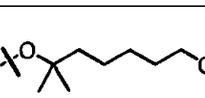
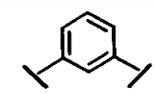
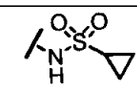
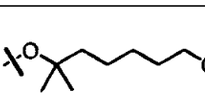
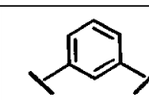
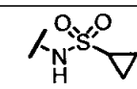
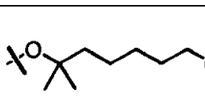
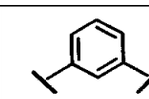
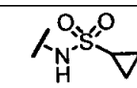
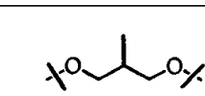
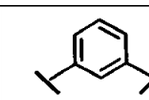
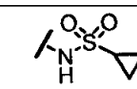
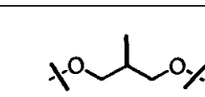
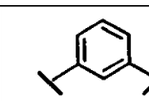
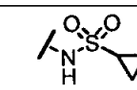
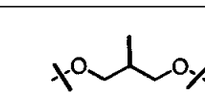
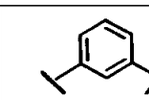
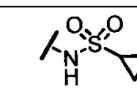
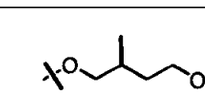
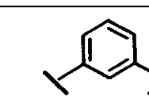
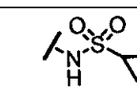
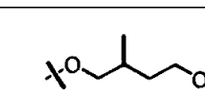
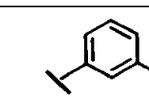
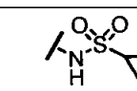
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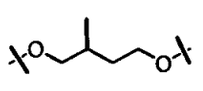
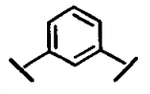
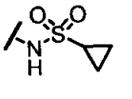
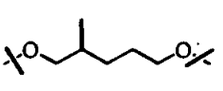
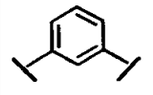
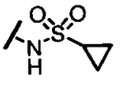
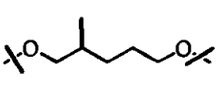
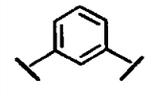
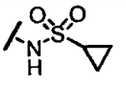
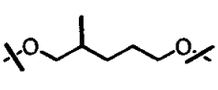
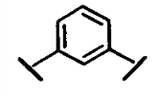
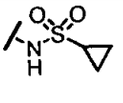
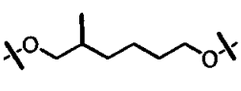
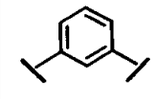
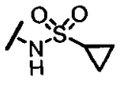
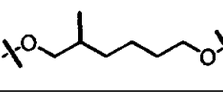
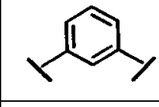
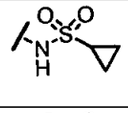
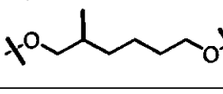
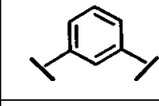
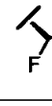
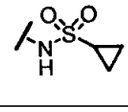
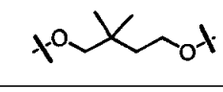
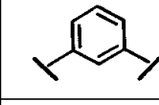
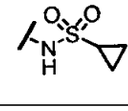
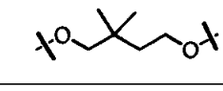
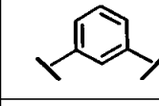
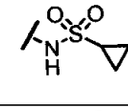
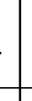
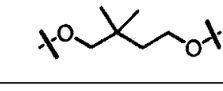
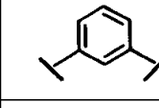
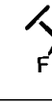
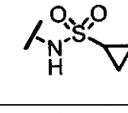
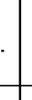
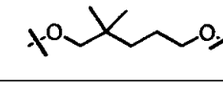
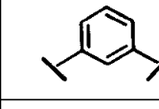
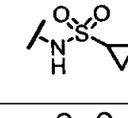
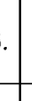
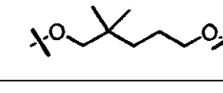
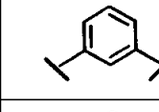
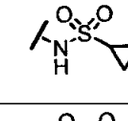
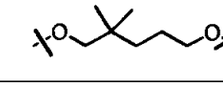
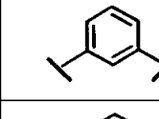
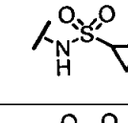
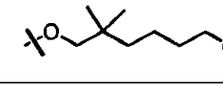
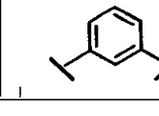
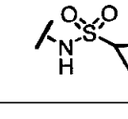
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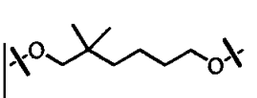
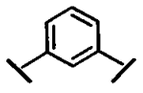
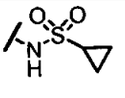
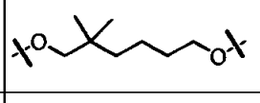
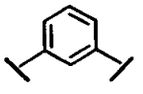
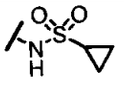
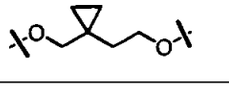
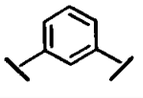
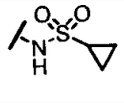
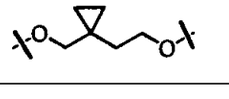
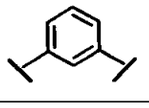
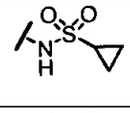
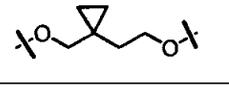
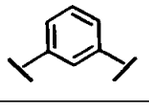
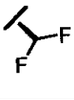
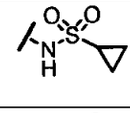
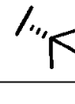
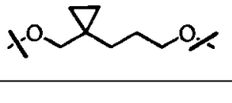
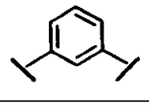
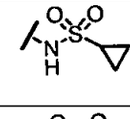
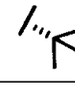
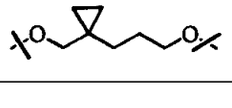
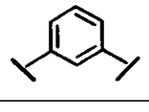
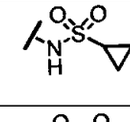
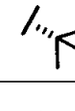
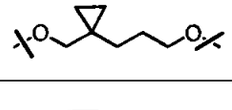
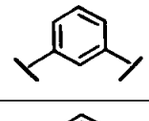
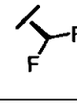
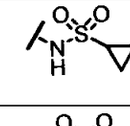
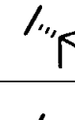
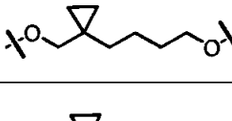
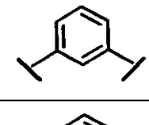
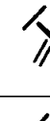
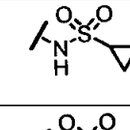
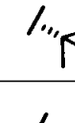
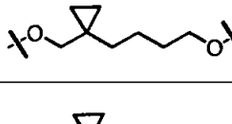
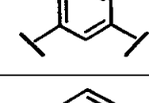
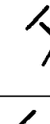
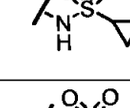
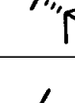
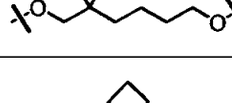
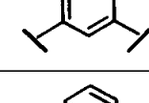
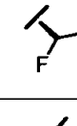
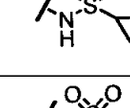
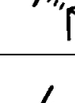
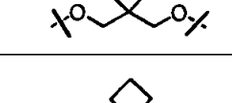
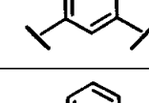
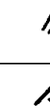
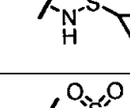
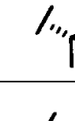
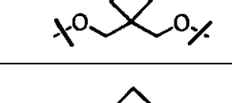
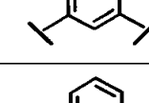
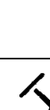
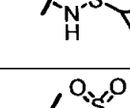
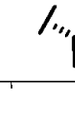
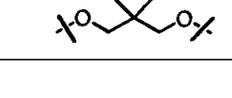
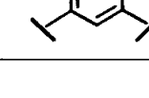
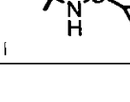
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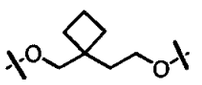
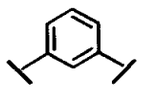
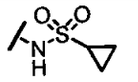
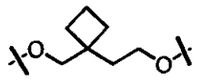
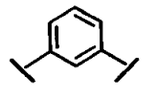
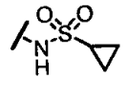
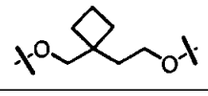
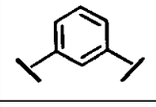
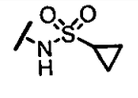
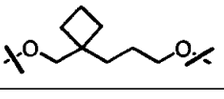
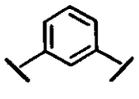
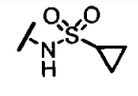
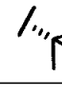
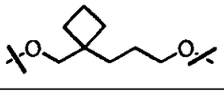
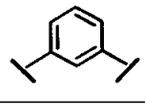
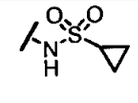
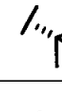
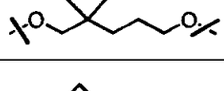
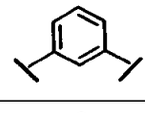
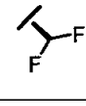
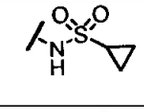
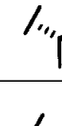
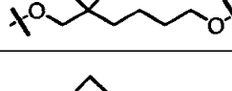
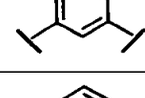
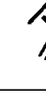
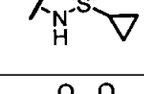
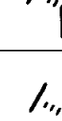
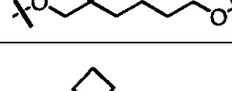
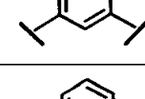
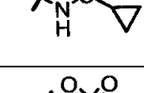
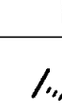
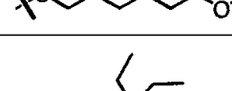
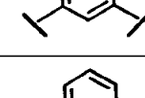
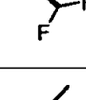
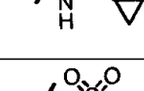
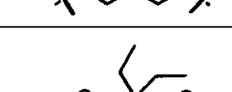
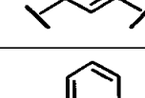
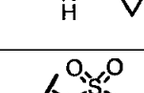
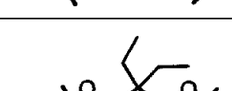
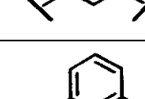
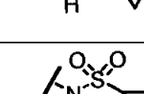
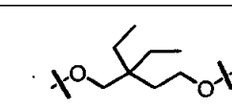
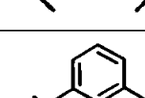
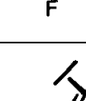
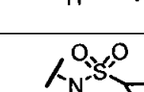
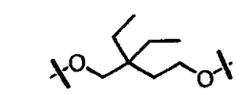
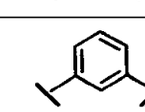
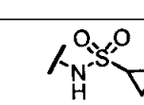
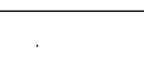
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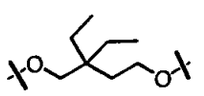
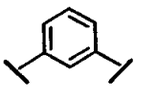
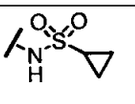
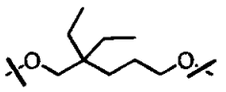
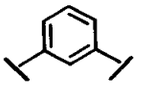
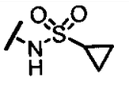
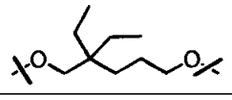
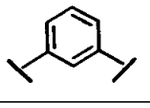
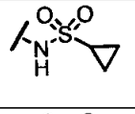
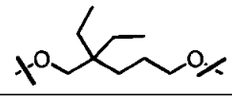
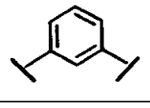
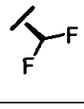
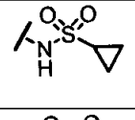
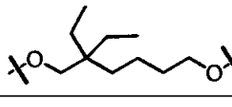
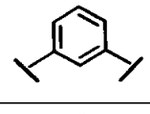
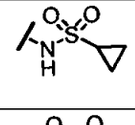
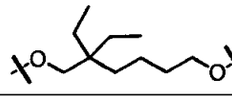
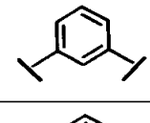
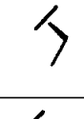
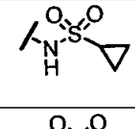
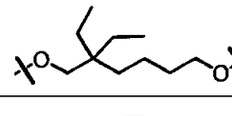
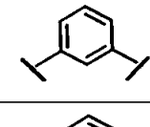
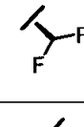
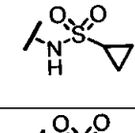
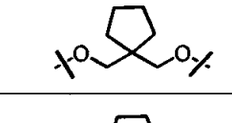
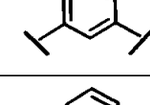
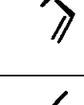
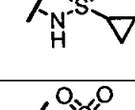
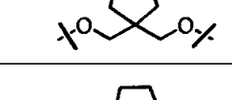
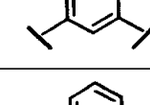
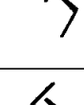
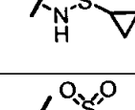
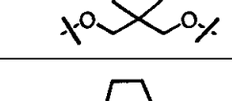
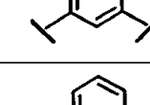
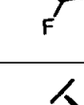
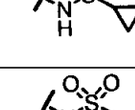
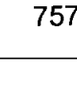
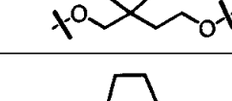
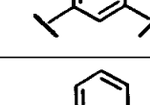
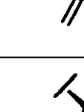
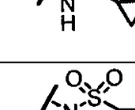
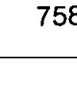
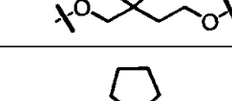
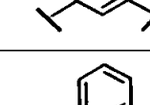
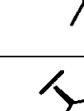
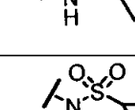
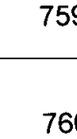
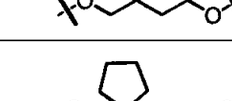
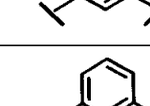
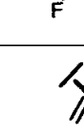
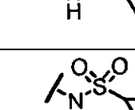
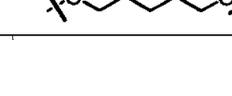
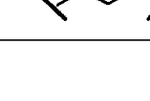
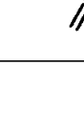
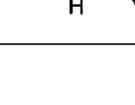
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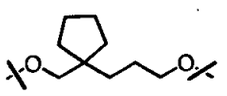
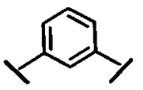
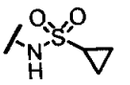
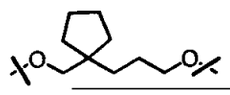
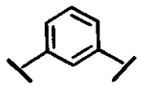
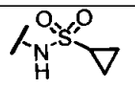
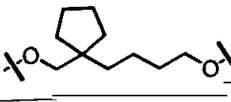
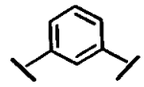
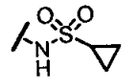
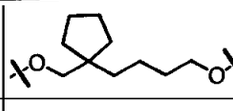
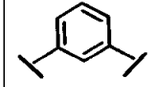
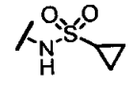
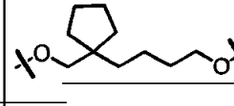
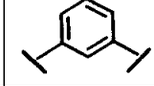
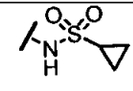
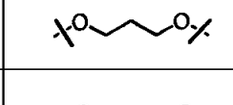
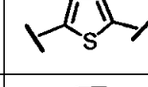
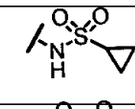
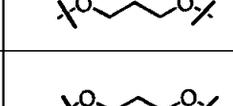
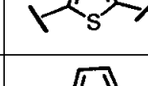
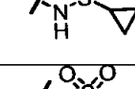
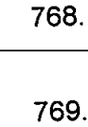
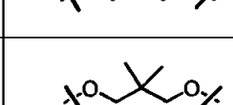
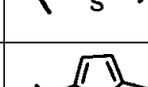
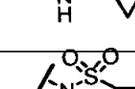
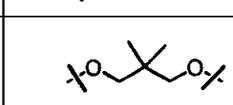
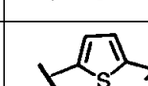
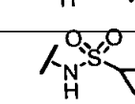
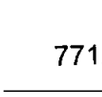
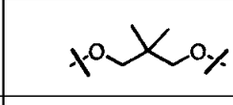
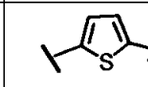
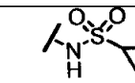
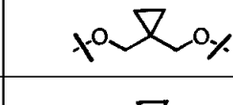
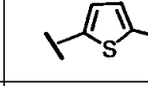
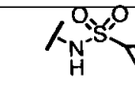
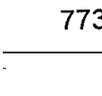
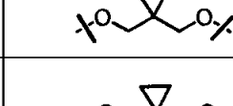
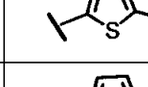
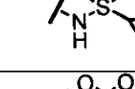
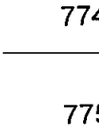
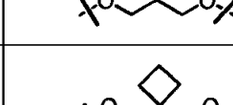
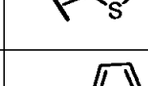
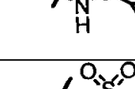
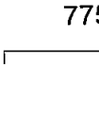
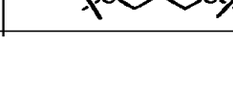
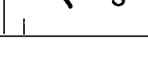
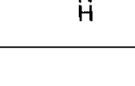
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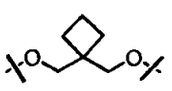
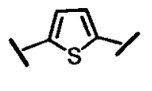
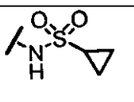
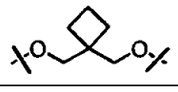
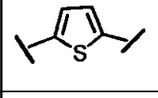
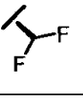
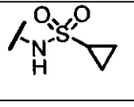
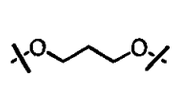
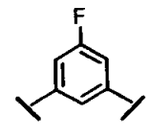
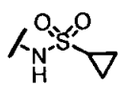
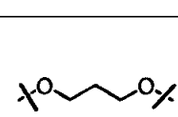
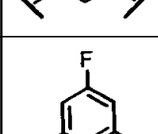
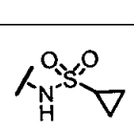
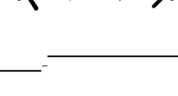
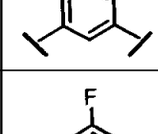
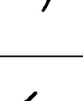
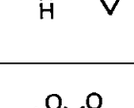
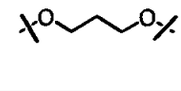
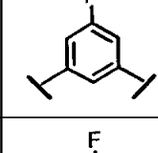
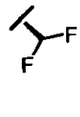
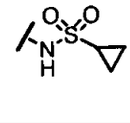
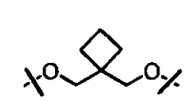
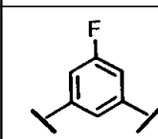
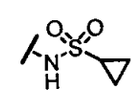
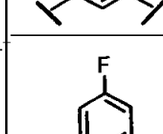
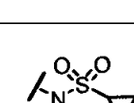
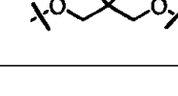
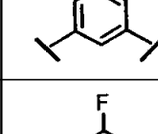
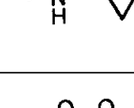
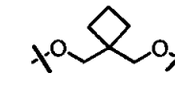
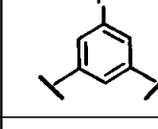
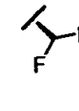
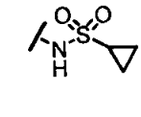
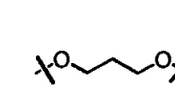
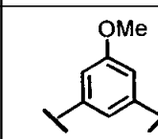
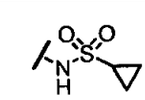
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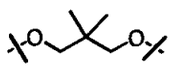
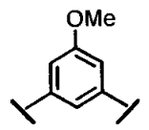
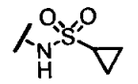
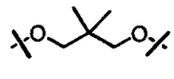
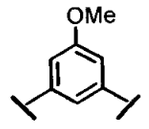
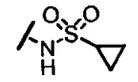
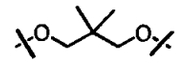
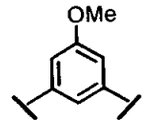
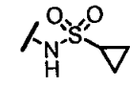
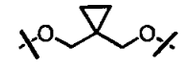
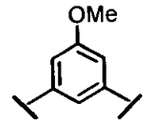
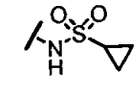
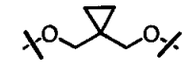
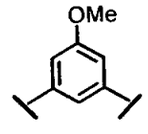
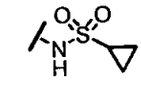
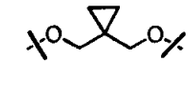
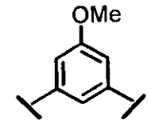
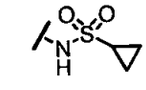
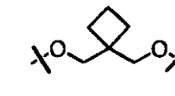
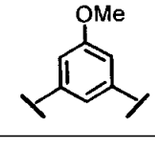
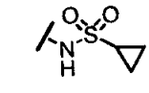
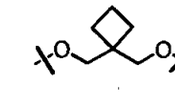
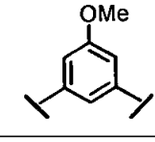
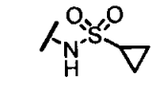
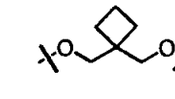
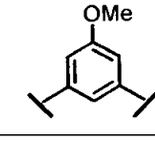
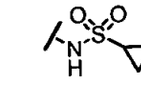
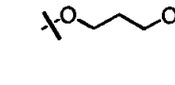
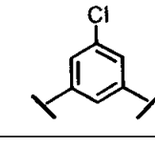
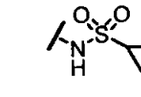
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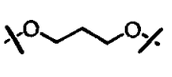
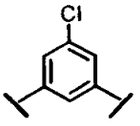
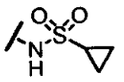
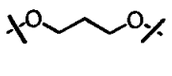
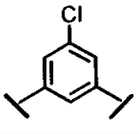
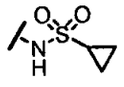
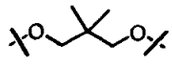
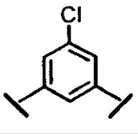
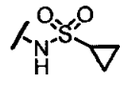
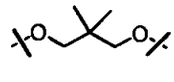
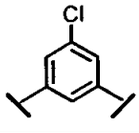
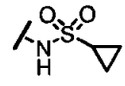
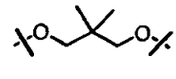
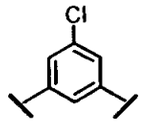
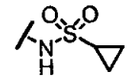
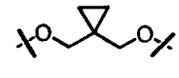
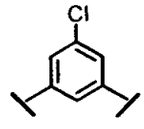
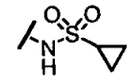
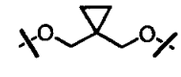
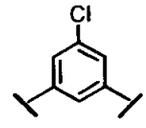
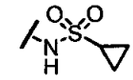
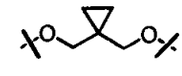
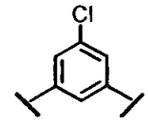
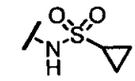
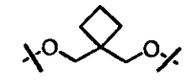
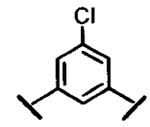
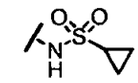
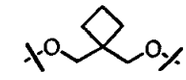
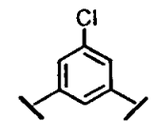
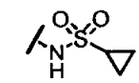
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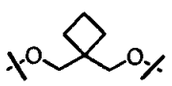
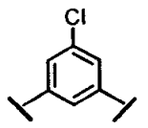
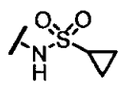
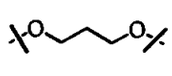
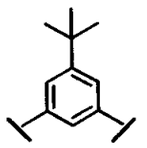
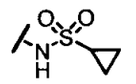
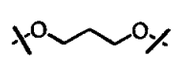
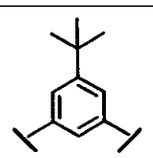
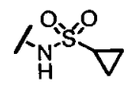
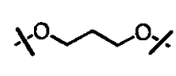
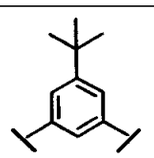
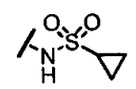
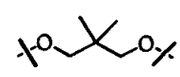
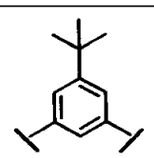
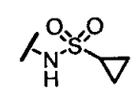
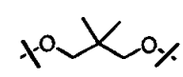
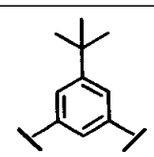
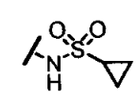
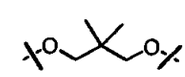
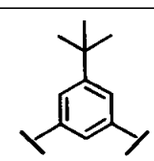
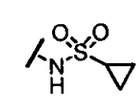
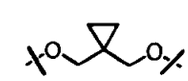
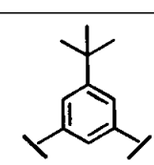
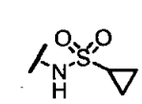
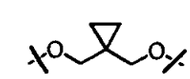
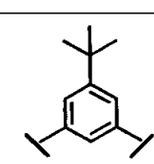
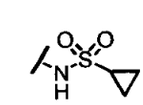
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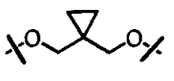
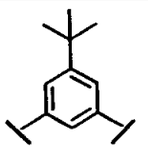
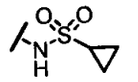
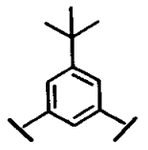
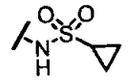
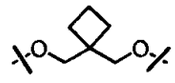
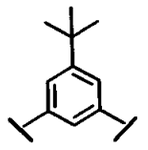
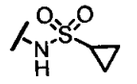
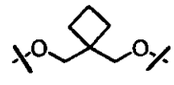
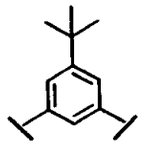
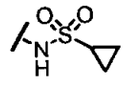
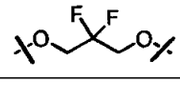
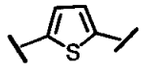
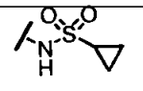
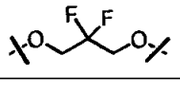
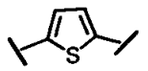
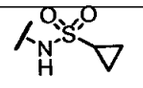
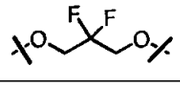
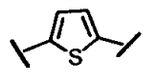
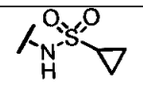
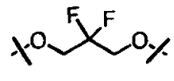
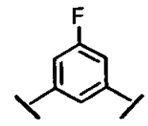
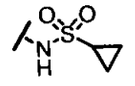
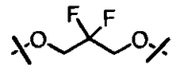
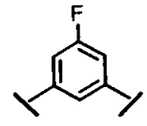
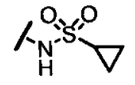
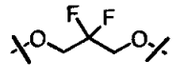
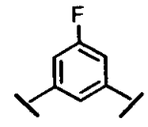
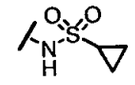
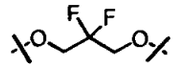
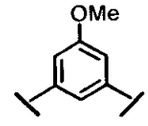
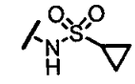
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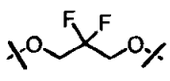
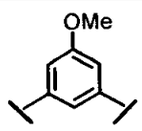
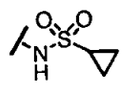
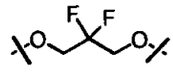
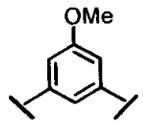
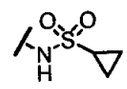
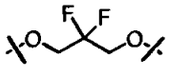
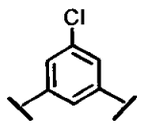
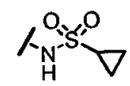
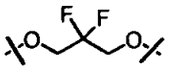
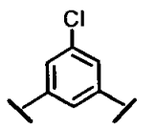
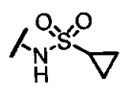
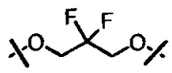
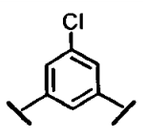
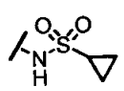
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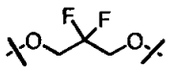
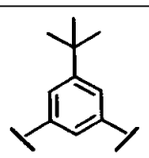
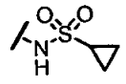
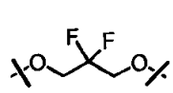
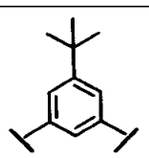
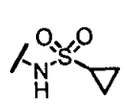
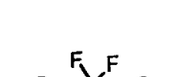
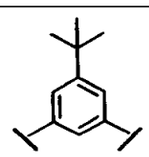
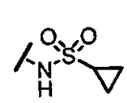
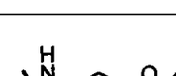
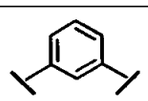
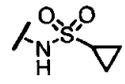
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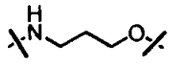
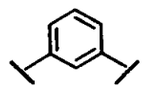
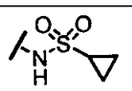
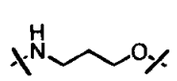
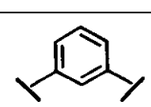
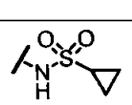
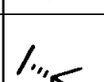
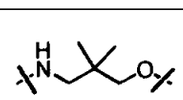
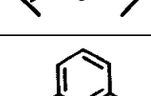
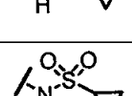
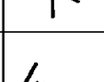
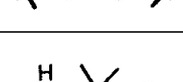
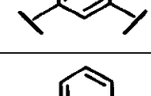
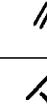
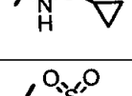
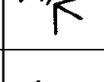
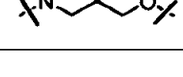
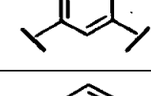
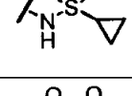
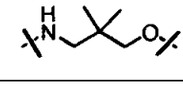
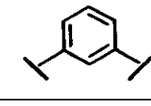
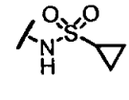
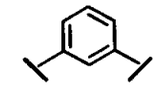
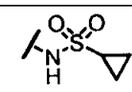
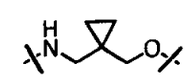
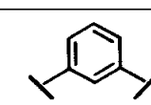
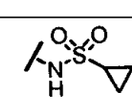
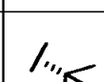
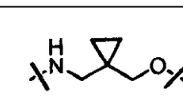
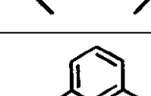
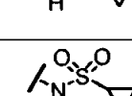
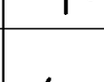
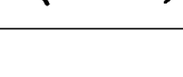
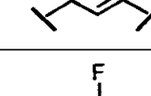
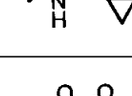
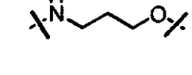
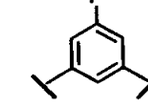
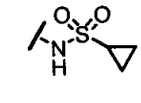
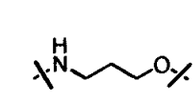
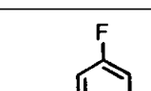
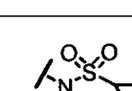
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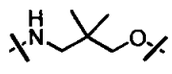
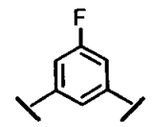
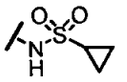
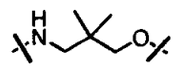
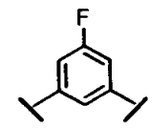
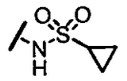
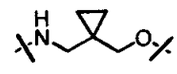
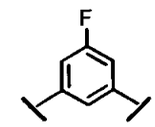
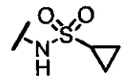
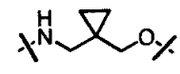
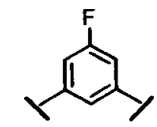
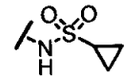
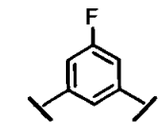
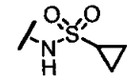
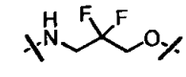
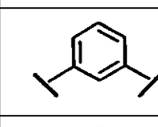
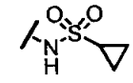
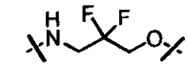
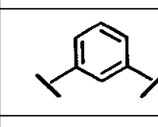
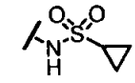
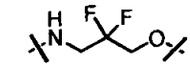
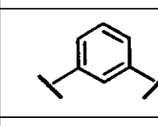
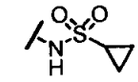
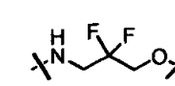
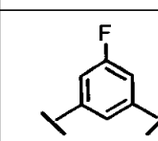
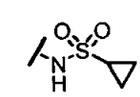
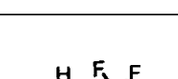
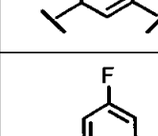
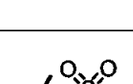
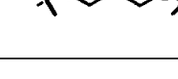
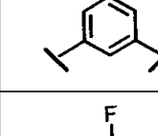
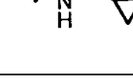
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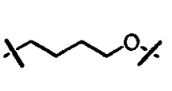
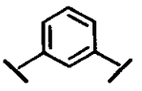
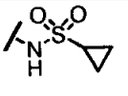
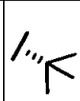
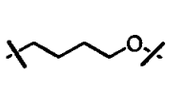
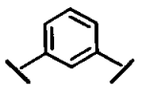
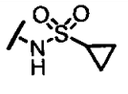
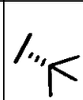
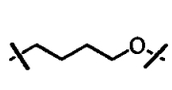
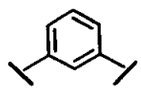
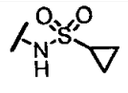
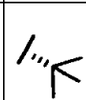
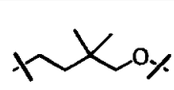
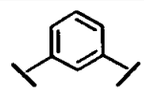
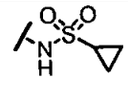
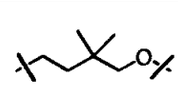
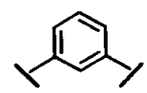
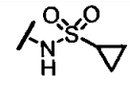
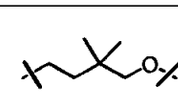
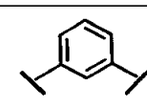
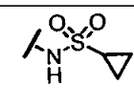
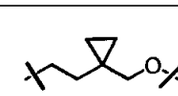
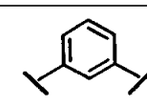
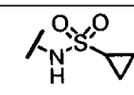
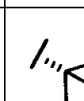
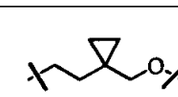
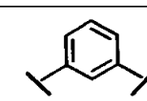
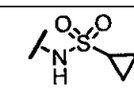
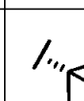
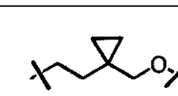
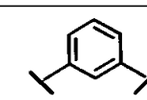
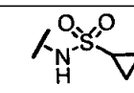
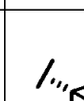
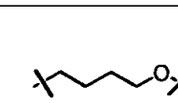
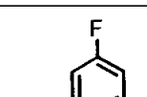
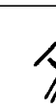
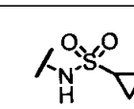
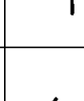
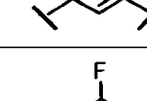
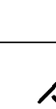
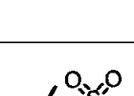
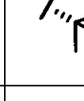
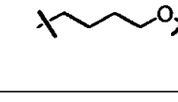
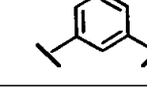
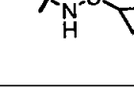
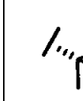
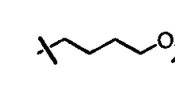
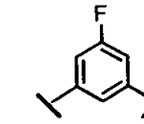
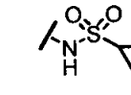
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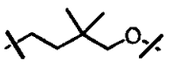
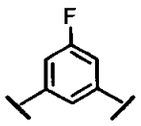
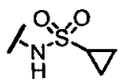
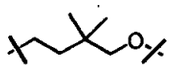
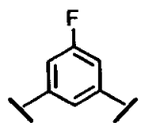
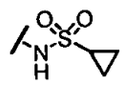
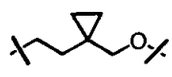
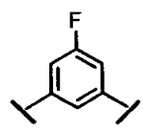
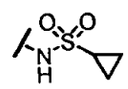
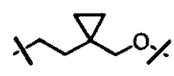
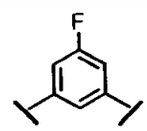
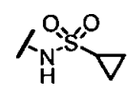
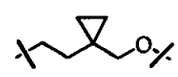
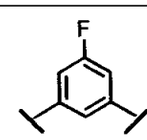
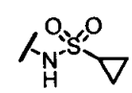
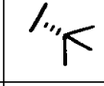
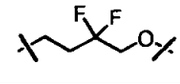
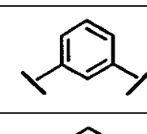
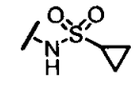
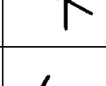
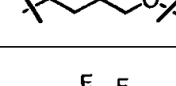
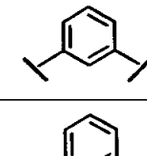
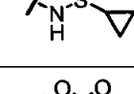
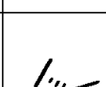
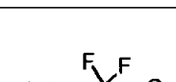
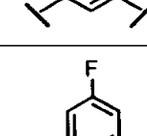
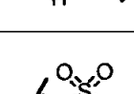
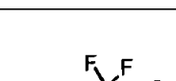
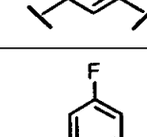
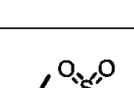
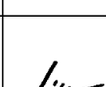
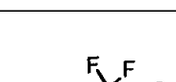
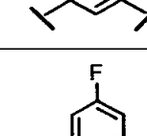
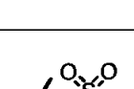
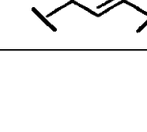
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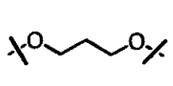
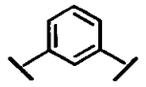
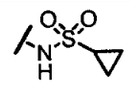
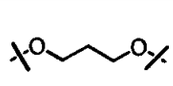
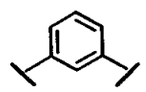
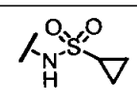
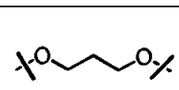
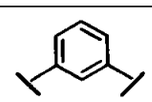
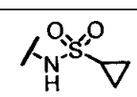
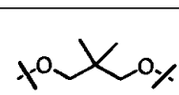
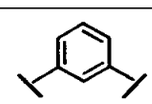
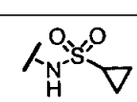
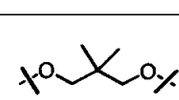
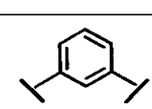
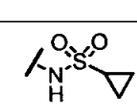
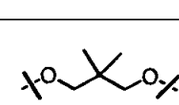
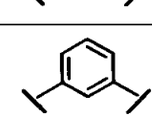
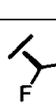
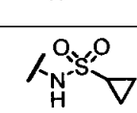
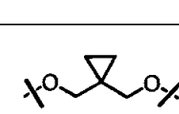
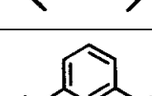
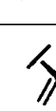
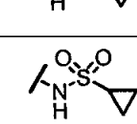
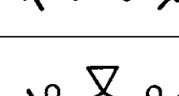
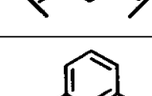
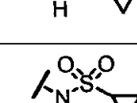
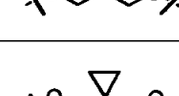
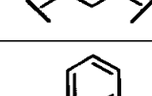
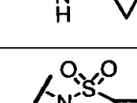
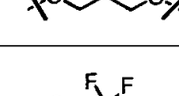
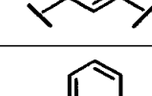
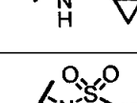
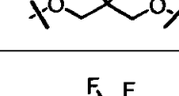
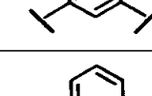
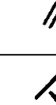
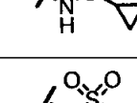
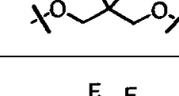
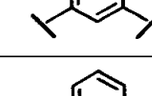
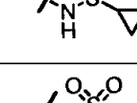
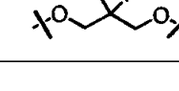
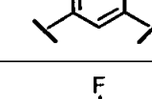
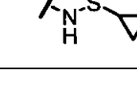
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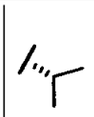
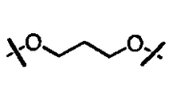
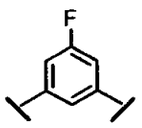
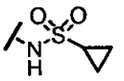
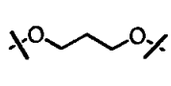
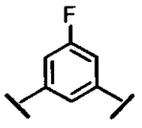
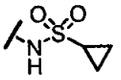
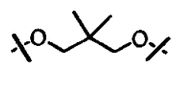
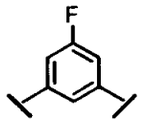
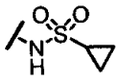
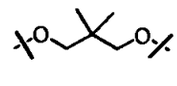
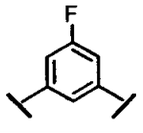
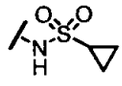
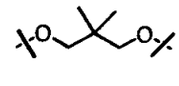
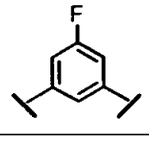
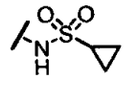
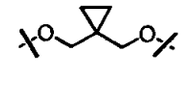
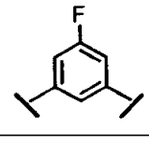
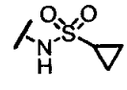
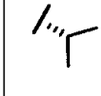
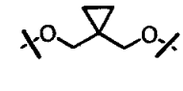
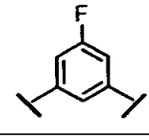
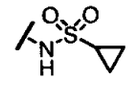
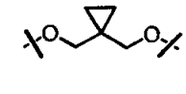
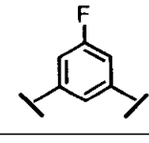
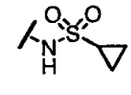
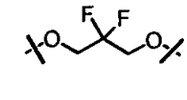
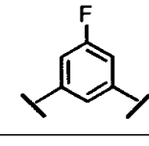
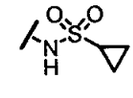
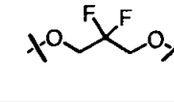
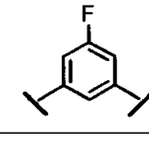
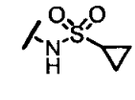
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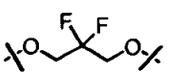
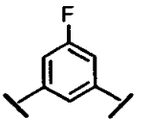
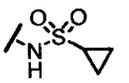
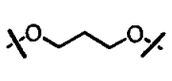
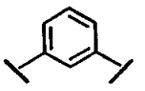
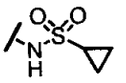
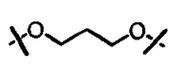
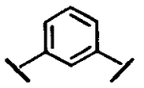
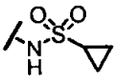
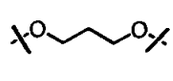
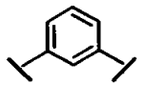
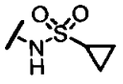
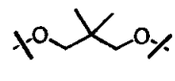
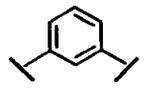
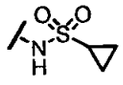
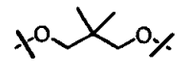
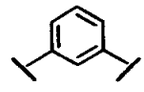
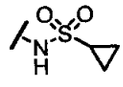
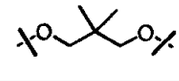
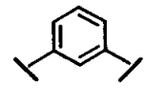
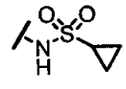
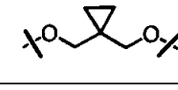
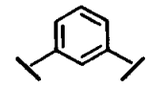
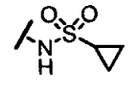
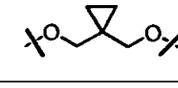
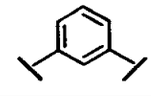
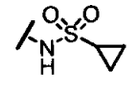
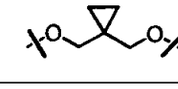
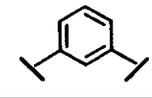
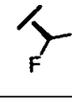
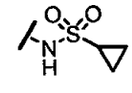
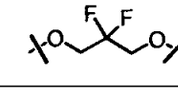
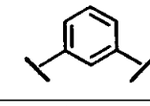
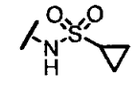
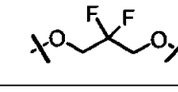
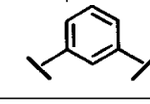
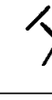
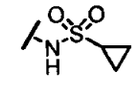
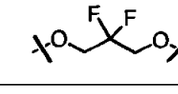
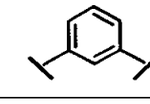
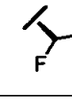
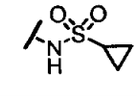
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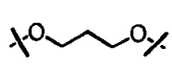
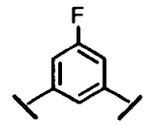
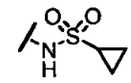
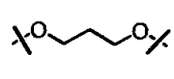
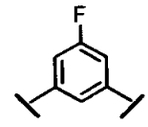
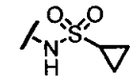
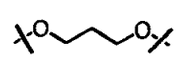
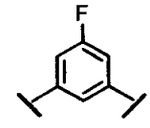
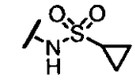
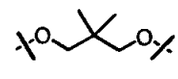
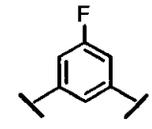
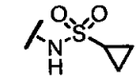
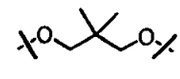
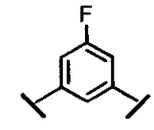
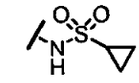
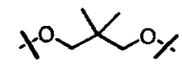
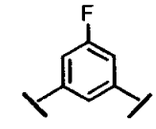
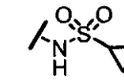
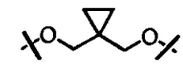
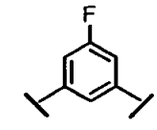
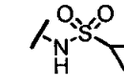
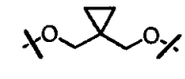
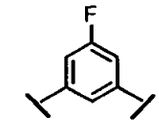
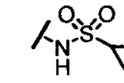
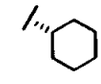
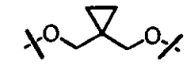
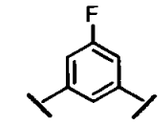
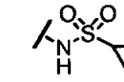
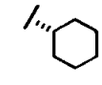
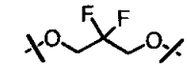
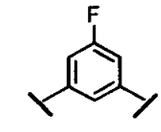
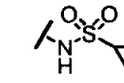
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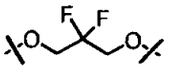
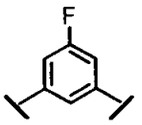
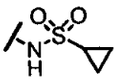
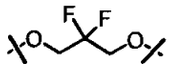
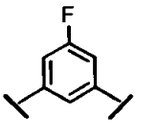
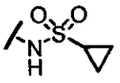
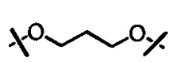
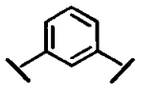
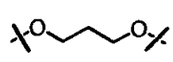
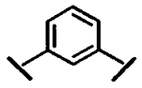
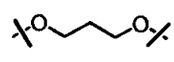
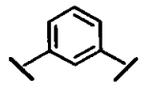
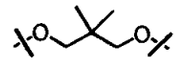
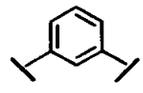
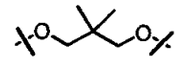
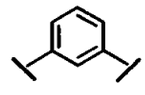
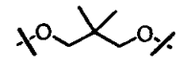
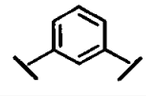
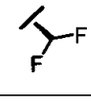
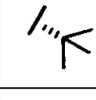
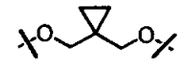
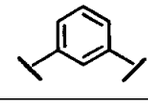
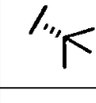
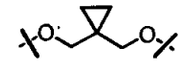
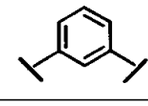
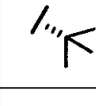
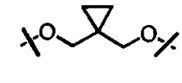
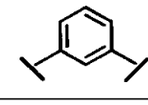
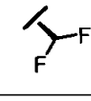
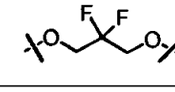
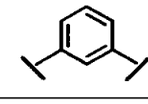
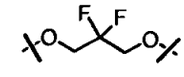
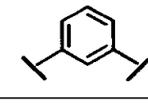
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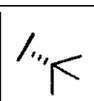
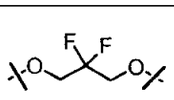
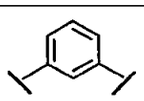
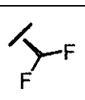
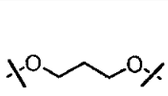
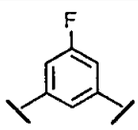
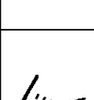
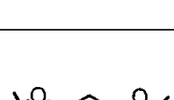
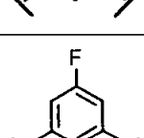
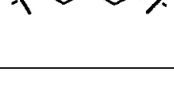
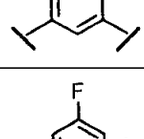
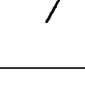
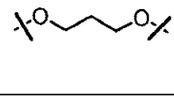
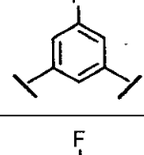
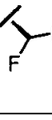
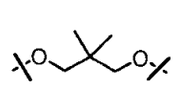
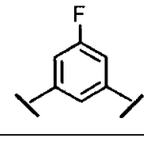
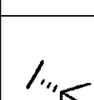
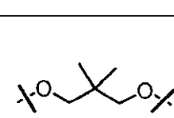
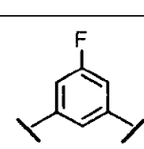
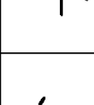
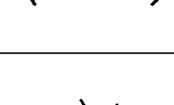
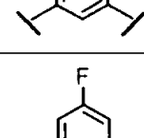
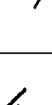
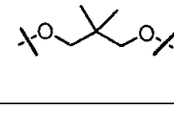
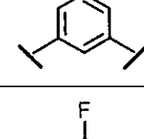
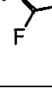
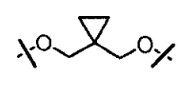
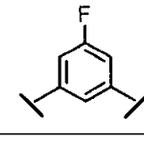
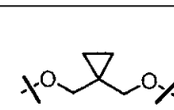
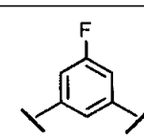
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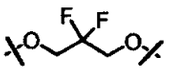
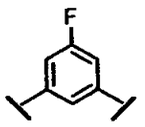
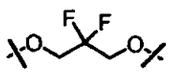
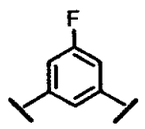
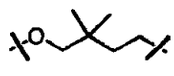
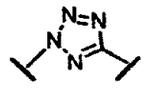
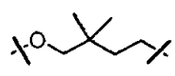
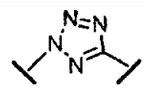
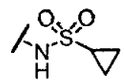
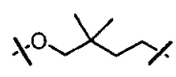
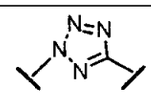
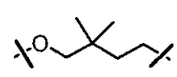
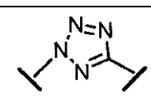
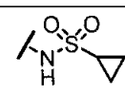
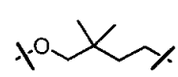
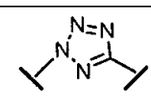
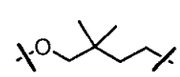
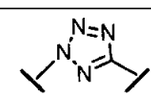
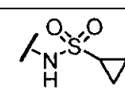
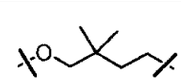
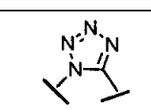
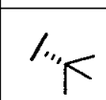
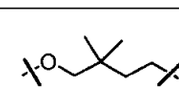
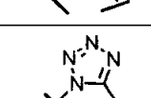
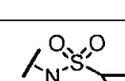
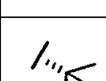
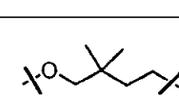
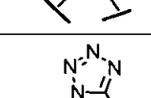
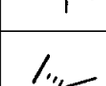
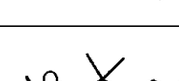
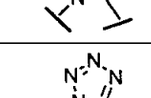
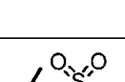
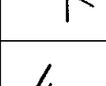
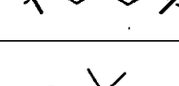
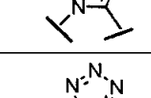
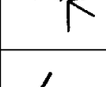
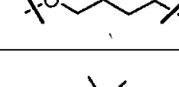
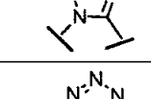
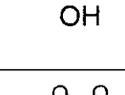
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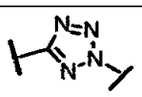
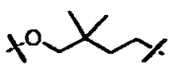
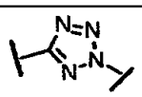
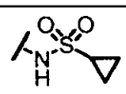
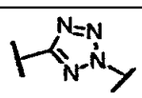
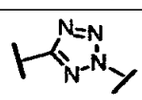
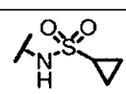
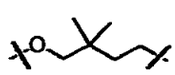
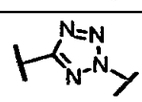
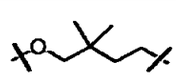
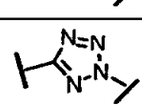
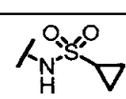
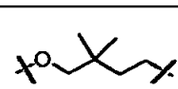
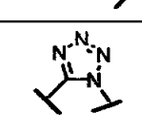
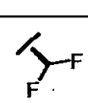
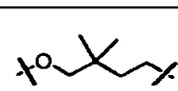
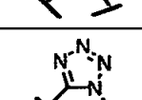
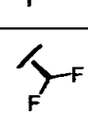
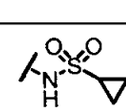
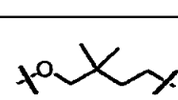
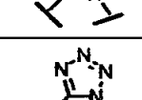
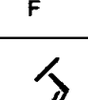
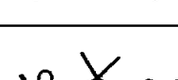
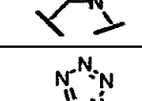
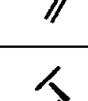
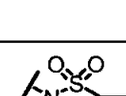
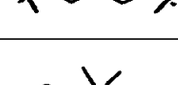
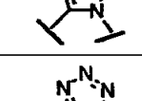
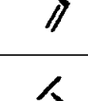
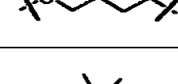
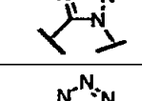
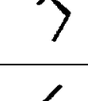
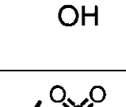
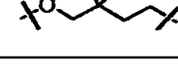
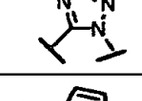
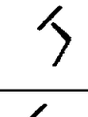
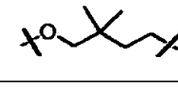
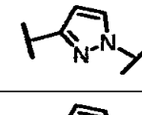
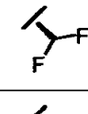
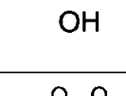
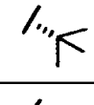
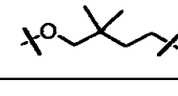
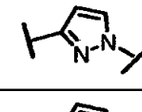
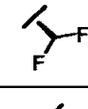
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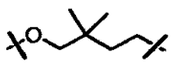
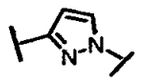
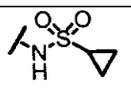
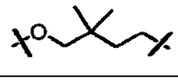
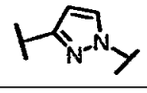
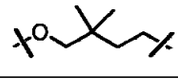
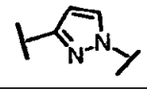
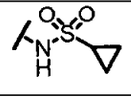
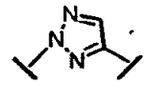
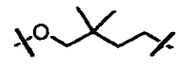
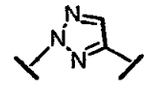
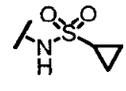
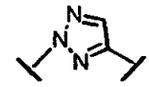
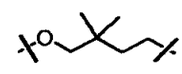
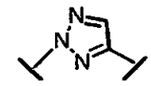
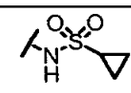
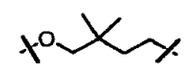
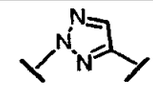
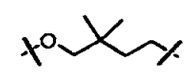
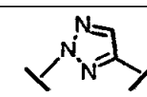
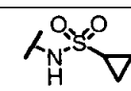
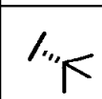
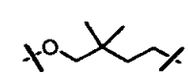
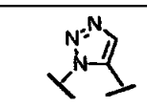
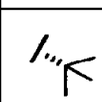
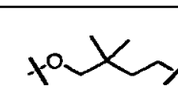
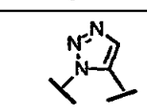
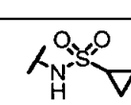
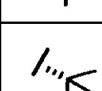
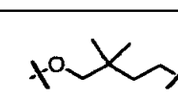
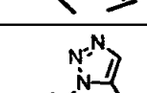
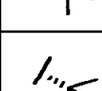
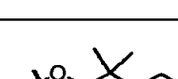
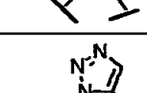
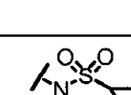
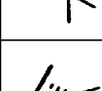
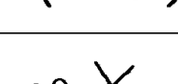
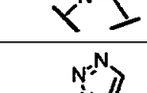
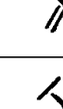
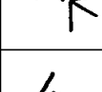
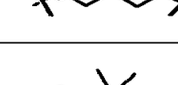
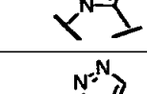
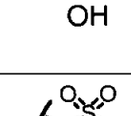
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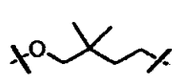
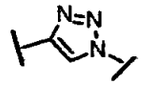
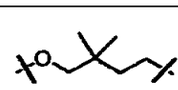
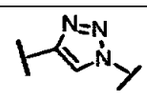
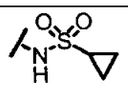
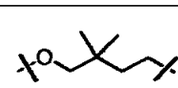
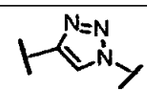
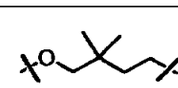
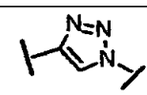
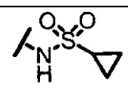
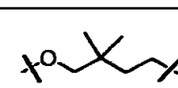
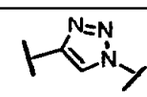
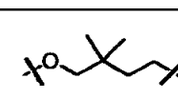
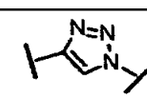
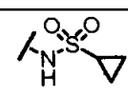
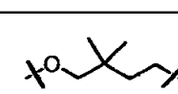
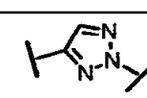
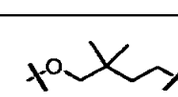
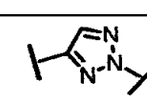
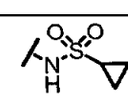
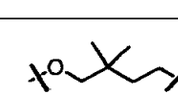
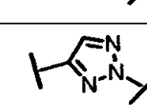
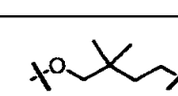
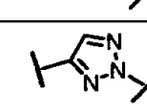
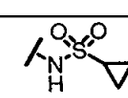
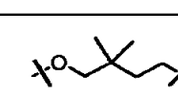
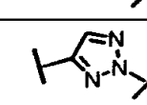
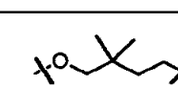
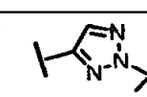
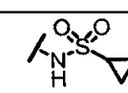
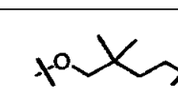
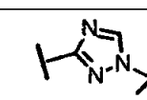
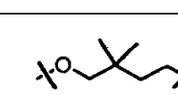
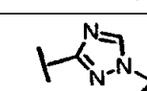
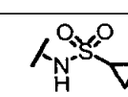
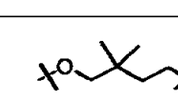
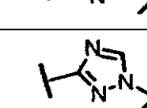
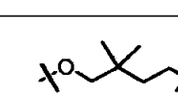
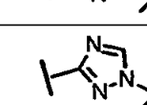
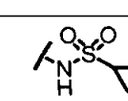
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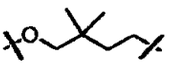
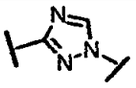
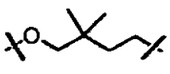
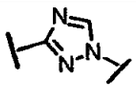
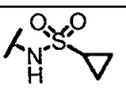
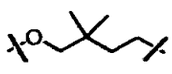
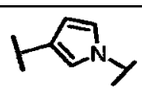
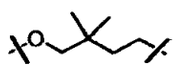
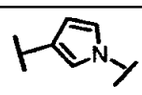
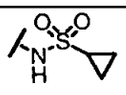
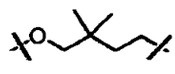
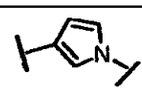
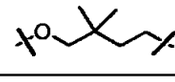
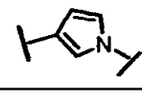
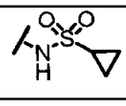
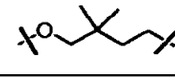
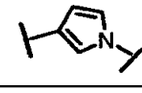
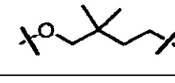
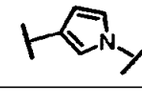
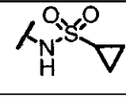
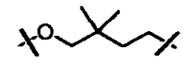
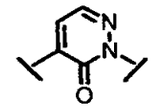
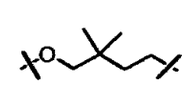
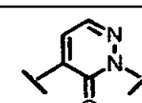
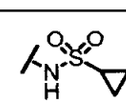
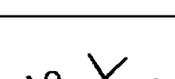
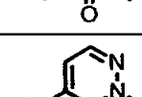
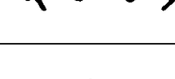
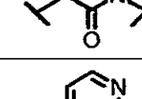
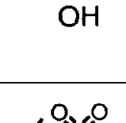
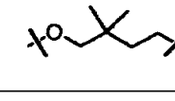
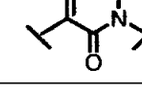
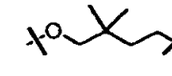
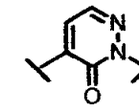
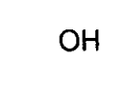
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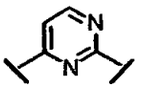
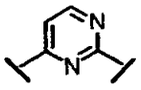
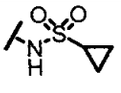
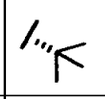
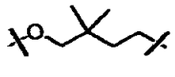
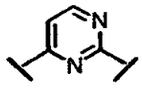
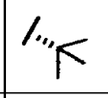
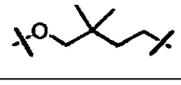
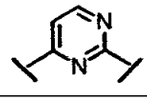
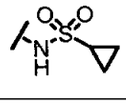
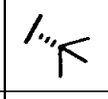
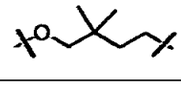
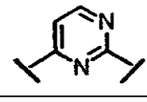
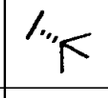
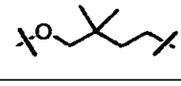
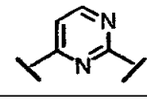
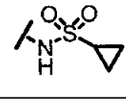
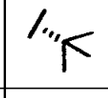
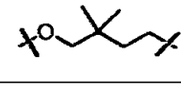
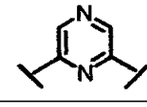
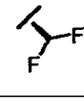
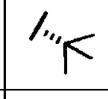
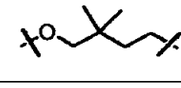
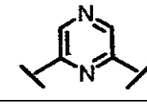
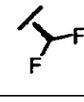
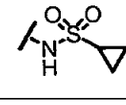
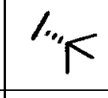
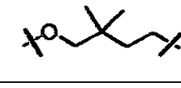
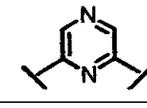
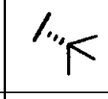
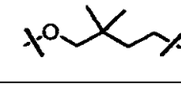
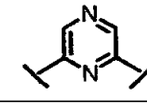
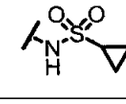
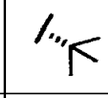
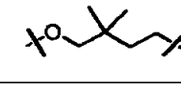
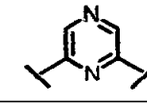
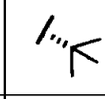
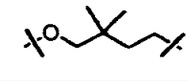
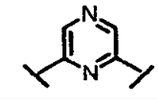
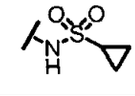
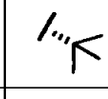
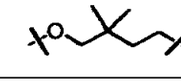
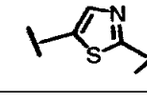
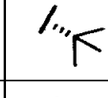
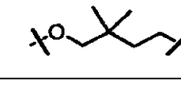
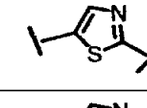
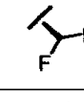
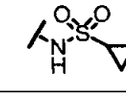
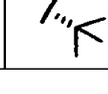
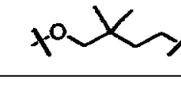
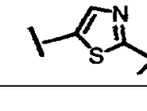
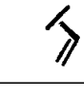
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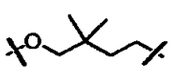
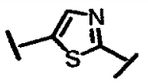
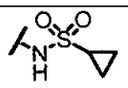
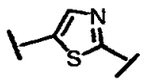
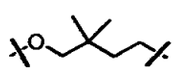
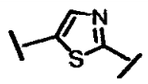
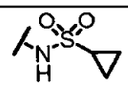
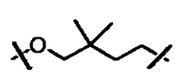
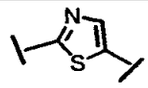
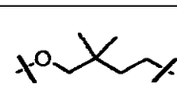
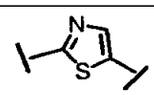
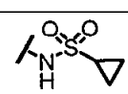
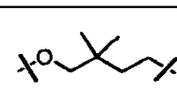
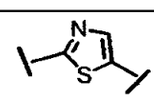
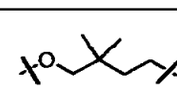
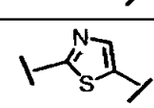
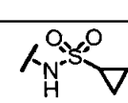
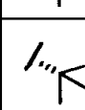
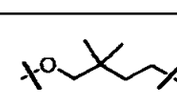
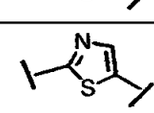
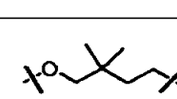
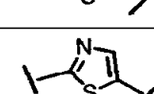
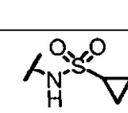
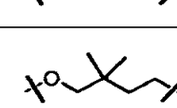
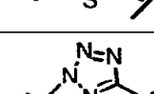
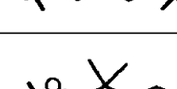
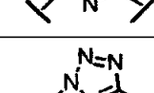
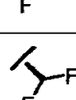
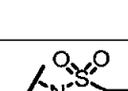
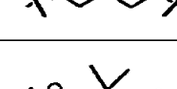
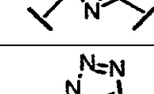
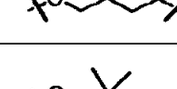
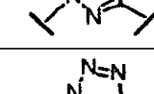
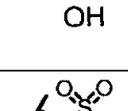
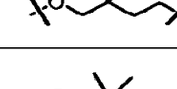
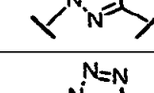
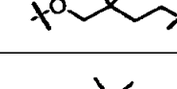
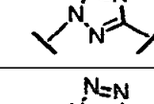
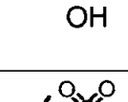
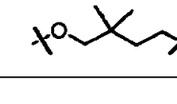
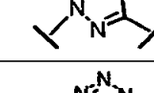
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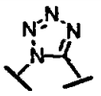
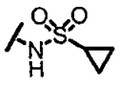
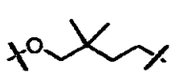
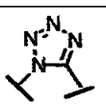
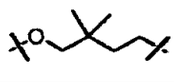
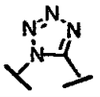
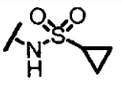
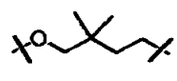
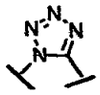
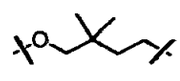
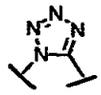
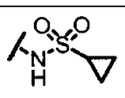
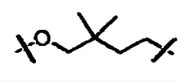
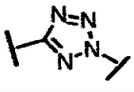
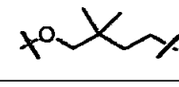
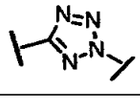
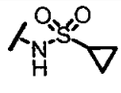
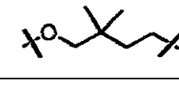
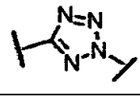
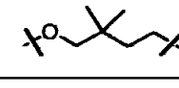
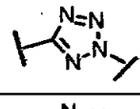
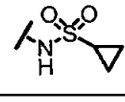
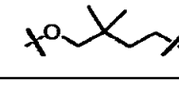
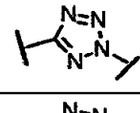
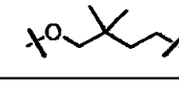
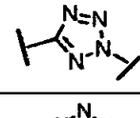
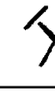
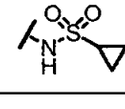
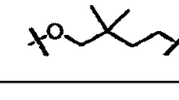
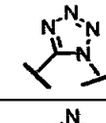
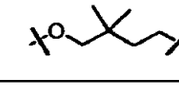
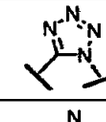
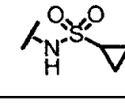
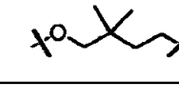
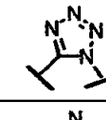
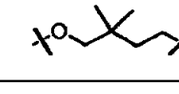
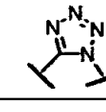
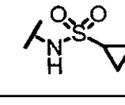
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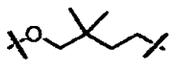
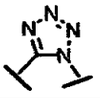
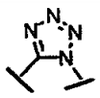
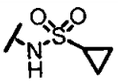
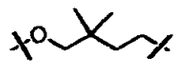
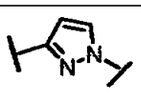
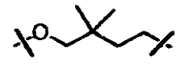
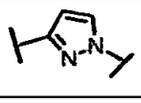
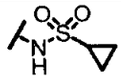
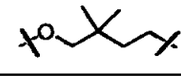
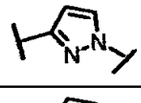
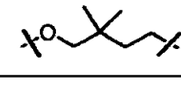
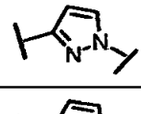
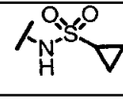
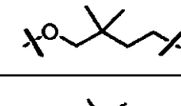
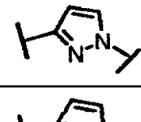
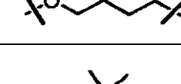
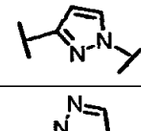
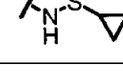
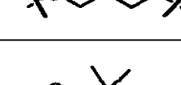
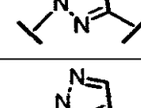
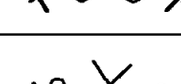
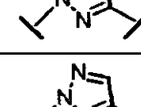
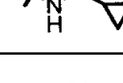
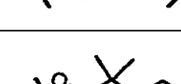
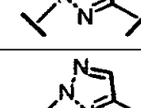
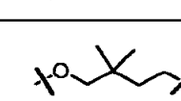
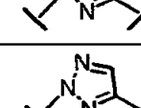
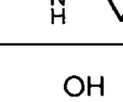
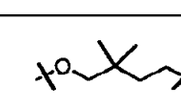
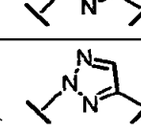
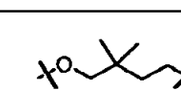
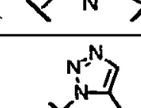
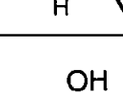
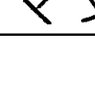
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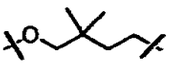
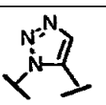
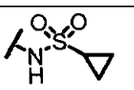
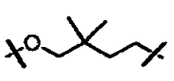
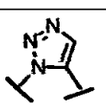
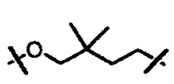
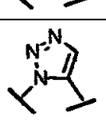
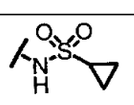
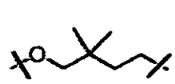
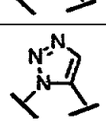
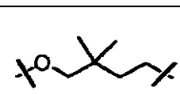
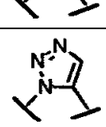
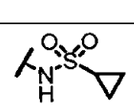
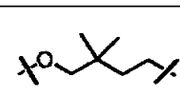
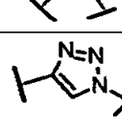
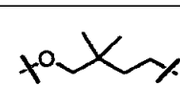
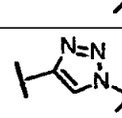
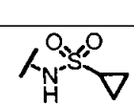
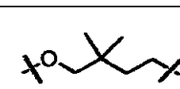
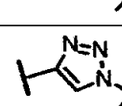
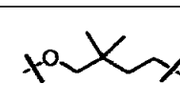
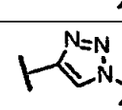
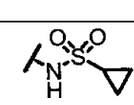
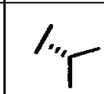
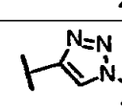
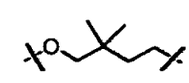
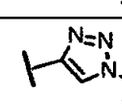
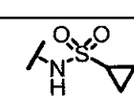
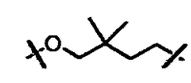
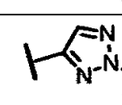
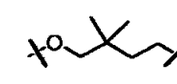
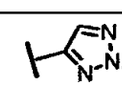
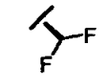
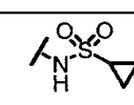
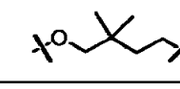
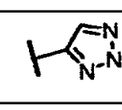
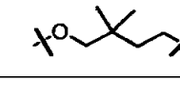
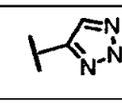
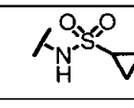
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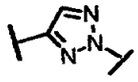
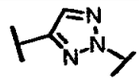
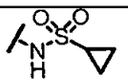
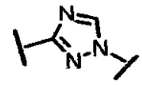
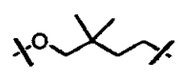
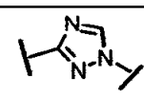
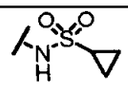
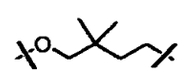
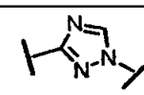
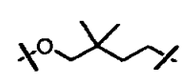
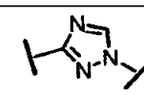
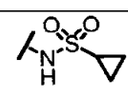
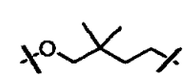
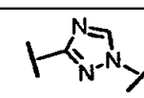
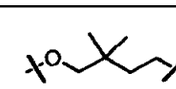
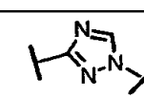
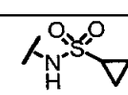
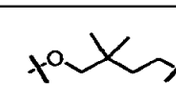
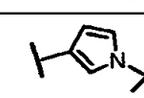
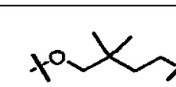
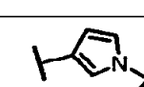
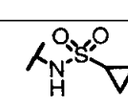
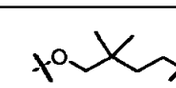
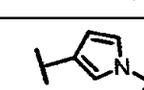
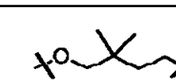
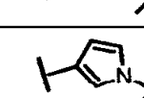
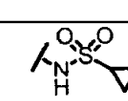
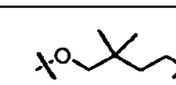
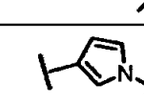
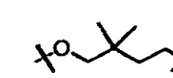
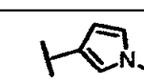
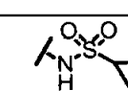
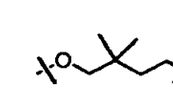
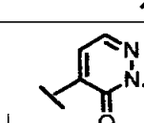
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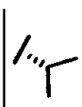
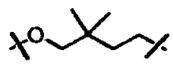
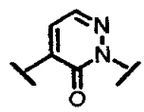
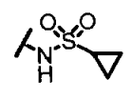
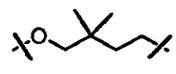
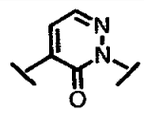
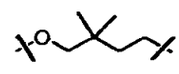
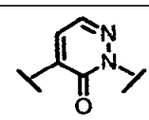
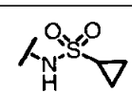
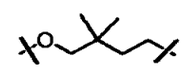
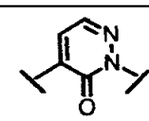
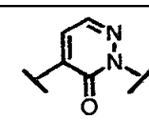
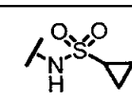
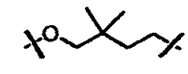
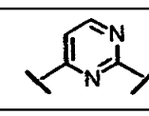
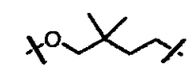
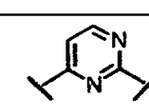
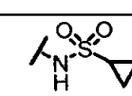
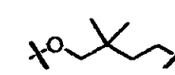
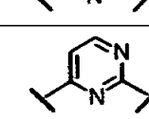
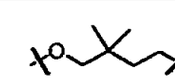
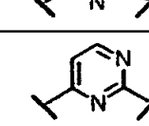
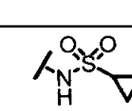
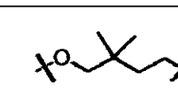
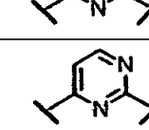
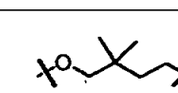
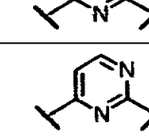
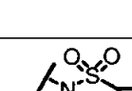
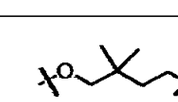
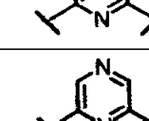
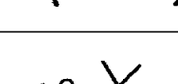
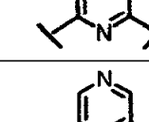
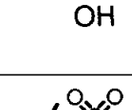
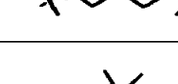
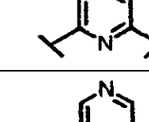
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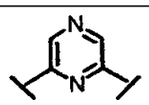
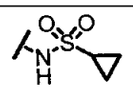
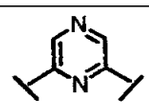
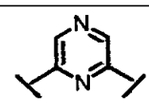
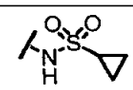
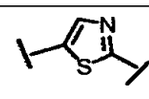
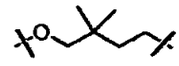
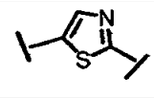
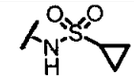
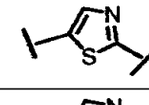
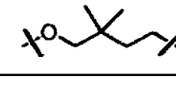
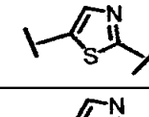
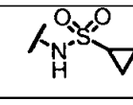
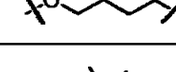
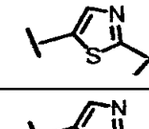
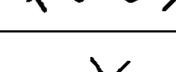
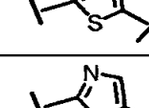
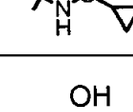
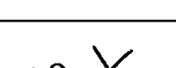
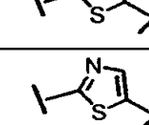
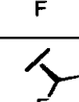
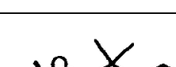
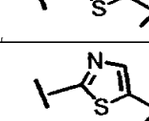
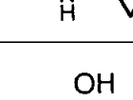
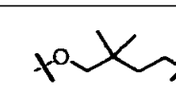
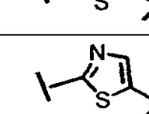
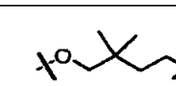
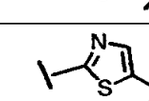
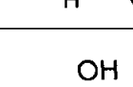
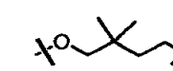
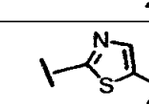
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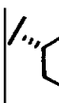
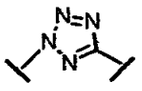
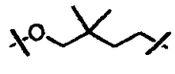
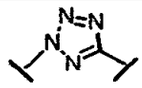
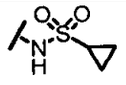
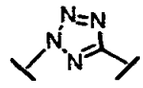
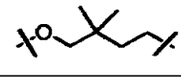
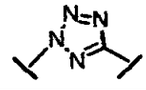
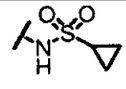
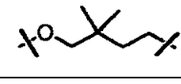
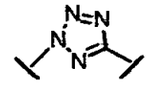
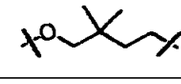
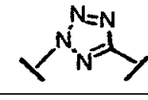
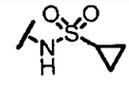
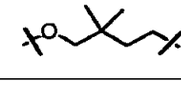
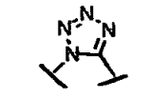
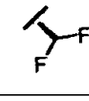
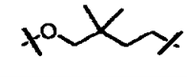
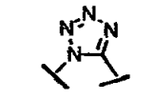
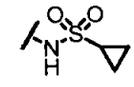
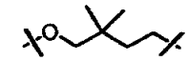
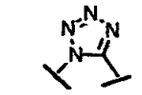
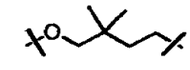
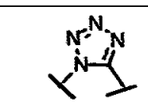
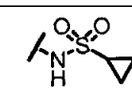
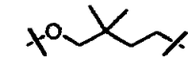
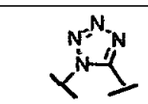
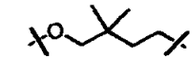
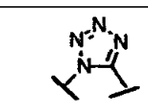
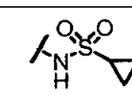
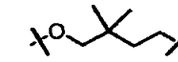
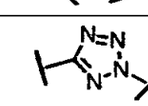
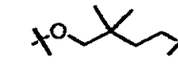
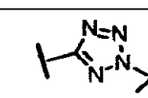
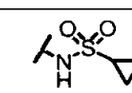
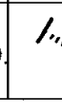
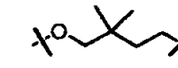
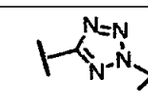
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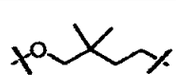
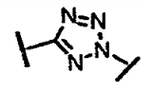
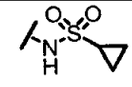
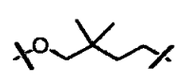
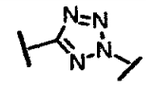
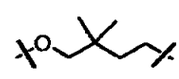
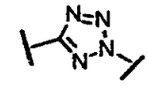
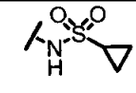
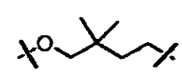
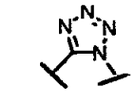
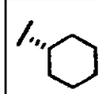
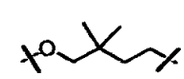
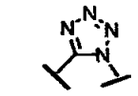
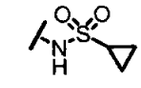
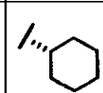
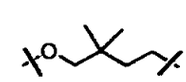
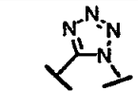
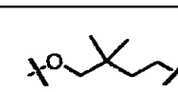
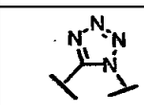
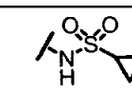
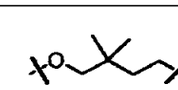
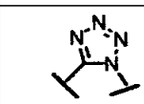
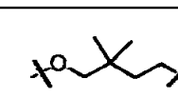
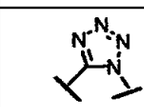
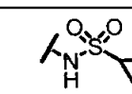
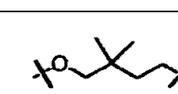
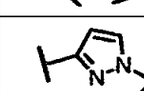
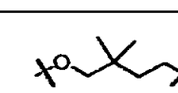
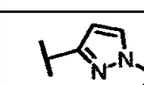
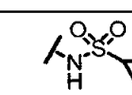
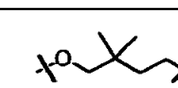
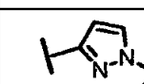
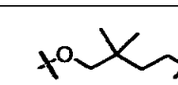
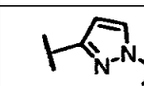
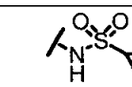
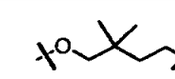
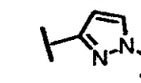
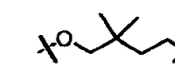
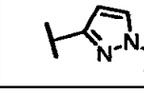
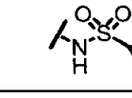
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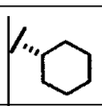
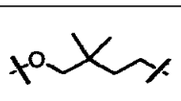
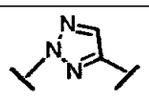
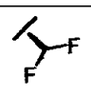
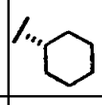
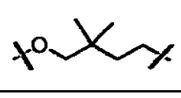
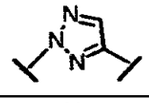
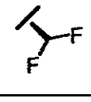
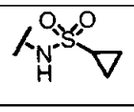
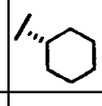
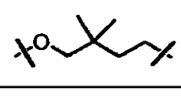
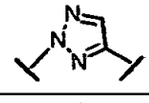
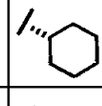
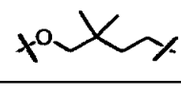
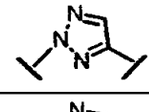
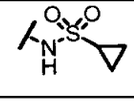
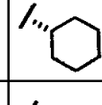
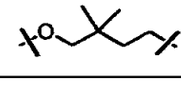
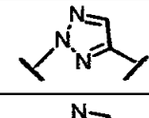
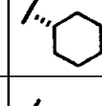
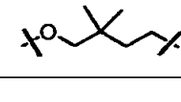
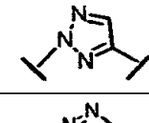
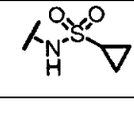
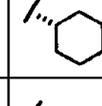
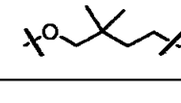
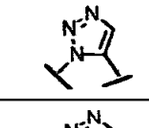
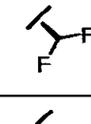
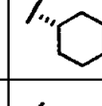
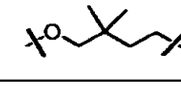
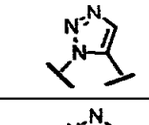
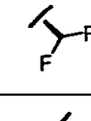
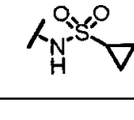
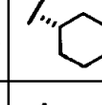
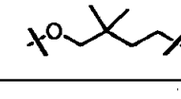
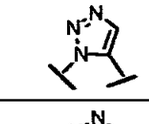
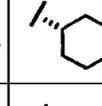
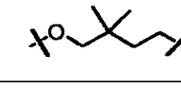
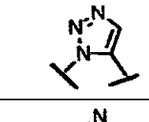
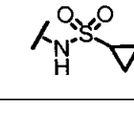
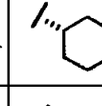
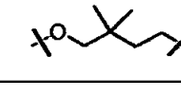
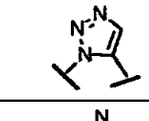
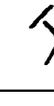
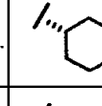
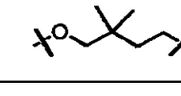
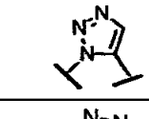
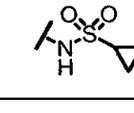
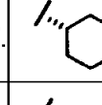
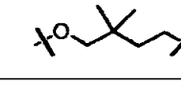
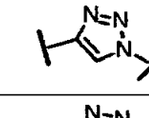
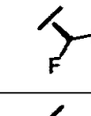
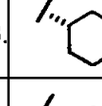
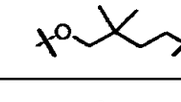
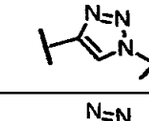
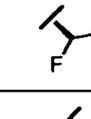
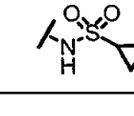
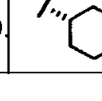
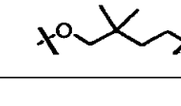
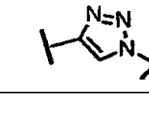
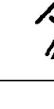
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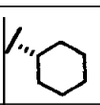
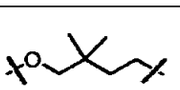
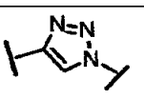
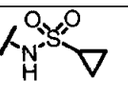
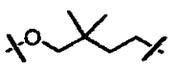
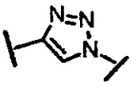
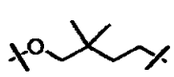
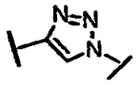
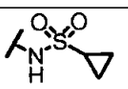
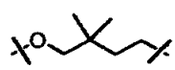
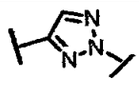
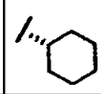
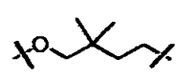
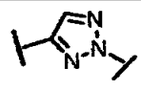
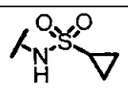
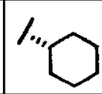
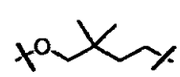
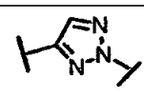
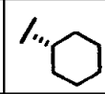
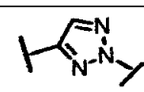
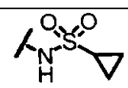
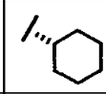
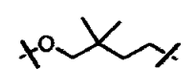
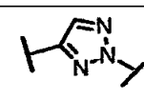
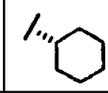
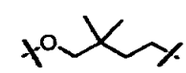
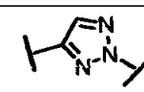
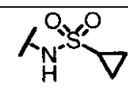
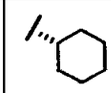
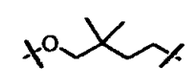
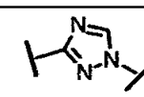
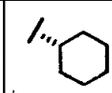
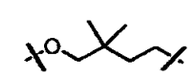
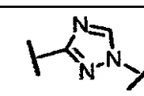
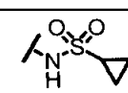
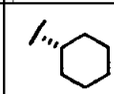
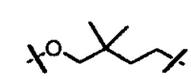
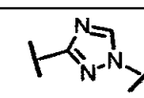
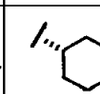
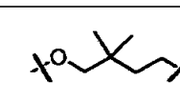
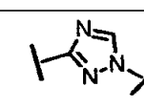
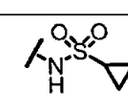
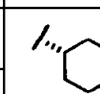
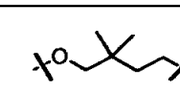
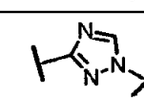
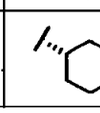
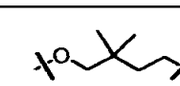
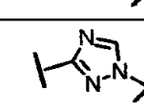
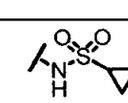
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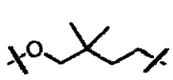
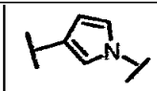
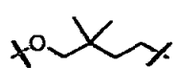
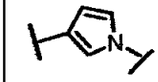
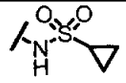
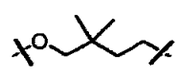
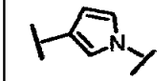
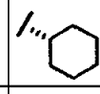
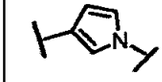
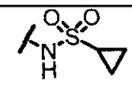
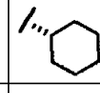
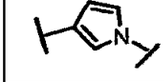
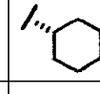
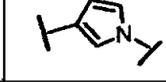
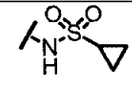
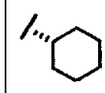
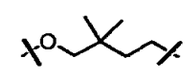
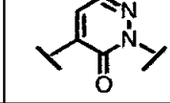
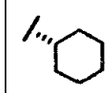
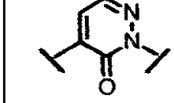
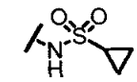
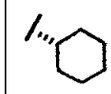
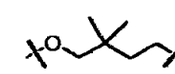
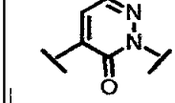
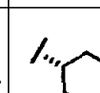
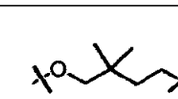
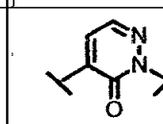
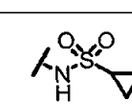
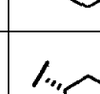
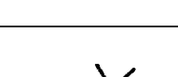
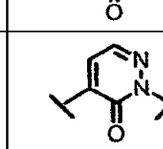
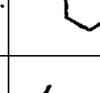
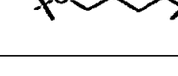
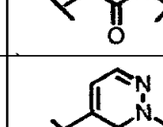
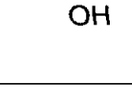
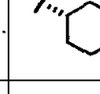
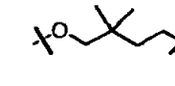
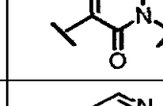
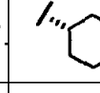
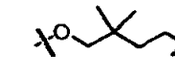
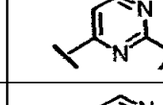
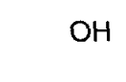
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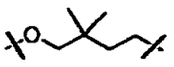
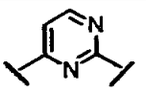
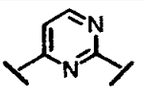
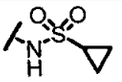
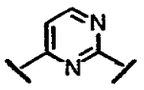
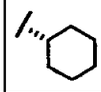
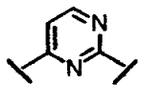
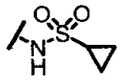
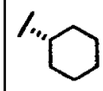
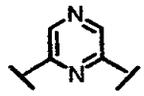
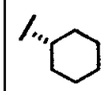
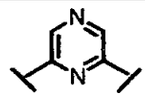
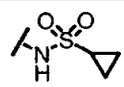
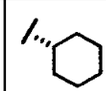
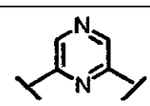
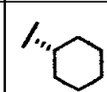
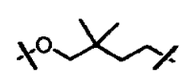
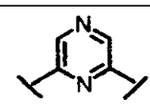
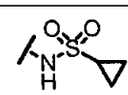
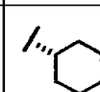
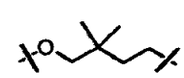
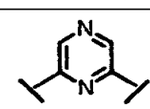
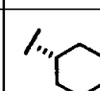
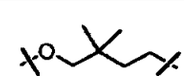
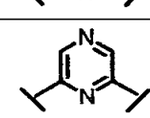
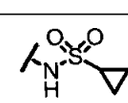
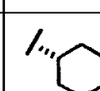
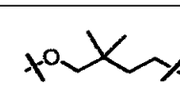
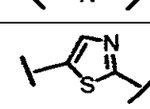
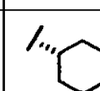
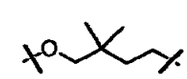
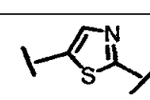
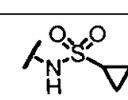
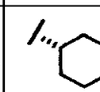
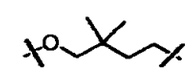
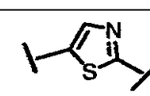
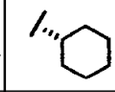
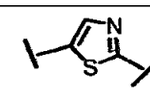
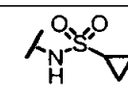
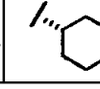
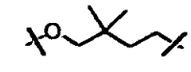
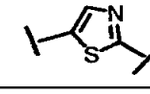
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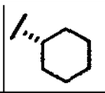
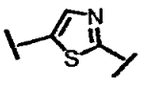
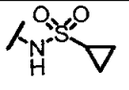
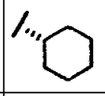
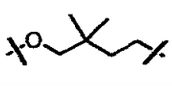
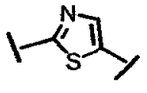
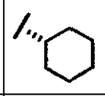
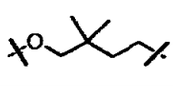
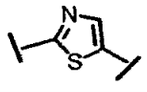
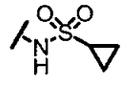
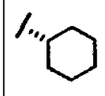
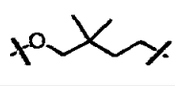
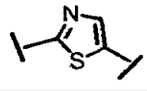
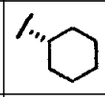
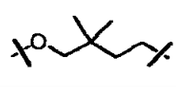
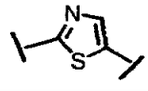
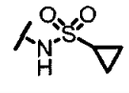
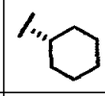
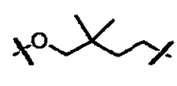
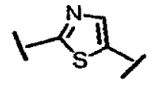
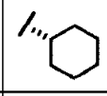
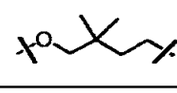
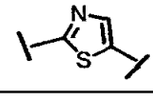
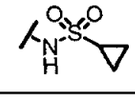
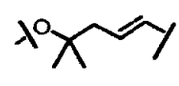
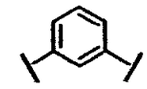
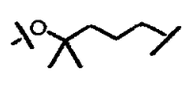
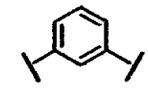
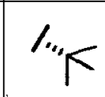
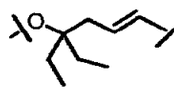
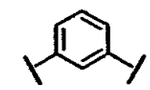
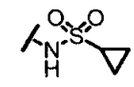
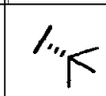
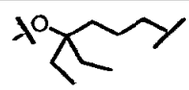
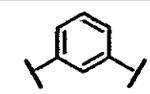
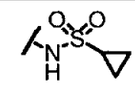
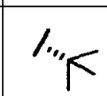
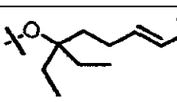
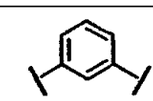
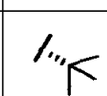
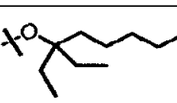
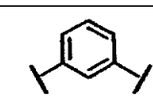
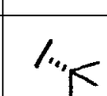
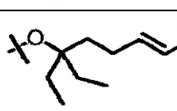
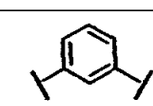
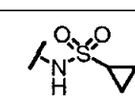
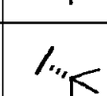
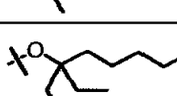
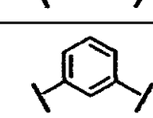
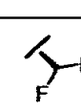
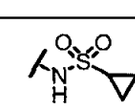
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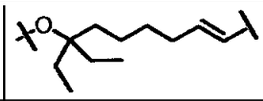
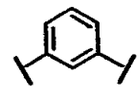
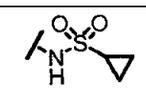
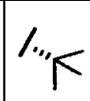
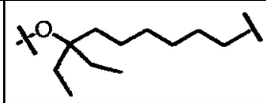
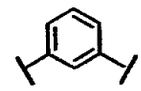
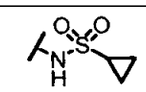
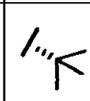
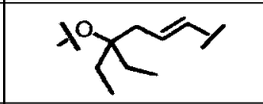
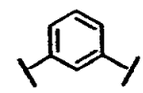
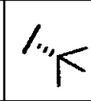
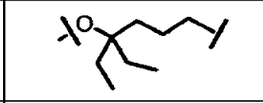
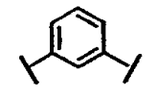
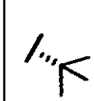
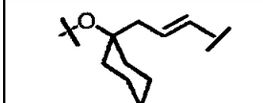
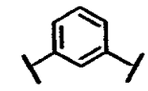
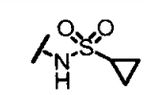
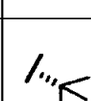
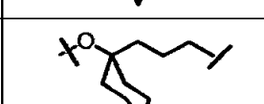
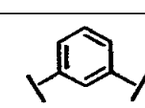
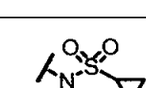
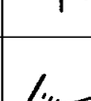
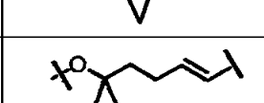
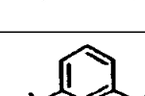
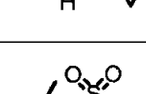
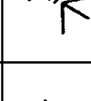
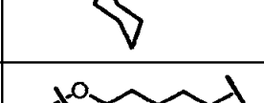
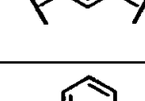
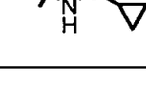
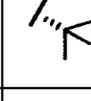
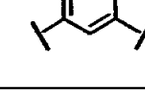
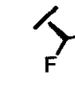
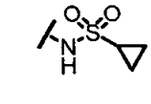
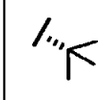
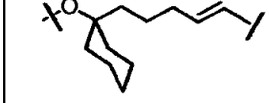
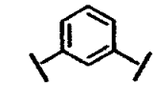
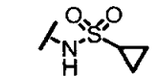
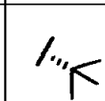
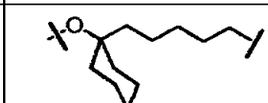
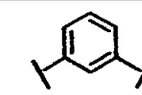
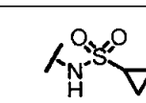
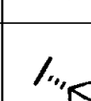
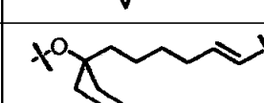
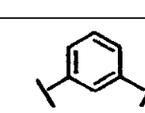
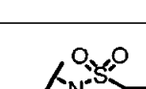
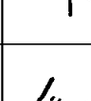
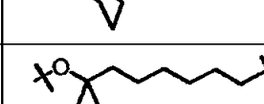
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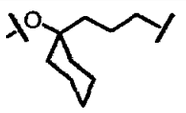
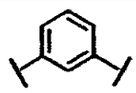
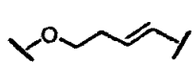
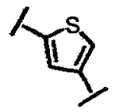
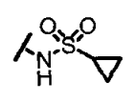
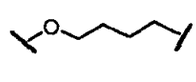
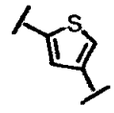
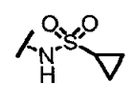
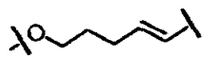
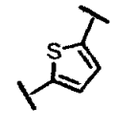
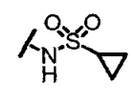
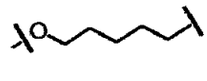
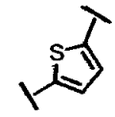
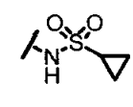
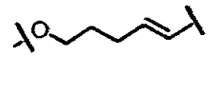
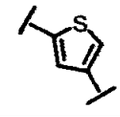
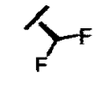
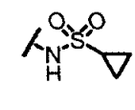
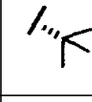
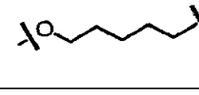
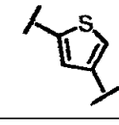
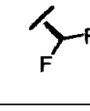
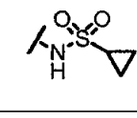
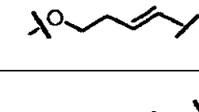
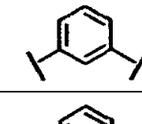
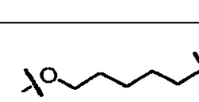
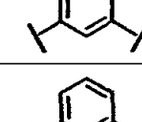
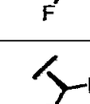
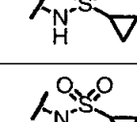
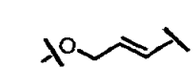
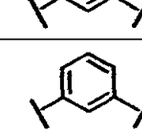
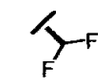
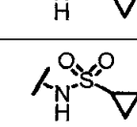
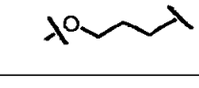
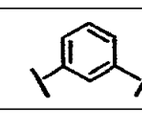
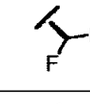
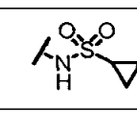
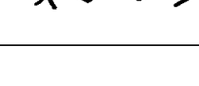
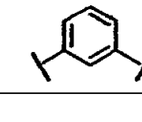
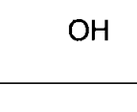
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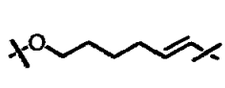
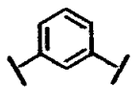
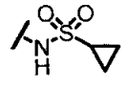
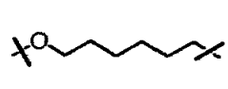
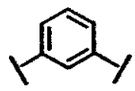
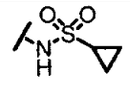
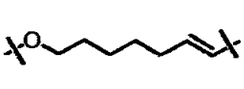
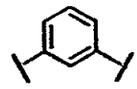
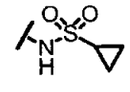
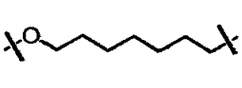
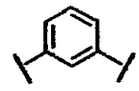
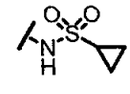
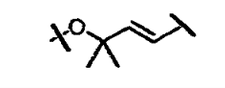
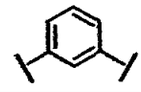
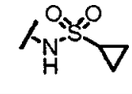
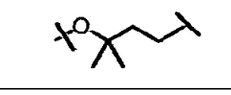
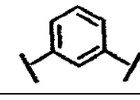
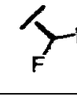
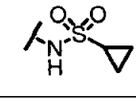
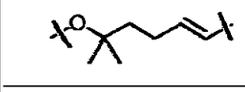
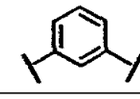
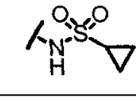
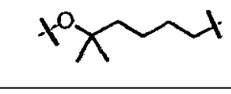
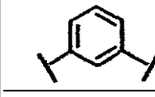
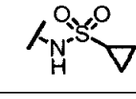
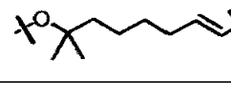
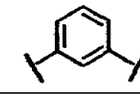
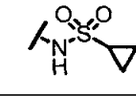
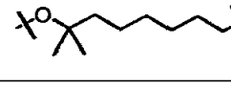
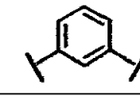
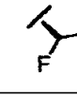
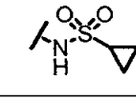
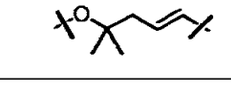
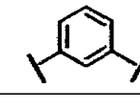
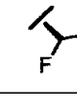
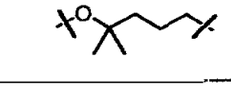
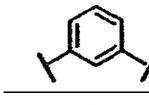
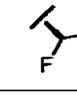
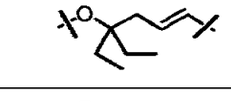
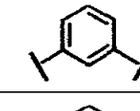
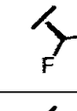
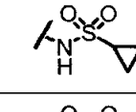
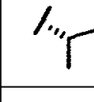
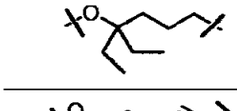
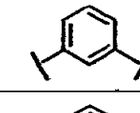
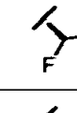
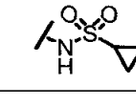
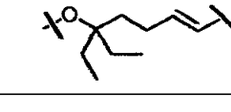
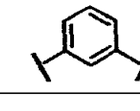
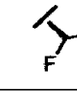
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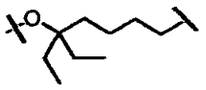
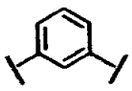
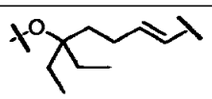
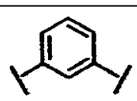
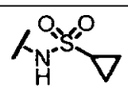
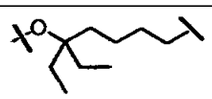
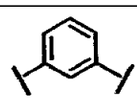
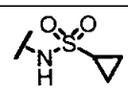
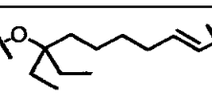
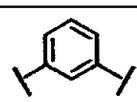
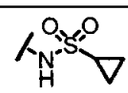
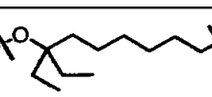
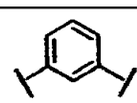
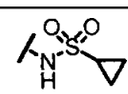
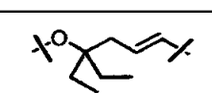
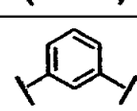
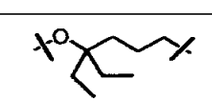
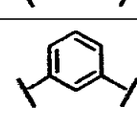
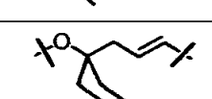
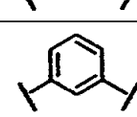
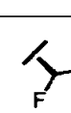
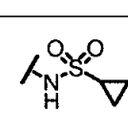
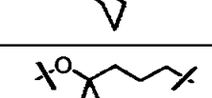
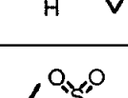
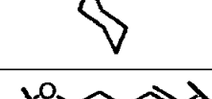
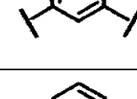
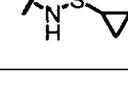
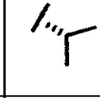
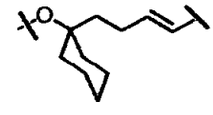
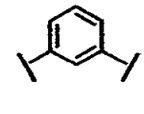
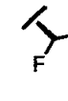
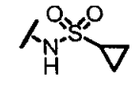
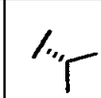
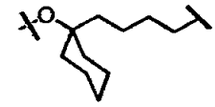
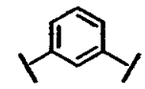
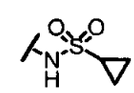
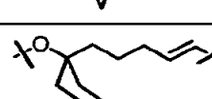
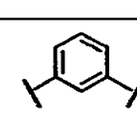
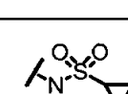
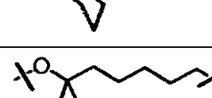
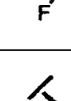
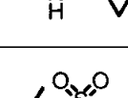
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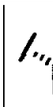
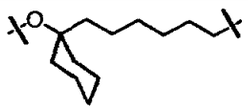
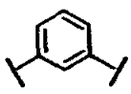
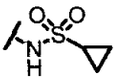
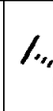
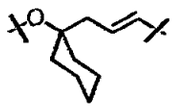
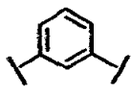
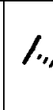
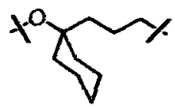
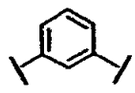
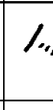
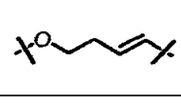
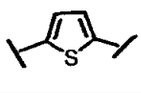
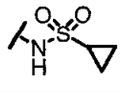
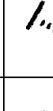
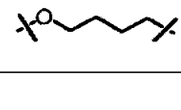
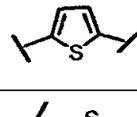
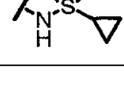
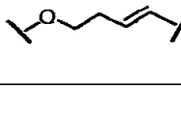
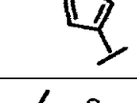
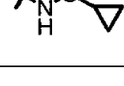
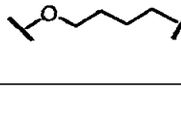
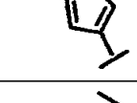
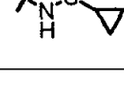
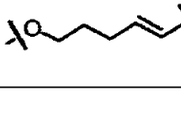
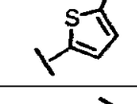
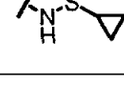
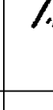
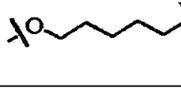
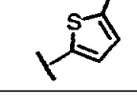
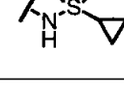
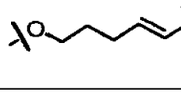
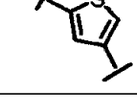
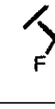
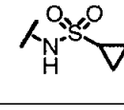
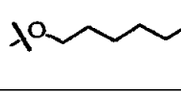
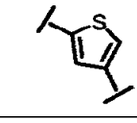
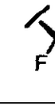
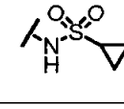
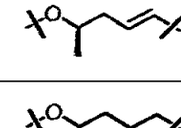
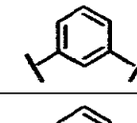
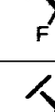
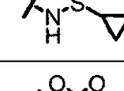
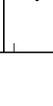
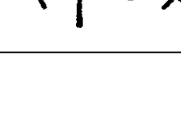
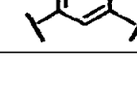
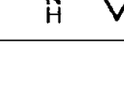
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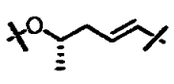
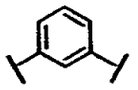
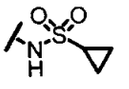
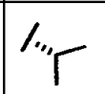
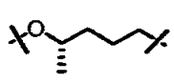
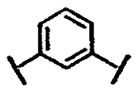
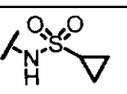
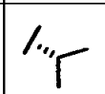
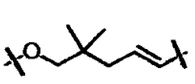
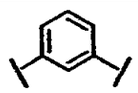
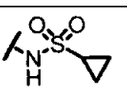
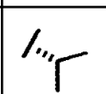
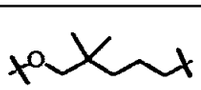
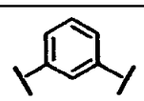
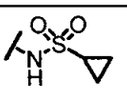
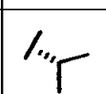
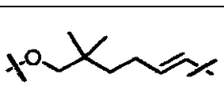
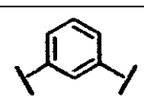
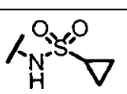
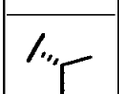
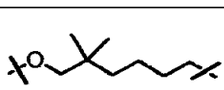
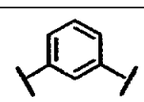
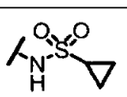
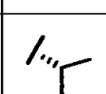
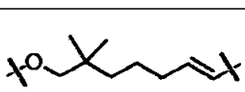
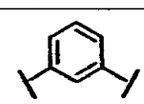
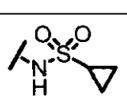
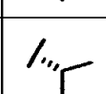
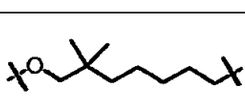
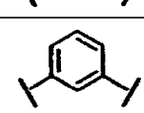
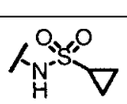
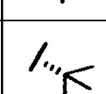
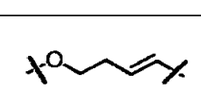
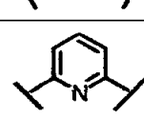
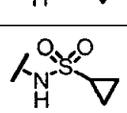
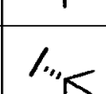
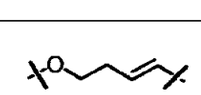
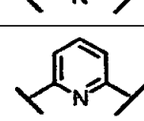
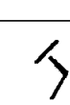
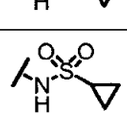
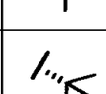
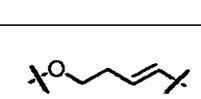
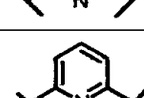
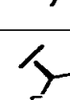
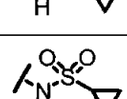
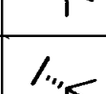
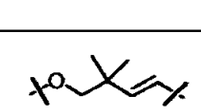
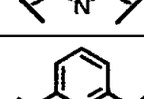
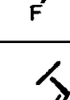
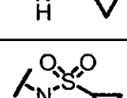
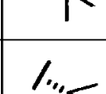
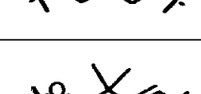
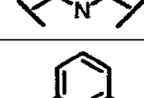
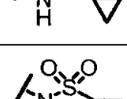
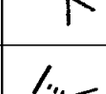
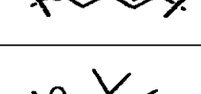
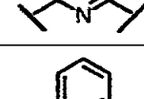
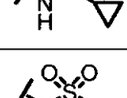
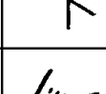
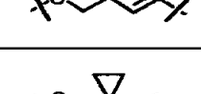
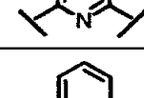
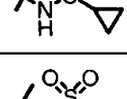
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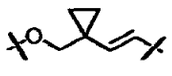
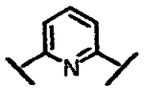
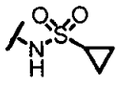
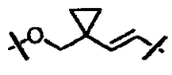
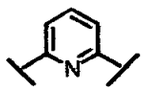
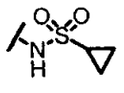
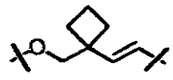
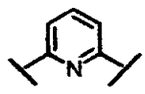
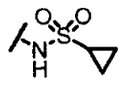
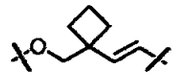
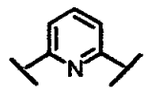
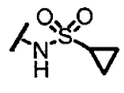
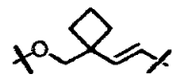
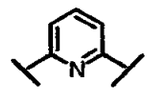
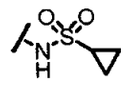
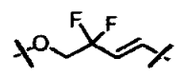
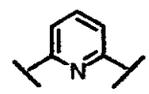
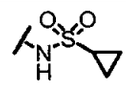
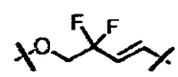
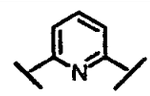
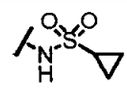
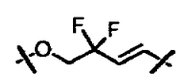
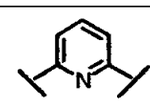
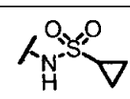
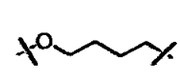
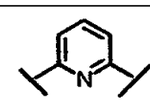
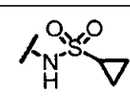
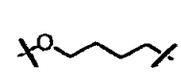
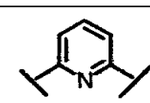
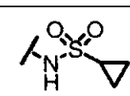
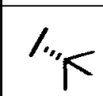
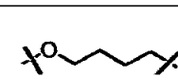
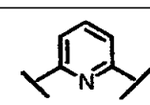
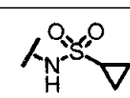
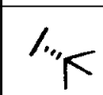
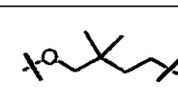
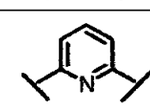
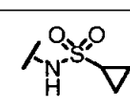
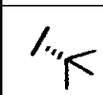
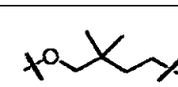
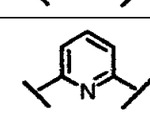
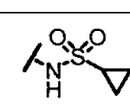
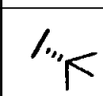
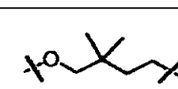
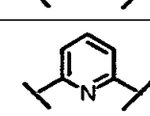
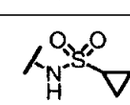
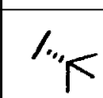
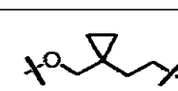
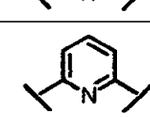
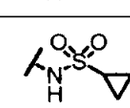
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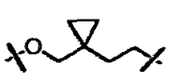
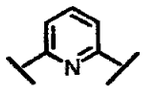
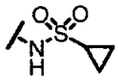
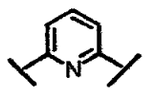
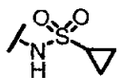
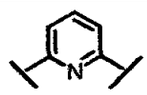
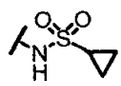
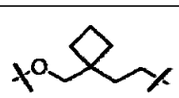
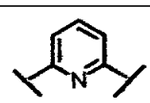
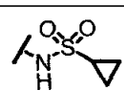
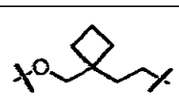
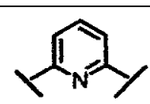
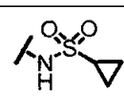
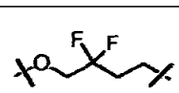
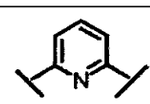
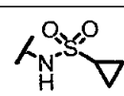
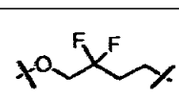
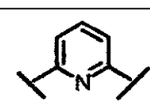
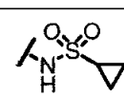
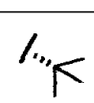
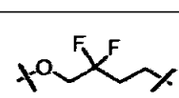
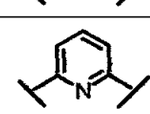
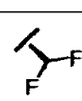
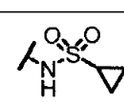
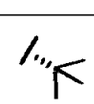
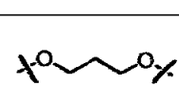
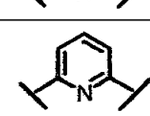
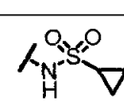
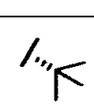
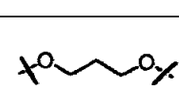
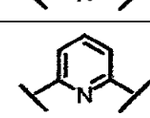
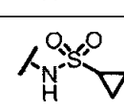
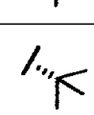
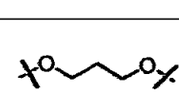
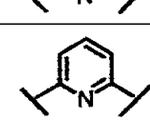
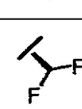
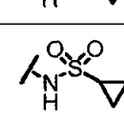
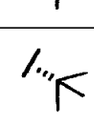
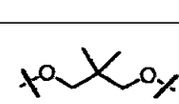
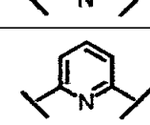
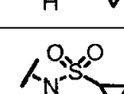
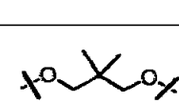
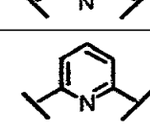
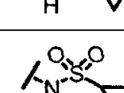
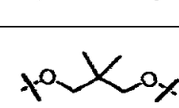
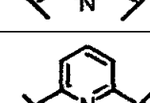
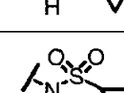
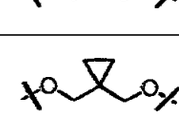
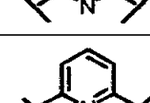
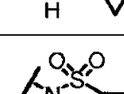
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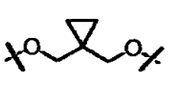
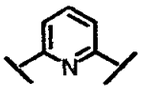
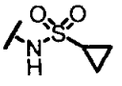
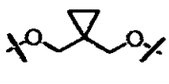
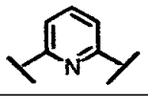
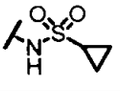
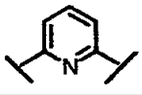
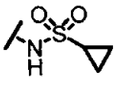
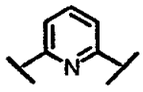
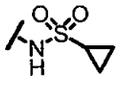
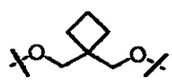
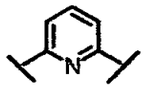
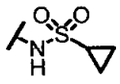
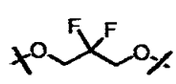
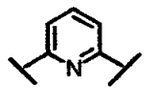
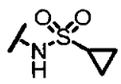
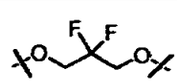
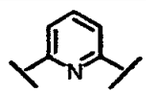
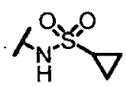
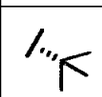
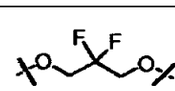
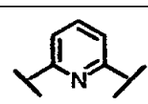
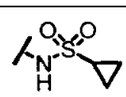
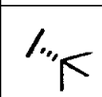
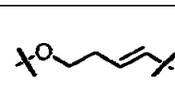
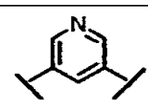
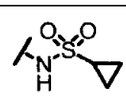
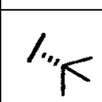
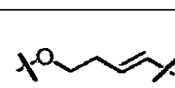
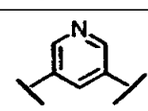
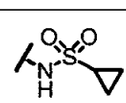
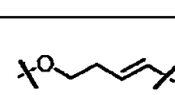
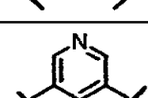
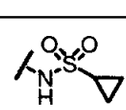
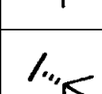
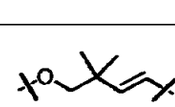
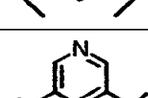
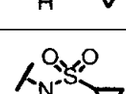
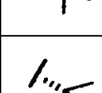
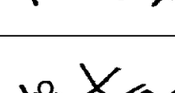
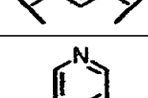
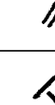
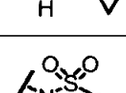
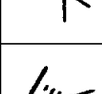
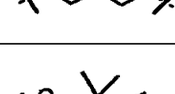
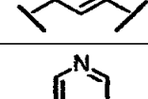
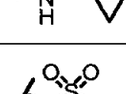
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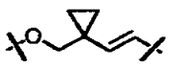
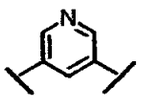
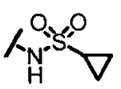
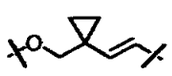
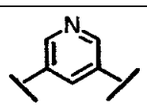
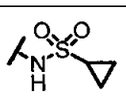
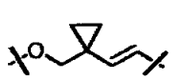
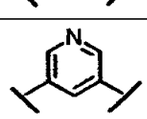
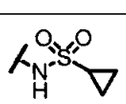
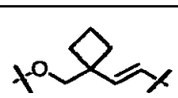
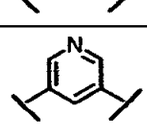
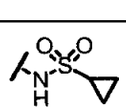
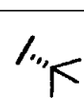
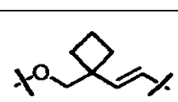
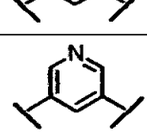
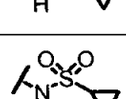
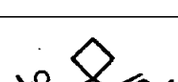
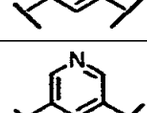
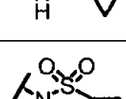
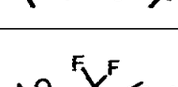
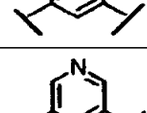
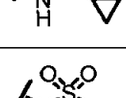
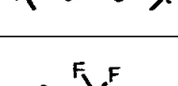
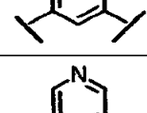
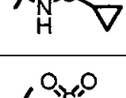
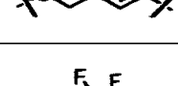
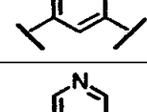
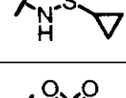
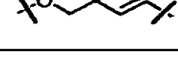
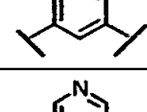
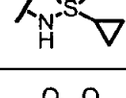
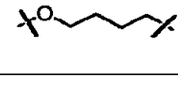
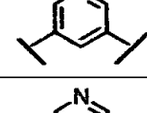
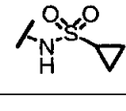
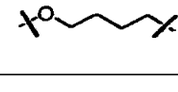
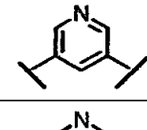
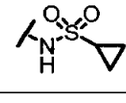
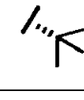
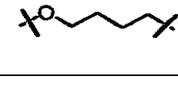
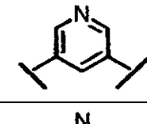
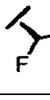
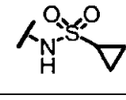
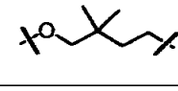
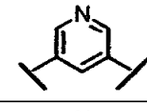
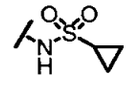
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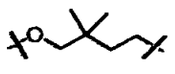
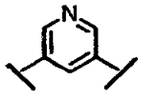
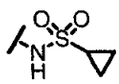
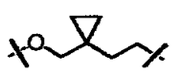
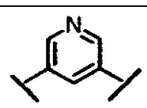
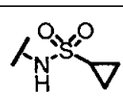
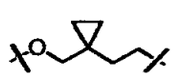
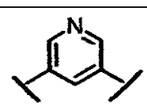
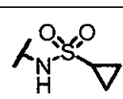
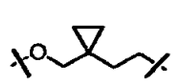
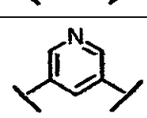
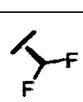
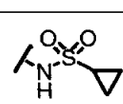
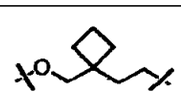
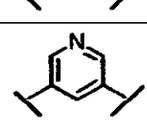
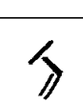
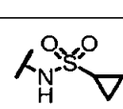
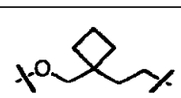
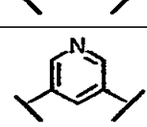
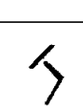
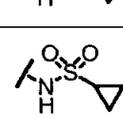
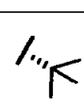
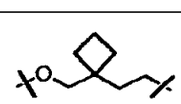
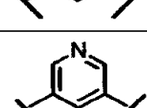
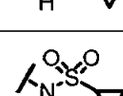
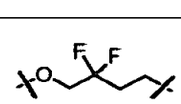
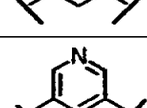
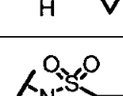
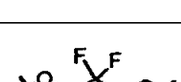
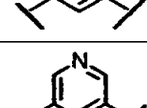
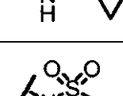
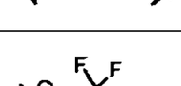
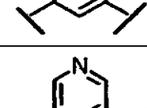
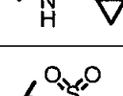
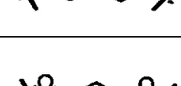
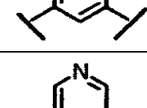
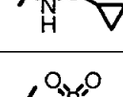
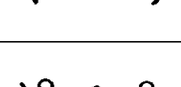
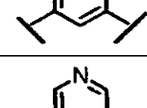
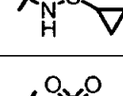
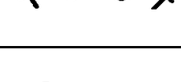
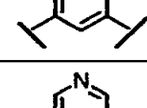
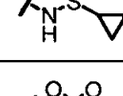
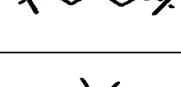
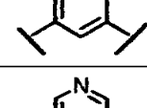
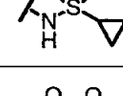
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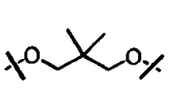
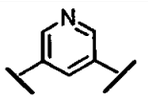
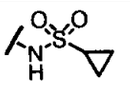
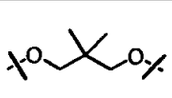
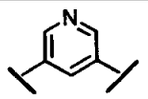
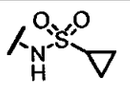
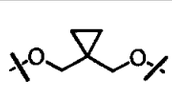
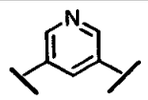
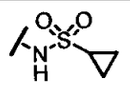
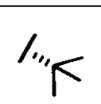
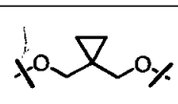
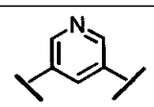
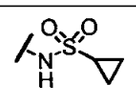
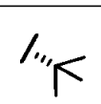
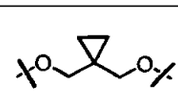
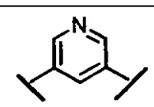
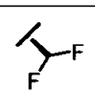
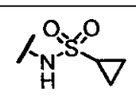
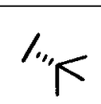
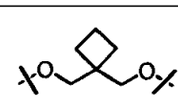
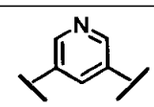
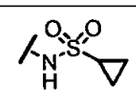
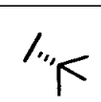
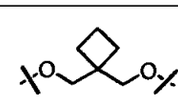
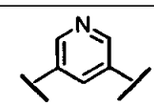
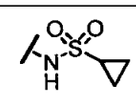
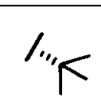
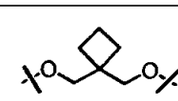
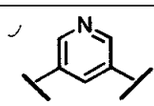
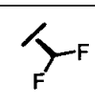
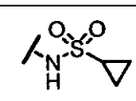
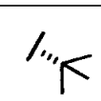
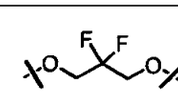
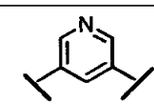
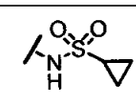
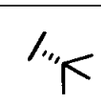
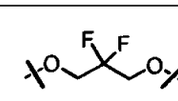
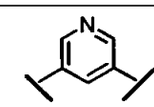
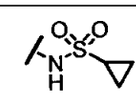
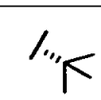
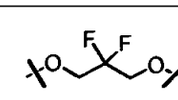
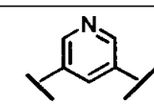
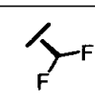
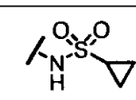
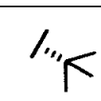
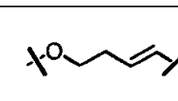
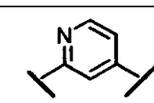
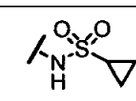
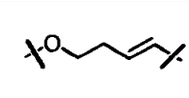
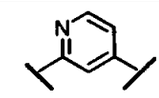
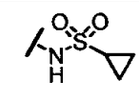
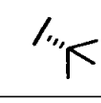
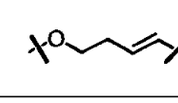
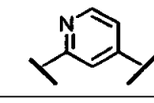
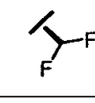
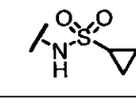
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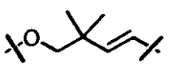
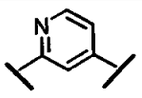
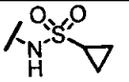
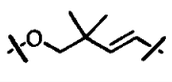
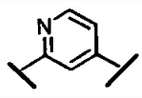
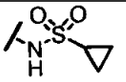
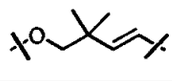
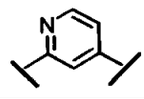
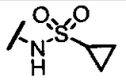
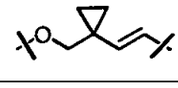
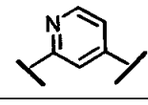
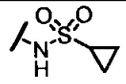
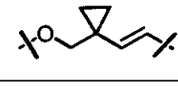
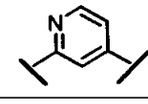
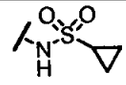
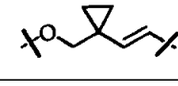
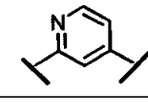
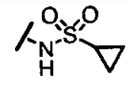
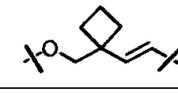
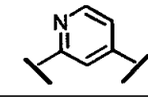
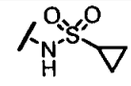
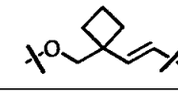
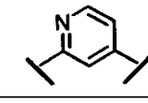
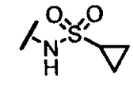
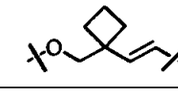
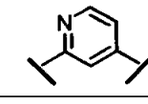
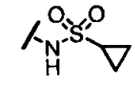
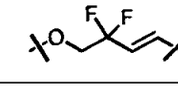
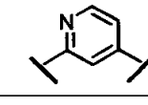
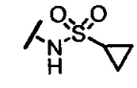
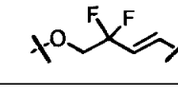
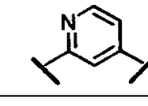
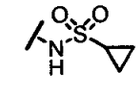
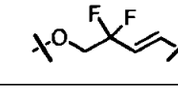
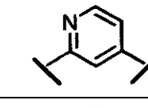
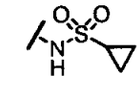
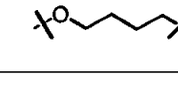
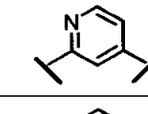
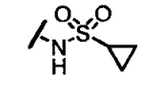
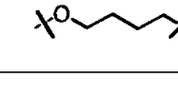
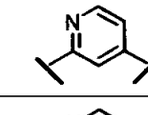
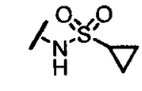
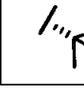
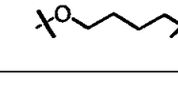
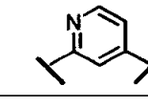
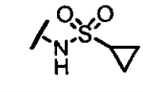
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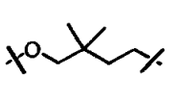
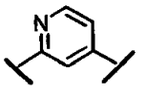
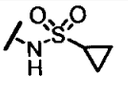
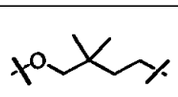
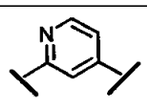
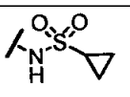
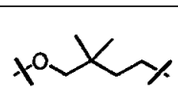
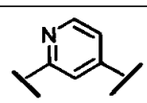
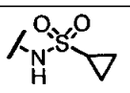
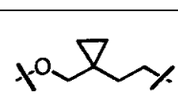
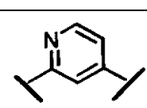
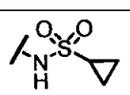
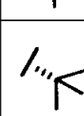
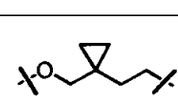
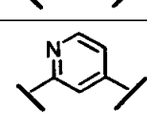
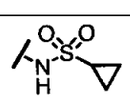
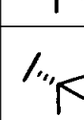
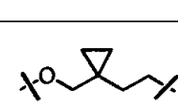
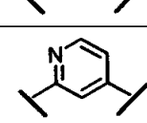
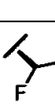
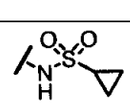
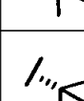
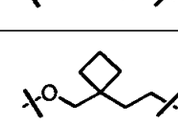
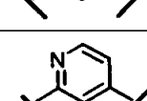
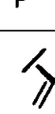
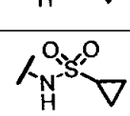
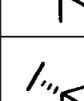
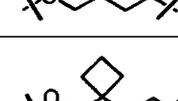
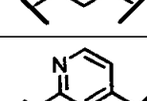
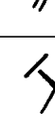
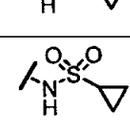
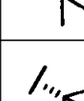
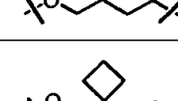
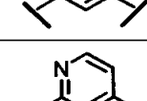
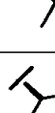
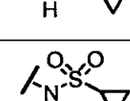
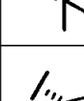
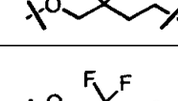
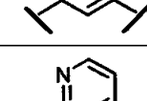
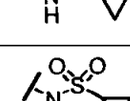
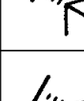
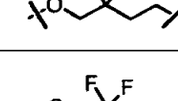
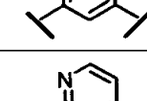
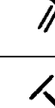
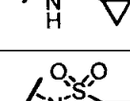
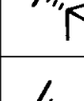
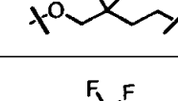
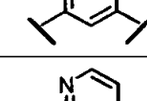
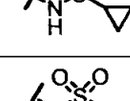
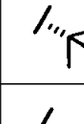
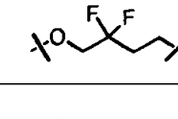
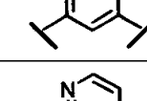
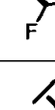
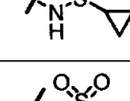
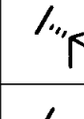
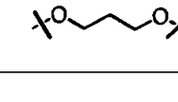
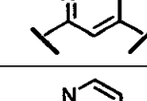
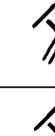
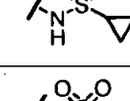
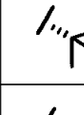
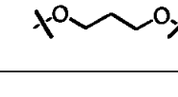
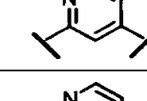
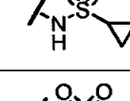
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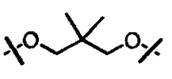
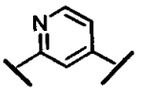
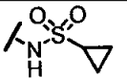
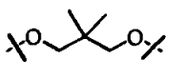
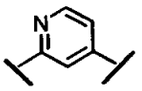
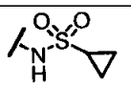
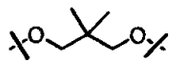
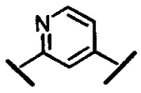
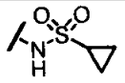
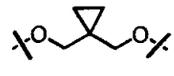
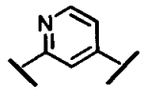
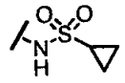
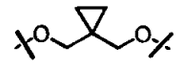
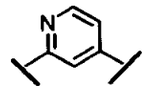
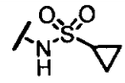
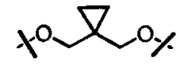
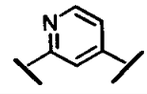
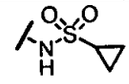
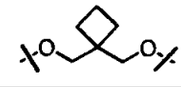
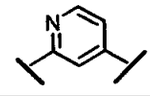
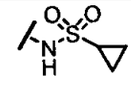
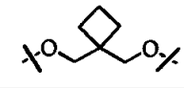
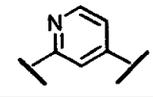
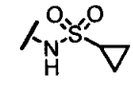
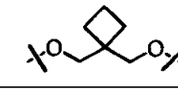
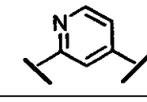
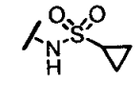
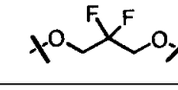
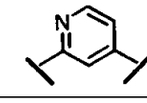
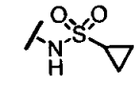
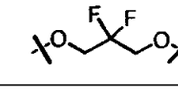
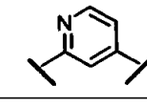
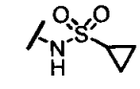
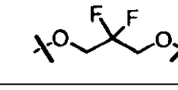
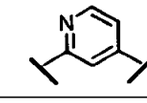
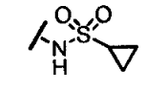
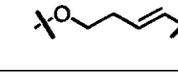
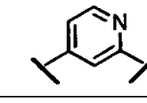
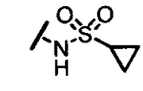
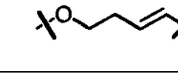
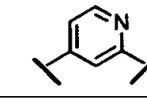
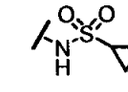
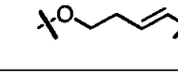
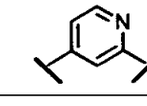
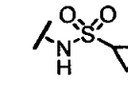
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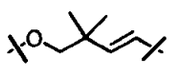
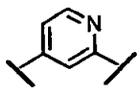
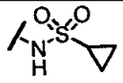
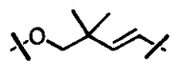
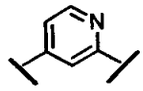
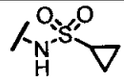
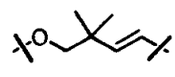
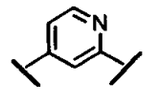
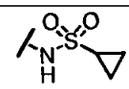
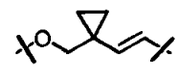
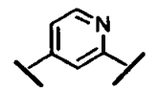
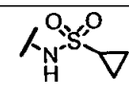
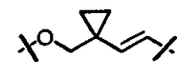
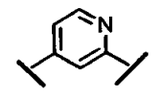
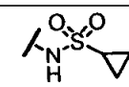
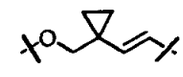
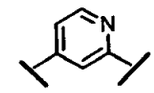
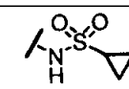
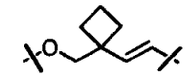
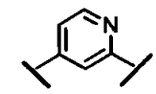
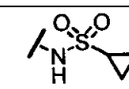
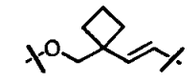
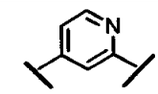
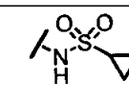
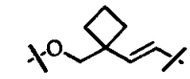
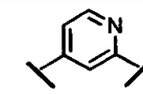
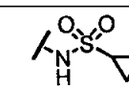
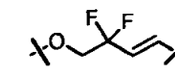
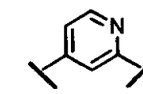
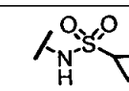
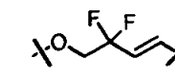
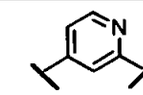
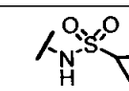
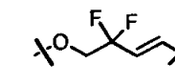
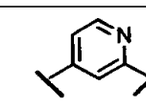
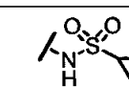
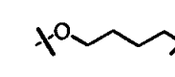
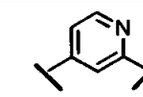
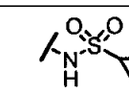
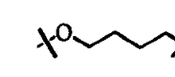
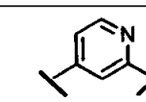
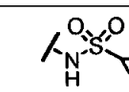
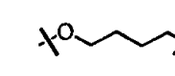
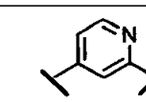
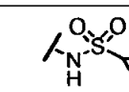
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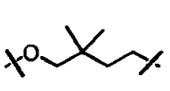
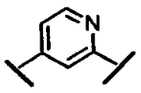
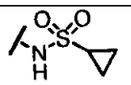
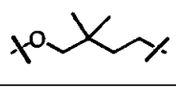
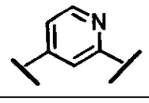
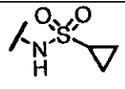
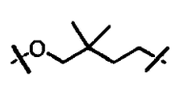
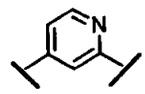
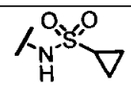
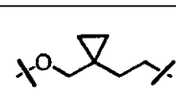
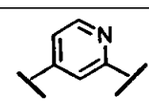
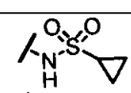
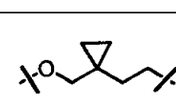
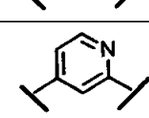
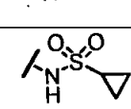
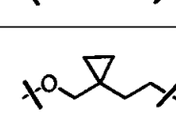
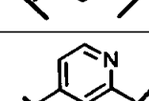
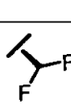
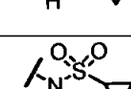
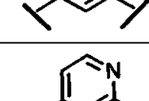
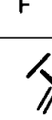
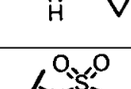
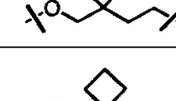
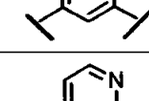
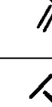
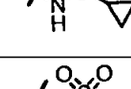
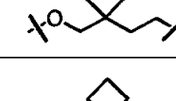
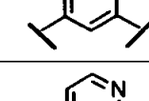
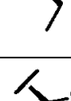
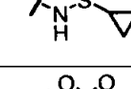
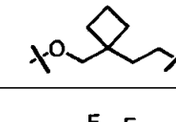
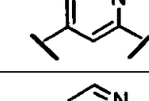
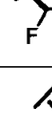
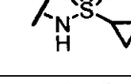
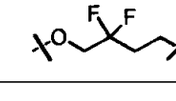
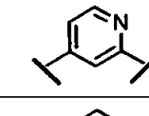
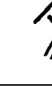
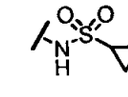
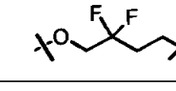
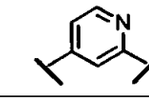
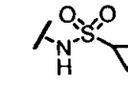
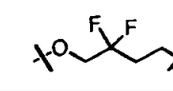
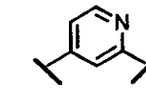
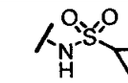
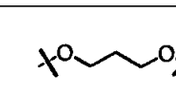
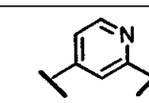
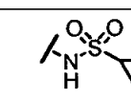
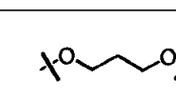
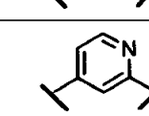
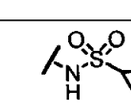
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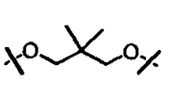
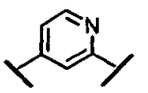
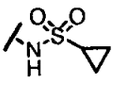
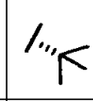
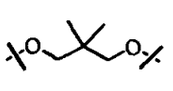
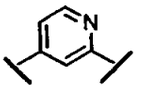
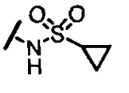
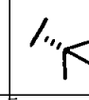
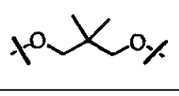
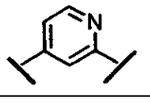
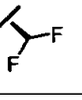
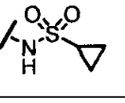
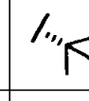
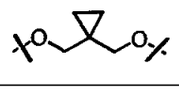
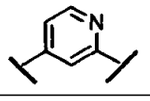
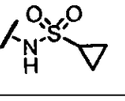
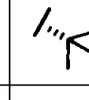
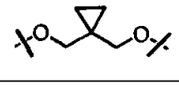
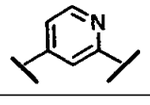
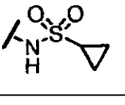
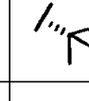
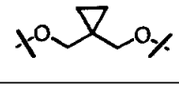
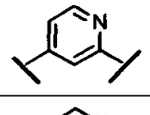
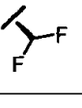
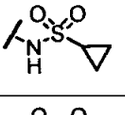
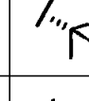
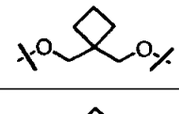
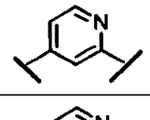
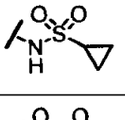
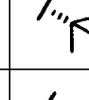
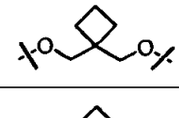
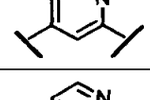
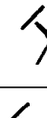
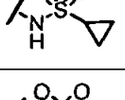
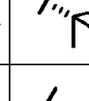
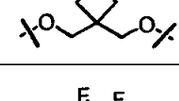
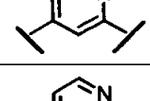
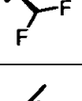
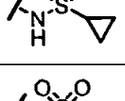
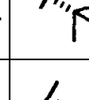
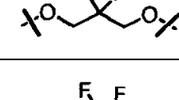
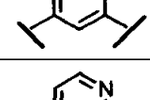
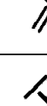
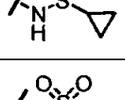
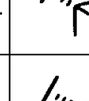
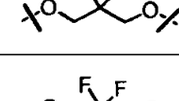
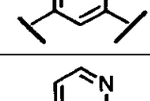
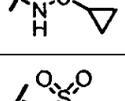
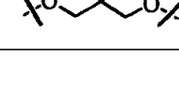
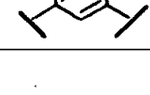
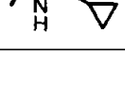
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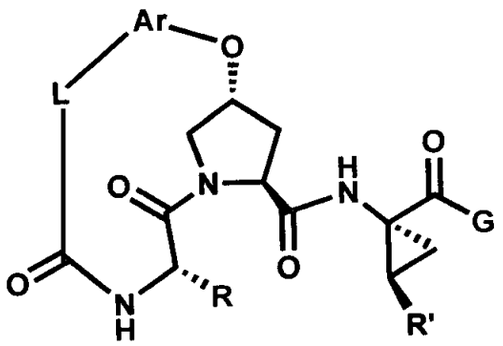
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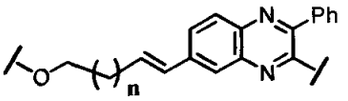
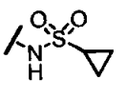
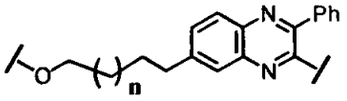
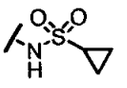
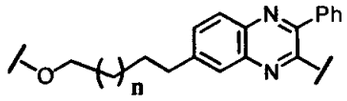
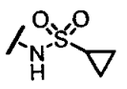
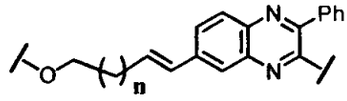
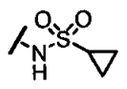
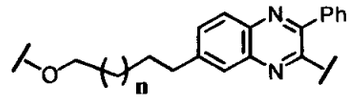
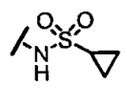
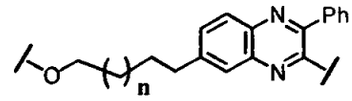
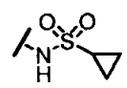
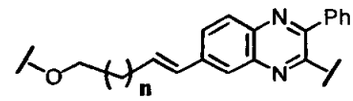
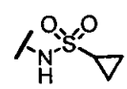
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Los compuestos representativos de la invención también incluyen, pero sin carácter taxativo, los siguientes compuestos (tabla 2) de acuerdo a la fórmula XVI en donde R, L-Ar, n, R' y G se describen para cada ejemplo en la tabla 2.

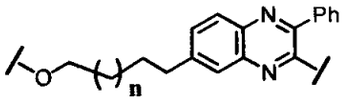
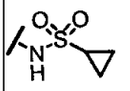
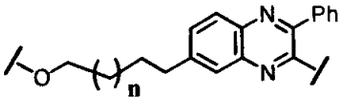
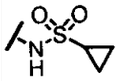
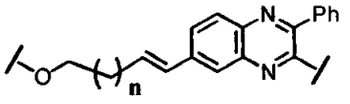
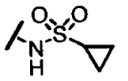
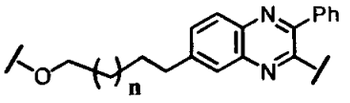
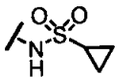
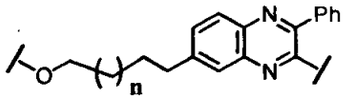
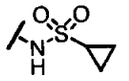
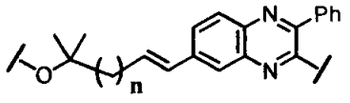
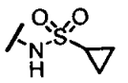
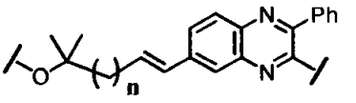
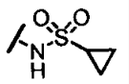
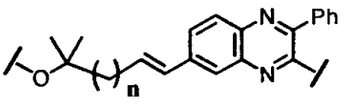
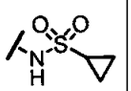
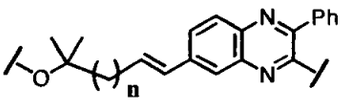
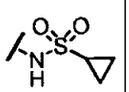
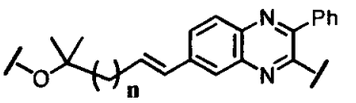
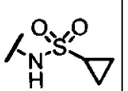
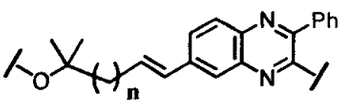
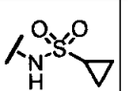
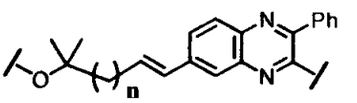
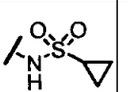


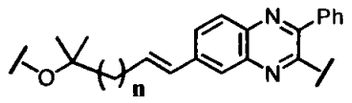
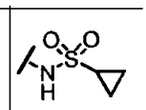
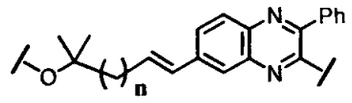
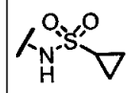
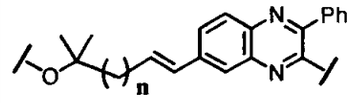
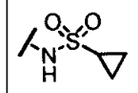
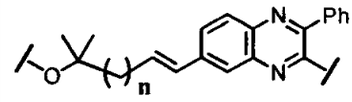
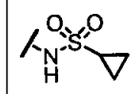
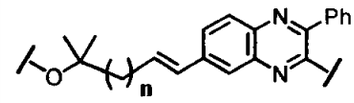
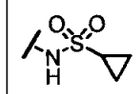
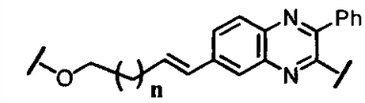
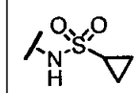
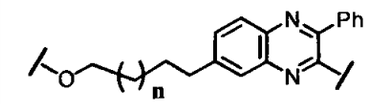
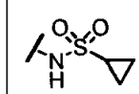
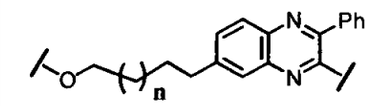
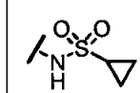
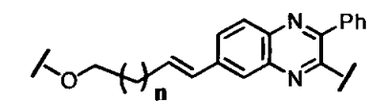
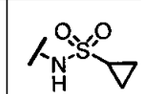
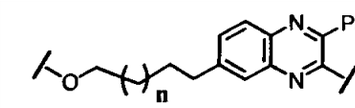
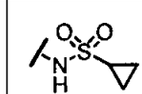
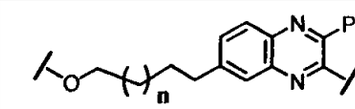
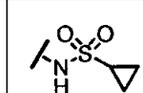
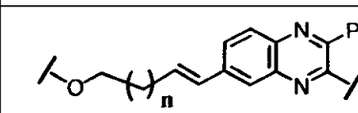
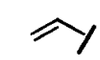
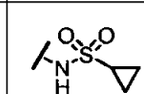
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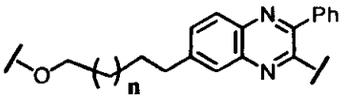
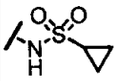
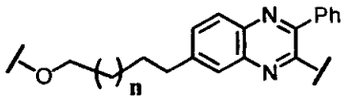
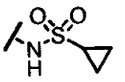
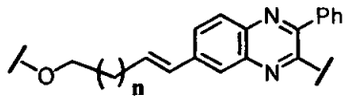
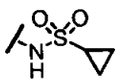
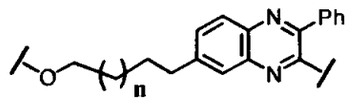
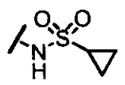
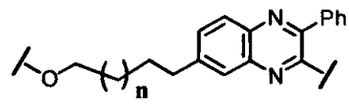
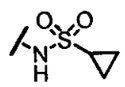
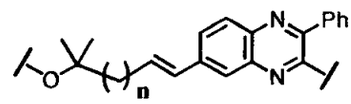
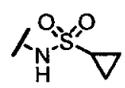
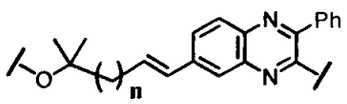
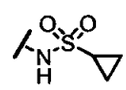
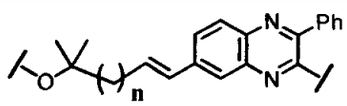
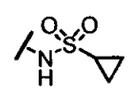
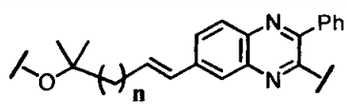
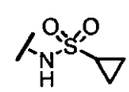
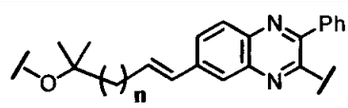
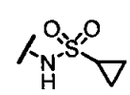
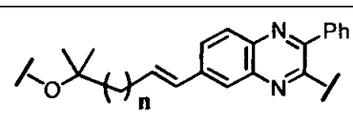
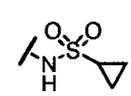
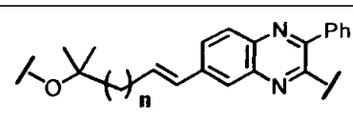
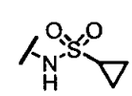
TABLA 2

Ejemplo#	R	L-Ar	n	R'	G
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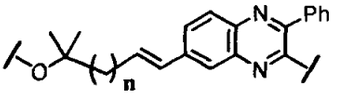
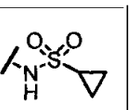
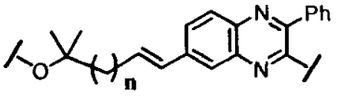
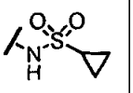
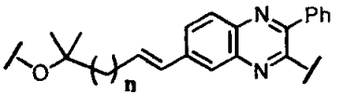
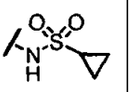
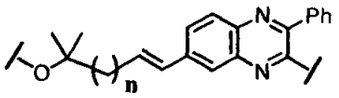
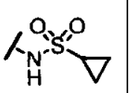
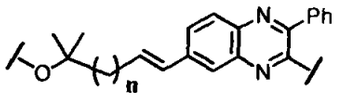
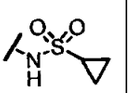
000392

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1424.			1		
1425.			1		
1426.			1		
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1429.			4		
1430.			3		
1431.			3		
1432.			3		
1433.			2		

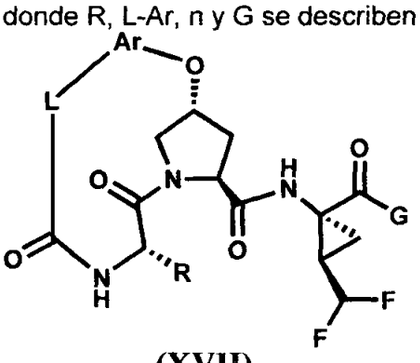
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1438.			1		
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1441.			4		
1442.			3		
1443.			3		
1444.			3		
1445.			2		

1446.			2		
1447.			2		
1448.			1		
1449.			1		
1450.			1		
1451.			4		
1452.			4		
1453.			4		
1454.			3		
1455.			3		
1456.			3		
1457.			2		

000395

1458.			**2**		
1459.			**2**		
1460.			**1**		
1461.			**1**		
1462.			**1**		

Los compuestos representativos de la invención también incluyen, pero sin carácter taxativo, los siguientes compuestos (tabla 3) de acuerdo a la fórmula XVII en donde R, L-Ar, n y G se describen para cada ejemplo en la tabla 3.

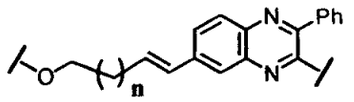
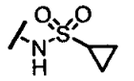
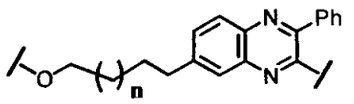
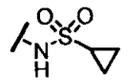
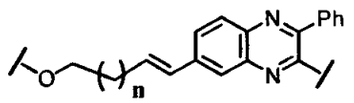
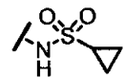
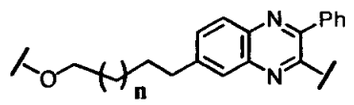
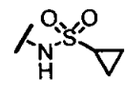
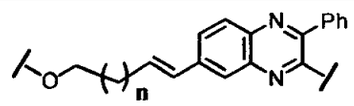
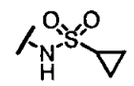
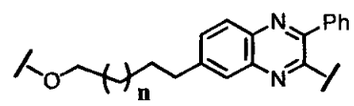
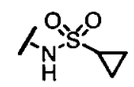
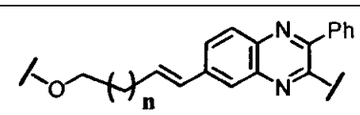
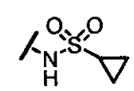
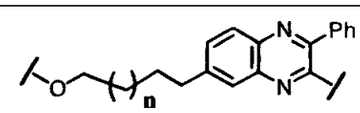
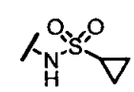
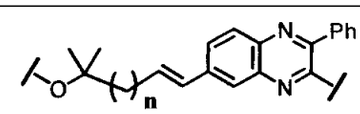
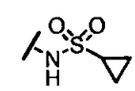
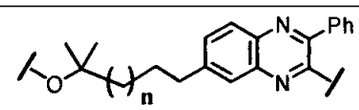
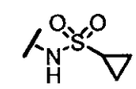
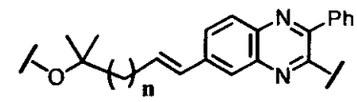
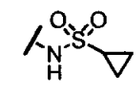
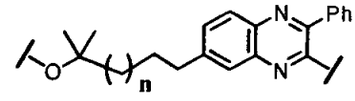
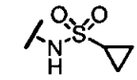


(XVII)

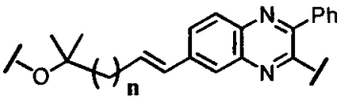
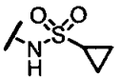
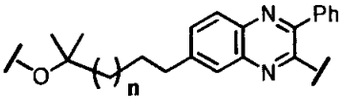
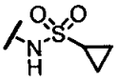
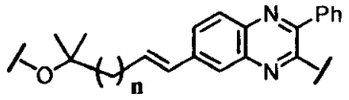
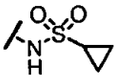
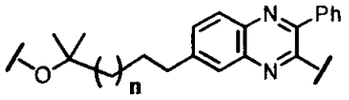
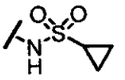
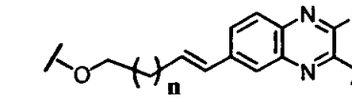
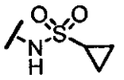
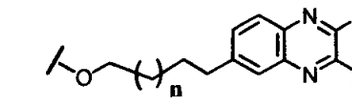
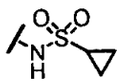
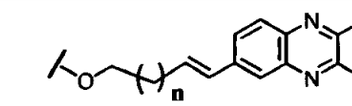
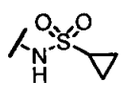
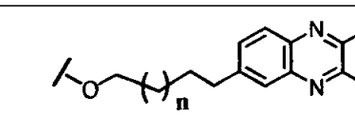
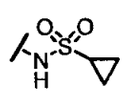
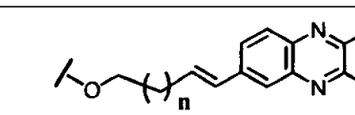
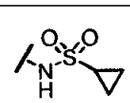
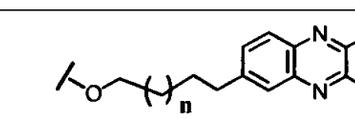
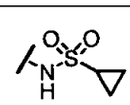
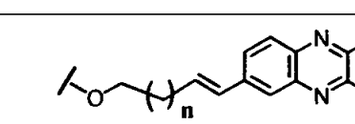
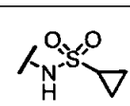
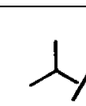
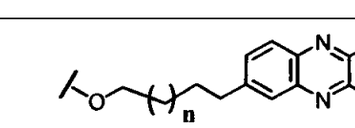
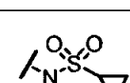
TABLA 3

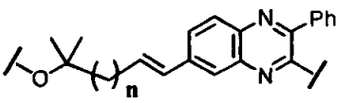
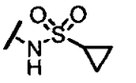
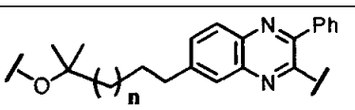
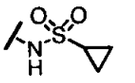
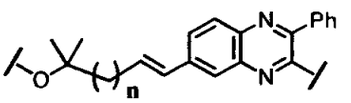
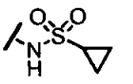
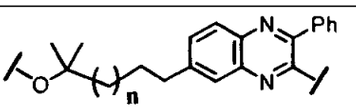
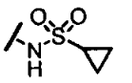
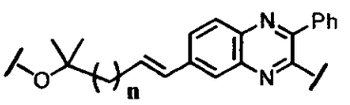
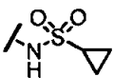
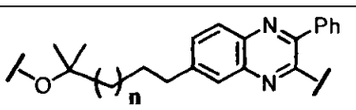
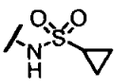
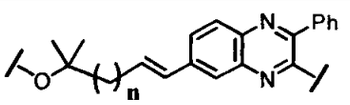
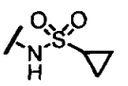
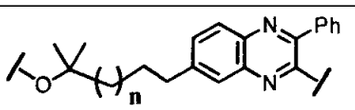
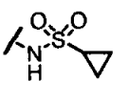
Ejemplo#	R	L-Ar	n	G

000396

1463.			4	
1464.			4	
1465.			3	
1466.			3	
1467.			2	
1468.			2	
1469.			1	
1470.			1	
1471.			4	
1472.			4	
1473.			3	
1474.			3	

000397

1475.			**2**	
1476.			**2**	
1477.			**1**	
1478.			**1**	
1479.			**4**	
1480.			**4**	
1481.			**3**	
1482.			**3**	
1483.			**2**	
1484.			**2**	
1485.			**1**	
1486.			**1**	

1487.			**4**	
1488.			**4**	
1489.			**3**	
1490.			**3**	
1491.			**2**	
1492.			**2**	
1493.			**1**	
1494.			**1**	

La presente invención presenta composiciones farmacéuticas que comprenden un compuesto de la presente invención, o una sal, éster o prodroga del mismo, aceptable para uso farmacéutico.

Los compuestos de la presente invención se pueden administrar como el único agente farmacéutico activo, o usado en combinación con uno o más agentes para tratar o prevenir las infecciones de hepatitis C o los síntomas asociados con la infección por VHC. Los otros agentes a ser administrados en combinación con un compuesto o combinación de compuestos de la invención incluyen terapias para enfermedades causadas por infección por VHC que suprimen la replicación viral de

VHC por mecanismos directos o indirectos. Estos incluyen agentes tales como moduladores de la inmunidad del huésped (por ejemplo, alfa-interferón, alfa-interferón tratado con PEG, beta-interferón, gama-interferón, oligonucléotidos CpG y similares), o compuestos antivirales que inhiben funciones celulares del huésped tales como inosina monofosfato deshidrogenasa (por ejemplo, ribavirina y similares). También se incluyen citoquinas que modulan la función inmune. También se incluyen vacunas que comprenden antígenos del VHC o combinaciones de antígeno adyuvante dirigido contra VHC. También se incluyen agentes que interaccionan con componentes celulares del huésped para bloquear la síntesis de proteínas virales por inhibición del paso de traducción de la replicación viral de VHC iniciado en el sitio interno de entrada al ribosoma (IRES) o por bloqueo de la maduración y liberación de la partícula viral con agentes dirigidos contra la familia de viroporinas de proteínas de membrana tales como, por ejemplo, VHC P7 y similares. Otros agentes a ser administrados en combinación con un compuesto de la presente invención incluyen cualquier agente o combinación de agentes que inhiben la replicación de VHC atacando a proteínas del genoma viral involucradas en la replicación viral. Estos agentes incluyen pero sin carácter taxativo otros inhibidores de la ARN polimerasa dependiente de ARN del VHC tales como, por ejemplo, inhibidores de la polimerasa del tipo nucleósido descritos en WO01 90121(A2), o en la Patente de los EE.UU. No. 6.348.587B1 ó WO0160315 ó WO0132153 o inhibidores no nucleósidos tales como, por ejemplo, bencimidazoles inhibidores de polimerasa descritos en la EP 1162196A1 ó WO0204425 o inhibidores de la proteasa de VHC tales como, por ejemplo, inhibidores del tipo peptidomiméticos tales como BILN2061 y similares o inhibidores de la helicasa del VHC.

Otros agentes a ser administrados en combinación con un compuesto de la presente invención incluyen cualquier agente o combinación de agentes que inhiben la

replicación de otros virus para individuos coinfectados. Estos agentes incluyen, pero sin carácter taxativo, terapias para enfermedades causadas por infecciones de hepatitis B (VHB) tales como, por ejemplo, adefovir, lamivudina, y tenofovir o terapias para enfermedades causadas por infección por el virus de inmunodeficiencia humana (VIH) tales como, por ejemplo, inhibidores de proteasas: ritonavir, lopinavir, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, tipranavir, TMC-114, fosamprenavir; inhibidores de la transcriptasa reversa: zidovudina, lamivudina, didanosina, estavudina, tenofovir, zalcitabina, abacavir, efavirenzo, nevirapina, delavirdina, TMC-125; inhibidores de integrasa: L-870812, S-1360, o inhibidores de entrada: enfuvirtida (T-20), T-1249.

Por lo tanto, un aspecto de la invención está dirigido a un método para el tratamiento o prevención de una infección causada por un virus que contiene ARN que comprende la coadministración a un paciente con necesidad de dicho tratamiento de uno o más agentes que se seleccionan del grupo formado por un modulador de la respuesta inmune del huésped y un segundo agente antiviral, o una combinación de los mismos, con una cantidad terapéuticamente eficaz de un compuesto o combinación de compuestos de la invención, o una sal, estereoisómero, tautómero, prodroga, sal de una prodroga, aceptable para uso farmacéutico, o una combinación de los mismos. Los ejemplos de moduladores de la inmunidad del huésped son, pero sin carácter taxativo, alfa-interferón, alfa-interferón tratado con PEG, beta-interferón, gama-interferón, una citoquina, una vacuna, y una vacuna que comprende un antígeno y un adyuvante, y el mencionado segundo agente antiviral inhibe la replicación del VHC por inhibición de las funciones celulares del huésped asociadas con la replicación viral o por ataque a proteínas del genoma viral.

Otro aspecto de la invención se encuentra dirigido a un método para el tratamiento o prevención de infección causada por un virus que contiene ARN que comprende la coadministración a un paciente con necesidad de dicho tratamiento de un agente o combinación de agentes para tratar o aliviar los síntomas de la infección por VHC que incluyen cirrosis e inflamación del hígado, con una cantidad terapéuticamente eficaz de un compuesto o combinación de compuestos de la invención, o una sal, estereoisómero, tautómero, prodroga, sal de una prodroga, aceptable para uso farmacéutico, o una combinación de los mismos. Aún otro aspecto de la invención provee un método para el tratamiento o prevención de una infección causada por un virus que contienen ARN que comprende la coadministración a un paciente con necesidad de dicho tratamiento uno o más agentes que sirvan para tratar pacientes con enfermedades causadas por infecciones de hepatitis B (VHB), con una cantidad terapéuticamente eficaz de un compuesto o una combinación de compuestos de la invención, o una sal, estereoisómero, tautómero, prodroga, sal de una prodroga, aceptable para uso farmacéutico, o una combinación de los mismos. Un agente para tratar pacientes con enfermedad causada por infección de hepatitis B (VHB) puede ser por ejemplo, pero sin carácter taxativo, L- desoxitimidina, adefovir, lamivudina o tenfovir, o cualquier combinación de los mismos. Los ejemplos de los virus que contienen ARN incluyen, pero sin carácter taxativo, virus de la hepatitis C (VHC).

Otro aspecto de la invención provee un método para el tratamiento o prevención de una infección causada por un virus que contiene ARN que comprende la coadministración a un paciente con necesidad de dicho tratamiento de uno o más agentes para tratar pacientes con enfermedades causadas por infección por el virus de inmunodeficiencia humana (HIV), con una cantidad terapéuticamente eficaz de un compuesto o una combinación de compuestos de la invención, o una sal,

estereoisómero, tautómero, prodroga, sal de una prodroga, aceptable para uso farmacéutico, o una combinación de los mismos. El agente para tratar enfermedades en pacientes causadas por infección por el virus de inmunodeficiencia humana (HIV) puede incluir, pero sin carácter taxativo, ritonavir, lopinavir, indinavir, nelfmavir, saquinavir, amprenavir, atazanavir, tipranavir, TMC-114, fosamprenavir, zidovudina, lamivudina, didanosina, estavudina, tenofovir, zalcitabina, abacavir, efavirenzo, nevirapina, delavirdina, TMC-125, L-870812, S-1360, enfuvirtida (T-20) o T-1249, o cualquier combinación de los mismos. Los ejemplos de virus que contienen ARN incluyen, pero sin carácter taxativo, virus de la hepatitis C (VHC). Además, la presente invención provee el uso de un compuesto o una combinación de compuestos de la invención, o una forma sal, estereoisómero, o tautómero, prodroga, sal de una prodroga, aceptable para uso farmacéutico, o una combinación de los mismos, y uno o más agentes que se seleccionan del grupo formado por un modulador de la inmunidad del huésped y un segundo agente antiviral, o una combinación de los mismos, para preparar un medicamento para el tratamiento de una infección causada por un virus que contiene ARN en un paciente, particularmente virus de la hepatitis C. Los ejemplos de moduladores de la inmunidad del huésped son, pero sin carácter taxativo, alfa-interferón, alfa-interferón tratado con PEG, beta-interferón, gama-interferón, una citoquina, una vacuna, y una vacuna que comprende un antígeno y un adyuvante, y el mencionado segundo agente antiviral inhibe la replicación del VHC por inhibición de las funciones celulares del huésped asociadas con la replicación viral o por ataque a proteínas del genoma viral.

Cuando se usa en el anterior u otros tratamientos, la combinación del compuesto o compuestos de la invención, junto con uno o más agentes tal como se define anteriormente en la presente documentación, se pueden emplear en forma pura

o, cuando tales formas existen, en forma de sal, prodroga, sal de una prodroga, aceptable para uso farmacéutico, o combinación de los mismos. Como alternativa, dicha combinación de agentes terapéuticos se puede administrar como una composición farmacéutica que contiene una cantidad terapéuticamente eficaz del compuesto o combinación de compuestos de interés, o sus formas sal, prodrogas, o sales de prodroga, aceptable para uso farmacéutico, en combinación con uno o más agentes tal como se define anteriormente en la presente documentación, y un vehículo aceptable para uso farmacéutico. Dichas composiciones farmacéuticas se pueden usar para inhibir la replicación de un virus que contiene ARN, particularmente virus de la hepatitis C (VHC), poniendo en contacto el mencionado virus con la mencionada composición farmacéutica. Además, dichas composiciones son útiles para el tratamiento o prevención de una infección causada por un virus que contiene ARN, particularmente virus de la hepatitis C (VHC).

Por lo tanto, otro aspecto de la invención se encuentra dirigido a un método para el tratamiento o prevención de una infección causada por un virus que contiene ARN, particularmente virus de la hepatitis C (VHC), que comprende la administración a un paciente en necesidad de dicho tratamiento de una composición farmacéutica que comprende un compuesto o combinación de compuestos de la invención o una sal, estereoisómero, o tautómero, prodroga, sal de una prodroga, aceptable para uso farmacéutico, o combinación de los mismos, uno o más agentes tal como se define anteriormente en la presente documentación, y un vehículo aceptable para uso farmacéutico.

Cuando se administran como una combinación, los agentes terapéuticos se pueden formular como composiciones separadas las cuales se administran al mismo

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tiempo o en un período de tiempo predeterminado, o los agentes terapéuticos se pueden administrar como una forma única de dosificación unitaria.

Los agentes antivirales contemplados para el uso en dicha terapia combinada incluye agentes (compuestos o productos biológicos) que son eficaces para inhibir la formación y/o replicación de un virus en un mamífero, incluyendo pero sin carácter taxativo agentes que interfieren con los mecanismos del huésped o del virus necesarios para la formación y/o replicación de un virus en un mamífero. Dichos agentes se pueden seleccionar de otro agente anti-VHC; un inhibidor de VIH; un inhibidor de VHA; y un inhibidor de VHB.

Otros agentes anti-VHC incluyen aquellos agentes que son eficaces para disminuir o prevenir la progresión síntomas o enfermedad relacionados con la hepatitis C. Dichos agentes incluyen, pero sin carácter taxativo, agentes inmunomoduladores, inhibidores de proteasa NS3 del VHC, otros inhibidores de polimerasa del VHC, inhibidores de otro blanco en el ciclo de vida del VHC y otros agentes anti-VHC, incluyendo, pero sin carácter taxativo, ribavirina, amantadina, levovirina y viramidina.

Los agentes inmunomoduladores incluyen aquellos agentes (compuestos o productos biológicos) que son eficaces para mejorar o potenciar la respuesta del sistema inmune en un mamífero. Los agentes inmunomoduladores incluyen, pero sin carácter taxativo, inhibidores de la inosina monofosfato deshidrogenasa tales como VX-497 (merimepodib, productos farmacéuticos Vertex), interferones de clase I, interferones de clase II, interferones consenso, asialo-interferones, interferones tratados con PEG e interferones conjugados, incluyendo, pero sin carácter taxativo, interferones conjugados con otras proteínas que incluyen, pero sin carácter taxativo, albúmina humana. Los interferones de clase I son un grupo de interferones que se unen todos a receptores de tipo I, incluyendo los interferones de clase I producidos

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natural o sintéticamente, mientras que los interferones de clase II se unen todos a receptores de tipo II. Los ejemplos de interferones de clase I incluyen, pero sin carácter taxativo, [alfa]-, [beta]-, [delta]-, [omega]-, y [tau]-interferones, mientras que los ejemplos de interferones de clase II incluyen, pero sin carácter taxativo, [gama]-interferones.

Los inhibidores de la proteasa NS3 del VHC incluyen agentes (compuestos o productos biológicos) que son eficaces para inhibir la función de la proteasa NS3 del VHC en un mamífero. Los inhibidores de la proteasa NS3 del VHC incluyen, pero sin carácter taxativo, aquellos compuestos descritos en WO 99/07733, WO 99/07734, WO 00/09558, WO 00/09543, WO 00/59929, WO 03/064416, WO 03/064455, WO 03/064456, WO 2004/030670, WO 2004/037855, WO 2004/039833, WO 2004/101602, WO 2004/101605, WO 2004/103996, WO 2005/028501 , WO 2005/070955, WO 2006/000085, WO 2006/007700 y WO 2006/007708 (todas de Boehringer Ingelheim), WO 02/060926, WO 03/053349, WO03/099274, WO 03/099316, WO 2004/032827, WO 2004/043339, WO 2004/094452, WO 2005/046712, WO 2005/051410, WO 2005/054430 (todas de BMS), WO 2004/072243, WO 2004/093798, WO 2004/113365, WO 2005/010029 (todas de Enanta), WO 2005/037214 (Intermune) y WO 2005/051980 (Schering), y todos los candidatos identificados como VX-950, ITMN-191 y SCH 503034.

Los inhibidores de la polimerasa del VHC incluyen agentes (compuestos o productos biológicos) que son eficaces para inhibir la función de una polimerasa del VHC. Dichos inhibidores incluyen, pero sin carácter taxativo, inhibidores no nucleósidos y nucleósidos de la polimerasa NS5B del VHC. Los ejemplos de los inhibidores de la polimerasa del VHC incluyen, pero sin carácter taxativo, aquellos compuestos descritos en: WO 02/04425, WO 03/007945, WO 03/010140, WO

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03/010141 , WO 2004/064925, WO 2004/065367, WO 2005/080388 y WO 2006/007693 (todas por Boehringer Ingelheim), WO 2005/049622 (Japan Tobacco), WO 2005/014543 (Japan Tobacco),WO 2005/012288 (Genelabs), WO 2004/087714 (IRBM), WO 03/101993 (Neogenesis), WO 03/026587 (BMS), WO 03/000254 (Japan Tobacco), y WO 01/47883 (Japan Tobacco), y los candidatos clínicos XTL-2125, VHC 796, R-1626 y NM 283.

Los inhibidores de otro blanco en el ciclo de vida del VHC incluyen agentes (compuestos o productos biológicos) que son eficaces para inhibir la formación y/o la replicación del VHC en lugar de inhibir la función de la proteasa NS3 del VHC. Dichos agentes pueden interferir tanto con los mecanismos del huésped o del virus del VHC necesarios para la formación y/o replicación del VHC. Los inhibidores de otro blanco en el ciclo de vida del VHC incluyen, pero sin carácter taxativo, inhibidores de entrada, agentes que inhiben un blanco seleccionado entre una helicasa, una proteasa NS2/3 y un sitio interno de entrada del ribosoma (IRES) y agentes que interfieren con la función de otros blancos virales incluyendo pero sin carácter taxativo una proteína NS5A y una proteína NS4B.

Puede ocurrir que un paciente se pueda coinfectar con virus de la hepatitis C y uno o más de otros virus, incluyendo, pero sin carácter taxativo, el virus de inmunodeficiencia humana (HIV), virus de la hepatitis A (HAV) y virus de la hepatitis B (HBV). Por lo tanto, también se contempla la terapia en combinación para tratar dichas coinfecciones por coadministración de un compuesto de acuerdo a la presente invención con al menos un inhibidor de HIV, un inhibidor de HAV y inhibidor de HBV.

De acuerdo a aún otra realización, las composiciones farmacéuticas de la presente invención pueden comprender además inhibidor(es) de otros blancos en el

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ciclo de vida del VHC, entre los que se incluye, pero sin carácter taxativo, helicasa, polimerasa, metaloproteasa, y sitio interno de entrada al ribosoma (IRES).

De acuerdo con otra realización, las composiciones farmacéuticas de la presente invención pueden comprender además otros agentes antivirales, antibacterianos, antifúngicos o anticancerosos, o un modulador inmunológico, u otro agente terapéutico.

De acuerdo a aún otra realización, la presente invención incluye métodos para el tratamiento de infección viral tales como, pero sin carácter taxativo, infecciones de hepatitis C en un sujeto en necesidad de dicho tratamiento por administración al mencionado sujeto de una cantidad eficaz de un compuesto de la presente invención o una sal, éster, o prodroga del mismo, aceptable para uso farmacéutico.

De acuerdo a otra realización, la presente invención incluye métodos para tratar infecciones por hepatitis C en un sujeto en necesidad de dicho tratamiento, mediante la administración a dicho sujeto de una cantidad eficaz como agente antiviral anti-VHC o una cantidad inhibitoria de una composición farmacéutica de la presente invención.

Una realización adicional de la presente invención incluye métodos de tratamiento de muestras biológicas que comprenden poner en contacto muestras biológicas con los compuestos de la presente invención.

Otro aspecto adicional de la presente invención es un proceso para preparar cualquiera de los compuestos de se indican en la presente documentación empleando cualquiera de los medios que se indican en la presente documentación.

Se espera que el inhibidor de la citocromo P450 monooxigenasa usado en esta invención inhiba el metabolismo de los compuestos de la invención. Por lo tanto, el inhibidor de la citocromo P450 monooxigenasa debería estar en una cantidad eficaz

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para inhibir el metabolismo del inhibidor de proteasa. Por lo tanto, el inhibidor de CYP se administra en una cantidad tal que la biodisponibilidad del inhibidor de proteasa aumenta en comparación con la biodisponibilidad en ausencia del inhibidor de CYP.

En una realización, la invención provee métodos para mejorar la farmacocinética de compuestos de la invención. Las ventajas de mejorar la farmacocinética de drogas son reconocidas en el arte (US 2004/0091527; US 2004/0152625; US 2004/0091527). Por lo tanto, una realización de esta invención provee un método para la administración de un inhibidor de CYP3A4 y un compuesto de la invención. Otra realización de esta invención provee un método para la administración de un compuesto de la invención y un inhibidor de isozima 3A4 ("CYP3A4"), isozima 2C19 ("CYP2C19"), isozima 2D6 ("CYP2D6"), isozima 1A2 ("CYP1A2"), isozima 2C9 ("CYP2C9"), o isozima 2E1 ("CYP2E1"). En una realización preferida, el inhibidor de CYP preferentemente inhibe CYP3A4. Cualquier inhibidor de CYP que mejore la farmacocinética de la proteasa NS3/4A de interés, se puede usar en un método de esta invención. Estos inhibidores de CYP incluyen, pero sin carácter taxativo, ritonavir (WO 94/14436), ketoconazol, troleandomicina, 4-metilpirazol, ciclosporina, clometiazol, cimetidina, itraconazol, fluconazol, miconazol, fluvoxamina, fluoxetina, nefazodona, sertralina, indinavir, nelfinavir, amprenavir, fosamprenavir, saquinavir, lopinavir, delavirdina, eritromicina, VX-944, y VX-497. Los inhibidores preferidos de CYP incluyen ritonavir, ketoconazol, troleandomicina, 4-metilpirazol, ciclosporina, y clometiazol.

Se entenderá que la administración de la combinación de la invención por medio de un envase único por paciente, o envases por paciente de cada formulación, conteniendo dentro las instrucciones de empleo para enseñarle al paciente el correcto uso de la invención, es una ventaja adicional deseable de esta invención.

De acuerdo a otro aspecto de la invención es un envase que comprende al menos un compuesto de la invención y un inhibidor de CYP de la invención y unas instrucciones de empleo que contienen las indicaciones de uso de la combinación de la invención. En una realización alternativa de esta invención, el envase del producto farmacéutico además comprende uno o más agentes adicionales tal como se describe anteriormente en la presente documentación. El agente o agentes adicionales pueden ser provistos en el mismo envase o en envases separados.

Otro aspecto de esta invención es un conjunto de elementos envasados para un paciente para uso en el tratamiento de infección por VHC o en la prevención de una infección por VHC, que comprende: una única o una variedad de formulaciones farmacéuticas de cada componente farmacéutico; un recipiente que contiene la o las formulaciones farmacéuticas durante el almacenamiento y previo a la administración; e instrucciones para realizar la administración de la droga de un modo eficaz para tratar o prevenir la infección por VHC.

Por lo tanto, esta invención provee conjuntos de elementos para la administración simultánea o secuencial de un inhibidor de proteasa NS3/4A de la invención y un inhibidor de CYP (y opcionalmente un agente adicional) o se preparan derivados de los mismos en una manera convencional. Generalmente, dicho conjunto de elementos comprenderá, por ejemplo una composición de cada inhibidor y opcionalmente el o los agentes adicionales en un vehículo aceptable para uso farmacéutico (y en una o en una variedad de formulaciones farmacéuticas) e instrucciones escritas para la administración simultánea o secuencial.

En otra realización, se provee un conjunto de elementos envasados que contiene una o más formas de dosificación para la autoadministración; una forma de recipiente, preferentemente sellado, para albergar las formas de dosificación durante

el almacenamiento y previo a su uso; e instrucciones para un paciente para realizar la administración de la droga. Las instrucciones generalmente serán instrucciones escritas en un material impreso dentro del envase, un rótulo, y/o en otros componentes del conjunto de elementos, y la forma o formas de dosificación son tal como se describe anteriormente en la presente documentación. Cada forma de dosificación puede ser contenida individualmente, tal como en una hoja de un laminado metálico o plástico con cada forma de dosificación aislada de las otras en celdas o burbujas individuales, o las formas de dosificación se pueden contener en un único envase, con en una botella plástica. Los presentes conjuntos de elementos generalmente incluirán medios para envasar los componentes individuales del conjunto de elementos, es decir, las formas de dosificación, la forma de envase, y las instrucciones de uso escritas. Dichos formas de envase pueden tener la forma de una caja de cartón o papel, una bolsa plástica o de hoja de aluminio, etc.

DEFINICIONES

A continuación se listan las definiciones de diferentes términos que se usan para describir esta invención. Estas definiciones se aplican a los términos tal como se usan a lo largo de esta memoria descriptiva y reivindicaciones, a menos que se limite de otra manera en casos específicos, ya sea en forma individual o como parte de un grupo más grande.

El término "infección viral" se refiere a la introducción de un virus dentro de células o tejido, por ejemplo, virus de la hepatitis C (VHC). En general, la introducción de un virus también se encuentra asociado con la replicación. La infección viral se puede determinar por medida del título de anticuerpos contra el virus en muestras de fluido biológico, tales como sangre, usando, por ejemplo, un inmunoensayo enzimático. Otros métodos adecuados de diagnóstico incluyen técnicas moleculares,

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tales como RT-PCR, ensayo directo de captura híbrida, amplificación en base a secuencia de ácido nucleico, y similares. Un virus puede infectar un órgano, por ejemplo, hígado, y causar una enfermedad, por ejemplo, hepatitis, cirrosis, enfermedad hepática crónica y carcinoma hepatocelular.

El término "agente anticancerígeno" se refiere a un compuesto o droga con capacidad de prevenir o inhibir la progresión del cáncer. Los ejemplos de dichos agentes incluyen cisplatino, actinomicina D, doxorubicina, vincristina, vinblastino, etopósido, amsacrina, mitoxantrona, tenipósido, taxol, colchicina, ciclosporina A, fenotiazinas o tioxantenos.

El término "agente antifúngico" se debe usar para describir un compuesto el cual se puede usar para tratar una infección fúngica diferente de 3-AP, 3-AMP o prodrogas de 3-AP y 3-AMP de acuerdo a la presente invención. Los agentes antifúngicos de acuerdo a la presente invención incluyen, por ejemplo, terbinafina, fluconazol, itraconazol, posaconazol, clotrimazol, griseofulvina, nistatina, tolnaftato, caspofungina, amfotericina B, amfotericina B liposomal, y amfotericina B en complejo lipídico.

El término "agente antibacteriano" se refiere tanto a antibióticos de origen natural producidos por microorganismos para suprimir el crecimiento de otros microorganismos, como a agentes sintetizados o modificados en el laboratorio que tienen o bien actividad bactericida o bien bacteriostática, por ejemplo, agentes antibacteriano β-lactámicos, glicopéptidos, macrólidos, quinolonas, tetraciclinas, y aminoglicósidos. En general, si un agente antibacteriano es bacteriostático, significa que el agente esencialmente detiene el crecimiento celular (pero no mata a las bacterias); si el agente es bactericida, significa que el agente mata a las células bacterianas (y puede detener el crecimiento antes de matar a las bacterias).

El término "modulador de la inmunidad" se refiere a cualquier sustancia cuyo objetivo sea alterar la acción del sistema inmune humoral o celular de un sujeto. Dichos moduladores de la inmunidad incluyen a inhibidores de la inflamación mediada por células mastocíticas, interferones, interleuquinas, prostaglandinas, esteroides, corticosteroides, factores estimulantes de colonias, factores quimiotácticos, etc.

El término "C_1-C_6 alquilo", o "C_1-C_8 alquilo", tal como se usa en la presente documentación, se refiere a un radical de hidrocarburo saturado, de cadena lineal o ramificada que contiene entre uno y seis, o entre uno y ocho átomos de carbono, respectivamente. Entre los ejemplos de radicales C_1-C_6 alquilo se incluyen, pero sin carácter taxativo, los radicales metilo, etilo, propilo, isopropilo, *n*-butilo, *ter*-butilo, neopentilo, n-hexilo, y entre los ejemplos de radicales alquilo C_1-C_{12} se incluye a, pero sin carácter taxativo, los radicales metilo, etilo, propilo, isopropilo, *n*-butilo, *ter*-butilo, neopentilo, *n*-hexilo, heptilo, octilo.

El término "C_2-C_6 alquenilo", o "C_2-C_8 alquenilo", en el contexto de la presente documentación, designa a un grupo derivado de una porción hidrocarbonada, en donde la porción hidrocarbonada tiene al menos un doble enlace carbono-carbono y contiene entre dos y seis, o entre dos y ocho átomos de carbono, respectivamente. Entre los grupos alquenilo se incluye a, pero sin carácter taxativo, por ejemplo, etenilo, propenilo, butenilo, 1-metil-2-buten-1-ilo, heptenilo, octenilo y similares.

El término "C_2-C_6 alquinilo" o "C_2-C_8 alquinilo" en el contexto de la presente documentación, designa a un grupo derivado de una porción hidrocarbonada, en donde la porción hidrocarbonada tiene al menos un triple enlace carbono-carbono y contiene entre dos y seis, o entre dos y ocho átomos de carbono, respectivamente. Entre los grupos alquinilo representativos se incluye a, pero sin carácter taxativo, por ejemplo, etinilo, 1-propinilo, 1-butinilo, heptinilo, octinilo y similares.

El término "C_3-C_8-cicloalquilo", o "C_3-C_{12}-cicloalquilo", tal como se usa en la presente documentación, designa a un grupo que deriva de un anillo carbocíclico saturado monocíclico o policíclico, en donde el compuesto anular carbocíclico saturado tiene entre 3 y 8, o entre 3 y 12 átomos de anillo, respectivamente. Entre los ejemplos de C_3-C_8 cicloalquilo se incluye a, pero sin carácter taxativo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclopentilo y ciclooctilo; y entre los ejemplos de cicloalquilo C_3-C_{12} se incluye a, pero sin carácter taxativo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, biciclo [2.2.1] heptilo, y biciclo [2.2.2] octilo.

El término "C_3-C_8-cicloalquenilo", o "C_3-C_{12}-cicloalquenilo", tal como se usa en la presente documentación, designa a un grupo que deriva de un compuesto anular carbocíclico monocíclico o policíclico que tiene al menos un doble enlace carbono-carbono, en donde el compuesto anular carbocíclico tiene entre 3 y 8, o entre 3 y 12, átomos de anillo, respectivamente. Entre los ejemplos de C_3-C_8 cicloalquenilo se incluye a, pero sin carácter taxativo, ciclopropenilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, y similares; y entre los ejemplos de C_3-C_{12} cicloalquenilo se incluye a, pero sin carácter taxativo, ciclopropenilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, y similares.

El término "arilo", tal como se usa en la presente documentación, se refiere a un sistema anular carbocíclico monocíclico o bicíclico que tiene uno o dos anillos aromáticos entre los que se incluye a, pero sin carácter taxativo, fenilo, naftilo, tetrahidronaftilo, indanilo, idenilo y similares.

El término "arilalquilo" en el contexto de la presente documentación, se refiere a un residuo C_1-C_3 alquilo o C_1-C_6 alquilo unido a un anillo arilo. Los ejemplos incluye a, pero sin carácter taxativo, bencilo, fenetilo y similares.

El término "heteroarilo," en el contexto de la presente documentación, se refiere a un radical o anillo mono, bi, o tricíclico aromático con entre cinco y diez átomos de anillo de los cuales al menos un átomo de anillo se selecciona entre S, O y N; en donde cualquier N ó S contenido dentro del anillo opcionalmente puede estar oxidado. Heteroarilo incluye a, pero sin carácter taxativo, piridinilo, pirazinilo, pirimidinilo, pirrolilo, pirazolilo, imidazolilo, tiazolilo, oxazolilo, isooxazolilo, tiadiazolilo, oxadiazolilo, tiofenilo, furanilo, quinolinilo, isoquinolinilo, bencimidazolilo, benzooxazolilo, quinoxalinilo y similares.

El término "heteroarilalquilo" en el contexto de la presente documentación, se refiere a un residuo C_1-C_3 alquilo o C_1-C_6 alquilo unido a un anillo heteroarilo. Los ejemplos incluye a, pero sin carácter taxativo, piridinilmetilo, pirimidiniletilo y similares.

El término "sustituido" tal como se usa en la presente documentación, se refiere al reemplazo independiente de uno, dos, o tres o más de los átomos de hidrógeno del compuesto por sustituyentes que incluyen a, pero sin carácter taxativo, -F, -Cl, -Br, -I, -OH, hidroxilo protegido, $-NO_2$, -CN, $-NH_2$, N_3, amino protegido, alcoxilo, tioalcoxilo, oxo, -halo- C_1-C_{12}-alquilo, -halo- C_2-C_{12}-alquenilo, -halo- C_2-C_{12}-alquinilo, -halo-C_3-C_{12}-cicloalquilo, -NH -C_1-C_{12}-alquilo, -NH -C_2-C_{12}-alquenilo, -NH -C_2-C_{12}-alquinilo, -NH -C_3-C_{12}-cicloalquilo, -NH -arilo, -NH -heteroarilo, -NH -heterocicloalquilo, -dialquilamino, -diarilamino, -diheteroarilamino, -O-C_1-C_{12}-alquilo, -O-C_2-C_{12}-alquenilo, -O-C_2-C_{12}-alquinilo, -O-C_3-C_{12}-cicloalquilo, -O-arilo, -O-heteroarilo, -O-heterocicloalquilo, -C(O)-C_1-C_{12}-alquilo, -C(O)- C_2-C_{12}-alquenilo, -C(O)- C_2-C_{12}-alquinilo, -C(O)-C_3-C_{12}-cicloalquilo, -C(O)-arilo, -C(O)-heteroarilo, -C(O)-heterocicloalquilo, $-CONH_2$, -CONH-C_1-C_{12}-alquilo, -CONH- C_2-C_{12}-alquenilo, -CONH- C_2-C_{12}-alquinilo, -CONH-C_3-C_{12}-cicloalquilo, -CONH-arilo, -CONH-heteroarilo, -CONH-heterocicloalquilo, $-OCO_2$- C_1-C_{12}-alquilo, $-OCO_2$- C_2-C_{12}-alquenilo, $-OCO_2$- C_2-C_{12}-alquinilo, $-OCO_2$-C_3-C_{12}-

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cicloalquilo, -OCO_2-arilo, -OCO_2-heteroarilo, -OCO_2-heterocicloalquilo, -$OCONH_2$, -OCONH- C_1-C_{12}-alquilo, -OCONH- C_2-C_{12}-alquenilo, -OCONH- C_2-C_{12}-alquinilo, -OCONH- C_3-C_{12}-cicloalquilo, -OCONH-arilo, -OCONH-heteroarilo, -OCONH-heterocicloalquilo, -NHC(O)- C_1-C_{12}-alquilo, -NHC(O)-C_2-C_{12}-alquenilo, -NHC(O)-C_2-C_{12}-alquinilo, -NHC(O)-C_3-C_{12}-cicloalquilo, -NHC(O)-arilo, -NHC(O)-heteroarilo, -NHC(O)-heterocicloalquilo, -$NHCO_2$-C_1-C_{12}-alquilo, -$NHCO_2$- C_2-C_{12}-alquenilo, -$NHCO_2$- C_2-C_{12}-alquinilo, -$NHCO_2$-C_3-C_{12}-cicloalquilo, -$NHCO_2$-arilo, -$NHCO_2$-heteroarilo, -$NHCO_2$-heterocicloalquilo, -$NHC(O)NH_2$, -NHC(O)NH- C_1-C_{12}-alquilo, -NHC(O)NH-C_2-C_{12}-alquenilo, -NHC(O)NH-C_2-C_{12}-alquinilo, -NHC(O)NH-C_3-C_{12}-cicloalquilo, -NHC(O)NH-arilo, -NHC(O)NH-heteroarilo, -NHC(O)NH-heterocicloalquilo, $NHC(S)NH_2$, -NHC(S)NH- C_1-C_{12}-alquilo, -NHC(S)NH-C_2-C_{12}-alquenilo, -NHC(S)NH-C_2-C_{12}-alquinilo, -NHC(S)NH-C_3-C_{12}-cicloalquilo, -NHC(S)NH-arilo, -NHC(S)NH-heteroarilo, -NHC(S)NH-heterocicloalquilo, -$NHC(NH)NH_2$, -NHC(NH)NH-C_1-C_{12}-alquilo, -NHC(NH)NH-C_2-C_{12}-alquenilo, -NHC(NH)NH-C_2-C_{12}-alquinilo, -NHC(NH)NH-C_3-C_{12}-cicloalquilo, -NHC(NH)NH-arilo, -NHC(NH)NH-heteroarilo, -NHC(NH)NH-heterocicloalquilo, -NHC(NH)-C_1-C_{12}-alquilo, -NHC(NH)-C_2-C_{12}-alquenilo, -NHC(NH)-C_2-C_{12}-alquinilo, -NHC(NH)-C_3-C_{12}-cicloalquilo, -NHC(NH)-arilo, -NHC(NH)-heteroarilo, -NHC(NH)-heterocicloalquilo, -C(NH)NH-C_1-C_{12}-alquilo, -C(NH)NH-C_2-C_{12}-alquenilo, -C(NH)NH-C_2-C_{12}-alquinilo, -C(NH)NH-C_3-C_{12}-cicloalquilo, -C(NH)NH-arilo, -C(NH)NH-heteroarilo, -C(NH)NH-heterocicloalquilo, -S(O)-C_1-C_{12}-alquilo, -S(O)-C_2-C_{12}-alquenilo, -S(O)-C_2-C_{12}-alquinilo, -S(O)-C_3-C_{12}-cicloalquilo, -S(O)-arilo, -S(O)-heteroarilo, -S(O)-heterocicloalquilo -SO_2NH_2, -SO_2NH-C_1-C_{12}-alquilo, -SO_2NH-C_2-C_{12}-alquenilo, -SO_2NH-C_2-C_{12}-alquinilo, -SO_2NH-C_3-C_{12}-cicloalquilo, -SO_2NH-arilo, -SO_2NH-heteroarilo, -SO_2NH-heterocicloalquilo, -$NHSO_2$-C_1-C_{12}-alquilo, -$NHSO_2$-C_2-C_{12}-alquenilo, -$NHSO_2$-C_2-C_{12}-alquinilo, -$NHSO_2$-C_3-C_{12}-cicloalquilo, -$NHSO_2$-arilo, -$NHSO_2$-heteroarilo, -

$NHSO_2$-heterocicloalquilo, $-CH_2NH_2$, $-CH_2SO_2CH_3$, -arilo, -arilalquilo, -heteroarilo, -heteroarilalquilo, -heterocicloalquilo, $-C_3$-C_{12}-cicloalquilo, polialcoxialquilo, polialcoxilo, -metoximetoxilo, -metoxietoxilo, -SH, -S-C_1-C_{12}-alquilo, -S-C_2-C_{12}-alquenilo, -S-C_2-C_{12}-alquinilo, -S-C_3-C_{12}-cicloalquilo, -S-arilo, -S-heteroarilo, -S-heterocicloalquilo, metiltiometilo, o –L'–R', en donde L' es C_1-C_6alquileno, C_2-C_6alquenileno o C_2-C_6-alquinileno, y R' es arilo, heteroarilo, heterociclilo, C_3-C_{12}cicloalquilo o C_3-C_{12}cicloalquenilo. Se entiende que los arilos, heteroarilos, alquilos, y similares pueden estar adicionalmente sustituidos. En algunos casos, cada sustituyente en una porción sustituida se encuentra además sustituida opcionalmente con uno o más grupos, y cada grupo se selecciona en forma independiente entre -F, -Cl, -Br, -I, -OH, $-NO_2$, -CN, o $-NH_2$. Cuando hay al menos dos reemplazos de los átomos de hidrógeno por sustituyentes, los dos sustituyentes se pueden tomar en conjunto para formar un anillo cicloalquílico, cicloalquenílico o heterocíclico.

De acuerdo con la invención, cualquiera de los arilos, arilos sustituidos, heteroarilos y heteroarilos sustituidos que se describen en la presente documentación, pueden ser cualquier grupo aromático. Los grupos aromáticos pueden estar sustituidos o sin sustituir.

Se entiende que cualquier grupo alquilo, alquenilo, alquinilo, cicloalquilo y cicloalquenilo que se describe en la presente documentación también puede ser reemplazado por un grupo alifático, un grupo alicíclico o un grupo heterocíclico. Un "grupo alifático" es un grupo no aromático que puede contener cualquier combinación de átomos de carbono, átomos de hidrógeno, átomos de halógeno, oxígeno, nitrógeno u otros átomos, y que opcionalmente puede contener una o más unidades de insaturación, por ejemplo, doble y/o triple enlace. Un grupo alifático puede ser de cadena lineal, ramificado o cíclico y preferiblemente contiene entre alrededor de 1 y

alrededor de 24 átomos de carbono, más generalmente entre alrededor de 1 y alrededor de 12 átomos de carbono. Además de grupos de hidrocarburo alifático, entre los grupos alifáticos se incluye, por ejemplo, polialcoxialquilos, tales como polialquilenglicoles, poliaminas, y poliiminas, por ejemplo. Dicho grupo alifático puede estar adicionalmente sustituido. Se entiende que se pueden usar grupos alifáticos en lugar de los grupos alquilo, alquenilo, alquinilo, alquileno, alquenileno, y alquinileno que se describen en la presente documentación.

El término "alicíclico" tal como se usa en la presente documentación, designa a un grupo que deriva de un compuesto anular carbocíclico saturado monocíclico o policíclico. Entre los ejemplos se incluye a, pero sin carácter taxativo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, biciclo [2.2.1] heptilo, y biciclo-[2.2.2]-octilo. Dichos grupos alicíclicos pueden estar adicionalmente sustituidos.

Los términos "heterocicloalquilo" y "heterociclilo" se pueden usar en forma intercambiable y se refieren a un anillo no aromático de 3, 4, 5, 6 ó 7 miembros o a un sistema de grupos fusionados bi o tricíclico, en donde (i) cada anillo contiene entre uno y tres heteroátomos que se seleccionan independientemente de oxígeno, azufre y nitrógeno, (ii) cada anillo de 5 miembros tiene entre 0 y 1 enlaces dobles y cada anillo de 6 miembros tiene entre 0 y 2 enlaces dobles, (iii) los heteroátomos de nitrógeno y azufre opcionalmente pueden estar oxidados, (iv) el heteroátomo de nitrógeno opcionalmente puede ser cuaternario, (v) cualquiera de los anillos anteriores pueden estar fusionados a un anillo de benceno, y (vi) el resto de los átomos de anillo son átomos de carbono que opcionalmente pueden estar oxosustituidos. Entre los grupos heterocicloalquilo representativos se incluyen, pero sin carácter taxativo, [1,3]dioxolano, pirrolidinilo, pirazolinilo, pirazolidinilo, imidazolinilo, imidazolidinilo, piperidinilo, piperazinilo, oxazolidinilo, isoxazolidinilo, morfolinilo, tiazolidinilo,

isotiazolidinilo, quinoxalinilo, piridazinonilo, y tetrahidrofurilo. Dichos grupos heterocíclicos pueden estar además sustituidos para dar heterociclos sustituidos.

Será evidente que en las diferentes realizaciones de la invención, el alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, cicloalquinilo, arilalquilo, heteroarialquilo, y heterocicloalquilo sustituido o sin sustituir tienen la intención de ser monovalentes o divalentes. Por consiguiente, los grupos alquileno, alquenileno, y alquinileno, cicloalquileno, cicloalquenileno, cicloalquinoleno, arilalquileno, hetoerarilalquileno y heterocicloalquileno se incluirán en las definiciones anteriores, y son aplicables para proveer las fórmulas de la presente con la valencia apropiada.

El término "grupo activador de hidroxilo", tal como se usa en la presente documentación, se refiere a un grupo químico lábil que en el arte se sabe que activa a un grupo hidroxilo de modo que el mismo saldrá durante los procedimientos de síntesis tales como en una reacción de sustitución o de eliminación. Entre los ejemplos de grupos activadores de hidroxilo se incluye a, pero sin carácter taxativo, mesilato, tosilato, triflato, *p*-nitrobenzoato, fosfonato y similares.

El término "hidroxi o hidroxilo activado", tal como se usa en la presente documentación, se refiere a un grupo hidroxilo activado con un grupo activador de hidroxilo, tal como se definió anteriormente, incluyendo a los grupos mesilato, tosilato, triflato, *p*-nitrobenzoato, fosfonato, por ejemplo.

El término "hidroxilo protegido" tal como se usa en la presente documentación, se refiere a un grupo hidroxilo protegido con un grupo protector de hidroxilo, tal como se definió anteriormente, incluyendo a los grupos benzoílo, acetilo, trimetilsililo, trietilsililo, metoximetilo.

Los términos "halo" o "halógeno" tal como se usan en la presente documentación, se refieren a un átomo que se selecciona de flúor, cloro, bromo e iodo.

Los compuestos que se describen en la presente contienen uno o más centros asimétricos y por lo tanto pueden dar origen a enantiómeros, diasteroisómeros, y otras formas esteroisoméricas que se pueden definir, en términos de estereoquímica absoluta, como (R)- o (S)- , o como (D)- o (L)- para aminoácidos. La presente invención pretende incluir todos estos posibles isómeros, así como sus formas racémicas y ópticamente puras. Los isómeros ópticos se pueden preparar a partir de sus respectivos precursores ópticamente activos por medio de los procedimientos que se describen en la presente documentación, o por medio de la separación de mezclas racémicas. La separación se puede llevar a cabo en presencia de un agente de separación, por medio de cromatografía o por medio de cristalización repetida o mediante alguna combinación de estas técnicas que son conocidas por aquellas personas con experiencia en la materia. Otros detalles con respecto a las separaciones se pueden encontrar en Jacques, et al., *Enantiomers, Racemates, and Resolutions* (Enantiómeros, racematos, y separaciones) (John Wiley & Sons, 1981). Cuando los compuestos que se describen en la presente documentación contienen dobles enlaces olefínicos, u otros centros de asimetría geométrica, y a menos que se especifique de otra manera, se tiene la intención de incluir a los compuestos tanto como isómeros geométricos E y Z. De forma similar, también se tiene la intención de incluir a todas las formas tautoméricas. La configuración de cualquier doble enlace carbono-carbono que aparece en la presente documentación se selecciona por conveniencia solamente, y no tiene la intención de designar una configuración en particular a menos que el texto así lo indique; por consiguiente un doble enlace

carbono-carbono que se represente arbitrariamente en la presente como *trans* puede ser *cis*, *trans*, o una mezcla de los dos en cualquier proporción.

El término "sujeto" tal como se usa en la presente se refiere a un animal. Un sujeto por lo tanto se refiere a, por ejemplo, perros, gatos, caballos, vacas, cerdos, conejillos de india y similares. Preferentemente el sujeto es un humano. Cuando el sujeto es un humano, en la presente documentación se lo puede mencionar como paciente.

Tal como se usa en la presente documentación, el término "sal aceptable para uso farmacéutico" se refiere a aquellas sales de los compuestos preparados de acuerdo con el proceso de la presente invención que son, dentro del alcance del juicio médico válido, apropiadas para usar en contacto con los tejidos de humanos y animales inferiores sin toxicidad, irritación, respuesta alérgica indebida y similar, y están en proporción con una relación beneficio/riesgo razonable. Las sales aceptables para uso farmacéutico son bien conocidas en el arte.

El término "grupo protector de hidroxilo," tal como se usa en la presente documentación, se refiere a un grupo químico lábil que en el arte se sabe que protege a un grupo hidroxilo contra reacciones indeseadas durante los procedimientos de síntesis. Luego de dicho(s) procedimiento(s) de síntesis, el grupo protector de hidroxilo, tal como se describe en la presente documentación, se puede eliminar en forma selectiva. Los grupos protectores de hidroxi que se conocen en el arte se describen en forma general en T.H. Greene y P.G. M. Wuts, *Protective Groups in Organic Synthesis* (Grupos protectores en síntesis orgánica), 3ra edición, John Wiley & Sons, Nueva York (1999). Entre los ejemplos de grupos protectores de hidroxilo se incluyen benciloxicarbonilo, 4-nitrobenciloxicarbonilo, 4-bromobenciloxicarbonilo, 4-metoxibenciloxicarbonilo, metoxicarbonilo, *tert*-butoxicarbonilo, isopropoxicarbonilo,

difenilmetoxicarbonilo, 2,2,2-tricloroetoxicarbonilo, 2-(trimetilsilil)etoxicarbonilo, 2-furfuriloxicarbonilo, aliloxicarbonilo, acetilo, formilo, cloroacetilo, trifluoroacetilo, metoxiacetilo, fenoxiacetilo, benzoílo, metilo, *t*-butilo, 2,2,2-tricloroetilo, 2-trimetilsilil etilo, 1,1-dimetil-2-propenilo, 3-metil-3-butenilo, alilo, bencilo, *para*-metoxibencildifenilmetilo, trifenilmetil (tritilo), tetrahidrofurilo, metoximetilo, metiltiometilo, benciloximetilo, 2,2,2-tricloroetoximetilo, 2-(trimetilsilil)etoximetilo, metanesulfonilo, *para*-toluenosulfonilo, trimetilsililo, trietilsililo, triisopropilsililo, y similares. Entre los grupos protectores de hidroxilo preferidos para la presente invención están el acetilo (Ac o -C(O)CH_3), benzoílo (Bz o -C(O)C_6H_5), y trimetilsililo (TMS o-Si(CH_3)$_3$). Berge, *et al.* describe en detalle las sales aceptables para uso farmacéutico en J. Pharmaceutical Sciences, 66: 1-19 (1977). Las sales se pueden preparar *in situ* durante el aislamiento final y purificación de los compuestos de la invención, o separadamente mediante reacción de la función base libre con un ácido orgánico apropiado. Entre los ejemplos de sales aceptables para uso farmacéutico se incluyen sin carácter taxativo las sales de adición ácida no tóxicas, por ejemplo, sales de un grupo amino formadas con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido fosfórico, ácido sulfúrico y ácido perclórico o con ácidos orgánicos tales como ácido acético, ácido maleico, ácido tartárico, ácido cítrico, ácido succínico o ácido malónico, o mediante el uso de otros métodos que se usan en el arte tales como intercambio iónico. Entre otras sales aceptables para uso farmacéutico se incluye a, pero sin carácter taxativo, sales de adipato, alginato, ascorbato, aspartato, bencenosulfonato, benzoato, bisulfato, borato, butirato, camforato, camforsulfonato, citrato, ciclopentanopropionato, digluconato, dodecilsulfato, etanosulfonato, formato, fumarato, glucoheptonato, glicerofosfato, gluconato, hemisulfato, heptanoato, hexanoato, iodhidrato, 2-hidroxi-etanosulfonato, lactobionato, lactato, laurato, lauril

sulfato, malato, maleato, malonato, metanosulfonato, 2-naftalenosulfonato, nicotinato, nitrato, oleato, oxalato, palmitato, pamoato, pectinato, persulfato, 3-fenilpropionato, fosfato, picrato, pivalato, propionato, estoarato, succinato, sulfato, tartrato, tiocianato, *p*-toluenosulfonato, undecanoato, valerato, y similares. Las sales de metales alcalinos o alcalinos térreos representativas incluyen sales de sodio, litio, potasio, calcio, magnesio, y similares. Otras sales aceptables para uso farmacéutico incluyen, cuando sea apropiado, cationes no tóxicos de amonio, amonio cuaternario, y cationes amina que se forman usando contraiones tales como haluro, hidróxido, carboxilato, sulfato, fosfato, nitrato, alquilo con entre 1 y 6 átomos de carbono, sulfonato y aril sulfonato.

El término "grupo protector de amino", tal como se usa en la presente documentación, se refiere a un grupo químico lábil que en el arte se sabe que protege a un grupo amino contra reacciones indeseadas durante los procedimientos de síntesis. Luego de dicho(s) procedimiento(s) de síntesis, el grupo protector de amino, tal como se describe en la presente documentación, se puede eliminar en forma selectiva. Los grupos protectores de amino que se conocen en el arte se describen en forma general en T.H. Greene y P.G. M. Wuts, *Protective Groups in Organic Synthesis* (Grupos protectores en síntesis orgánica), 3ra edición, John Wiley & Sons, Nueva York (1999). Entre los ejemplos de grupos protectores de amino se incluye a, pero sin carácter taxativo, *t*-butoxicarbonilo, 9-fluorenilmetoxicarbonilo, benciloxicarbonilo, y similares.

Según se usa en la presente documentación, el término "éster aceptable para uso farmacéutico" se refiere a ésteres de los compuestos obtenidos por el proceso de la presente invención que hidrolizan *in vivo* e incluyen aquellos que se descomponen fácilmente en el cuerpo humano para dejar el compuesto de origen o una sal del mismo. Los grupos éster apropiados incluyen, por ejemplo, aquellos derivados de

ácidos carboxílicos alifáticos aceptables para uso farmacéutico, en particular ácidos alcanoico, alquenoico, cicloalcanoico y alcanodioico, donde cada unidad alquilo o alquenilo con ventaja no tiene más de 6 átomos de carbono. Entre los ejemplos de ésteres particulares se incluye a, pero sin carácter taxativo, formatos, acetatos, propionatos, butiratos, acrilatos y etilsuccinatos.

El término "prodrogas aceptables para uso farmacéutico" tal como se usa en la presente se refiere a aquellas prodrogas de los compuestos obtenidos por el proceso de la presente invención que son, dentro del alcance del juicio médico válido, apropiadas para uso en contacto con los tejidos de humanos y de animales inferiores sin toxicidad, irritación, respuesta alérgica indebida, y similares, con una proporción razonable de relación beneficio/riesgo, y efectivas para el uso que se pretende, así como las formas zwiteriónicas, cuando es posible, de los compuestos de la presente invención. "Prodroga", en el contexto de la presente se refiere a un compuesto, que se puede convertir *in vivo* por medios metabólicos (por ejemplo, por hidrólisis) para dar cualquier compuesto que responda a las fórmulas de la presente invención. En el arte se conocen diversas formas de prodrogas o profármacos, por ejemplo, los que se analizan en Bundgaard, (ed.), *Design of Prodrugs,* (Diseño de prodrogas, Elsevier (1985); Widder, et al. (ed.), Methods in Enzymology (Métodos en enzimología, vol. 4, Academic Press (1985); Krogsgaard-Larsen, et al., (ed). "Design and Appplication of Prodrugs, Textbook of Drug Design and Development, (Diseño y aplicación de prodrogas, libro de diseño y desarrollo de drogas) Capítulo 5, 113-191 (1991); Bundgaard, et al., *Journal of Drug Deliver Reviews*, 8:1-38(1992); Bundgaard, *J. of Pharmaceutical Sciences*, 77:285 y sig. (1988); Higuchi y Stella (eds.) *Pro-drugs as Novel Drug Delivery Systems* (Prodrogas como nuevos sistemas de administración), American Chemical Society (1975); y Bernard Testa & Joachim Mayer, *"Hidrolysis In*

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Drug and Prodrug Metabolism: Chemistry, Biochemistry and enzymology, (Hidrólisis en el metabolismo de drogas y prodrogas: química, bioquímica y enzimología)" John Wiley y Sons, Ltd. (2002).

El término "acilo" incluye residuos que derivan de ácidos, entre los que se incluye a, pero sin carácter taxativo, ácidos carboxílicos, ácidos carbámicos, ácidos carbónicos, ácidos sulfónicos, y ácidos fosforosos. Entre los ejemplos se incluye a carbonilos alifáticos, carbonilos aromáticos, sulfonilos alifáticos, sulfinilos aromáticos, sulfinilos alifáticos, fosfatos aromáticos y fosfatos alifáticos. Entre los ejemplos de carbonilos alifáticos se incluye a, pero sin carácter taxativo, acetilo, propionilo, 2-fluoroacetilo, butirilo, 2-hidroxiacetilo, y similares.

El término "solvente aprótico", tal como se usa en la presente documentación, se refiere a un solvente que es relativamente inerte a la actividad de los protones, o sea, que no actúa como donador de protones. Entre los ejemplos se incluye a, pero sin carácter taxativo, hidrocarburos, tales como hexano y tolueno, por ejemplo, hidrocarburos halogenados, tales como, por ejemplo, cloruro de metileno, cloruro de etileno, cloroformo, y similares, compuestos heterocíclicos, tales como, por ejemplo, tetrahidrofurano y *N*-metilpirrolidinona, y éteres tales como éter dietílico, éter bis-metoximetílico. Dichos solventes son bien conocidos por una persona con experiencia en la materia, y se pueden preferir solventes individuales o mezclas de los mismos para compuestos y condiciones de reacción específicas, dependiendo de factores tales como la solubilidad de los reactivos, reactividad de los reactivos y rangos de temperatura preferidos, por ejemplo. Otros detalles sobre los solventes apróticos se pueden encontrar en libros de química orgánica o en monografías especializadas, por ejemplo: *Organic Solvents: Physical Properties and Methods of Purification* (Solventes orgánicos: propiedades físicas y métodos de purificación), 4ta ed., editado por John A.

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Riddick *et al.*, Vol. II, en *Techniques of Chemistry Series* (Series de técnicas de química), John Wiley & Sons, NY, 1986.

Los términos "solvente orgánico protogénico", o "solvente prótico", tal como se usan en la presente documentación, se refieren a un solvente que tiende a proveer protones, tales como un alcohol, por ejemplo, metanol, etanol, propanol, isopropanol, butanol, *t*-butanol, y similares. Dichos solventes son bien conocidos por una persona con experiencia en la materia, y se pueden preferir solventes individuales o mezclas de los mismos para compuestos y condiciones de reacción específicas, dependiendo de factores tales como la solubilidad de los reactivos, reactividad de los reactivos y rangos de temperatura preferidos, por ejemplo. Otros detalles sobre los solventes protogénicos se pueden encontrar en libros de química orgánica o en monografías especializadas, por ejemplo: *Organic Solvents: Physical Properties and Methods of Purification* (Solventes orgánicos: propiedades físicas y métodos de purificación), 4ta ed., editado por John A. Riddick *et al.*, Vol. II, en *Techniques of Chemistry Series* (Series de técnicas de química), John Wiley & Sons, NY, 1986.

Las combinaciones de sustituyentes y variables vislumbradas por esta invención son solamente aquellas que resultan en la formación de compuestos estables. El término "estable", tal como se usa en la presente documentación, se refiere a compuestos que poseen estabilidad suficiente para permitir la fabricación y que mantienen la integridad del compuesto durante un período de tiempo suficiente para ser útiles para los propósitos que se detallan en la presente documentación (por ejemplo, administración terapéutica o profiláctica a un sujeto).

Los compuestos sintetizados se pueden separar de una mezcla de reacción y posteriormente purificar por medio de un método tal como cromatografía en columna, cromatografía liquida de alta resolución, o recristalización. Además, los diferentes

pasos de síntesis se pueden llevar a cabo en una secuencia u orden alternado para dar los compuestos deseados. Además, los solventes, temperaturas, duración de las reacciones, etc. que se ilustran en la presente documentación son solamente con fines ejemplificativos y las variaciones en las condiciones de reacción pueden producir los productos macrocíclicos con puente deseados de la presente invención. Las transformaciones químicas de síntesis y las metodologías de grupos protectores (protección y desprotección) que son útiles en la síntesis de compuestos incluyen a, por ejemplo, aquellos que se describen en R. Larock, *Comprehensive Organic Transformations* (Transformaciones orgánicas detalladas), VCH Publishers (1989); T.W. Greene y P.G.M. Wuts, *Protective Groups in Organic Synthesis* (Grupos protectores en síntesis orgánica), 2da. Ed., John Wiley and Sons (1991); L. Fieser y M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis* (Reactivos de Fieser y Fieser para síntesis orgánica), John Wiley and Sons (1994); y L. Paquette, ed., *Enciclopedia of Reagents for Organic Synthesis* (Enciclopedia de reactivos para síntesis orgánica), John Wiley and Sons (1995).

Los compuestos de esta invención se pueden modificar agregando diversas funcionalidades por medio de las vías sintéticas que se describen en la presente documentación para aumentar las propiedades de selectividad biológica. Dichas modificaciones incluyen aquellas que incrementan la penetrancia biológica en un sistema biológico dado (por ejemplo, sangre, sistema linfático, sistema nervioso central), que incrementan la disponibilidad oral, que incrementan la solubilidad para permitir la administración por inyección, que alteran el metabolismo y que alteran la tasa de excreción.

COMPOSICIONES FARMACÉUTICAS

Las composiciones farmacéuticas de la presente invención comprenden una cantidad terapéuticamente eficaz de un compuesto de la presente invención formulado junto con uno o más vehículos aceptables para uso farmacéutico. Según se usa en la presente documentación, el término "vehículo aceptable para uso farmacéutico" significa una carga, diluyente, material encapsulante o auxiliar de formulación no tóxica, inerte, sólido, semisólido o líquido de cualquier tipo. Algunos ejemplos de materiales que pueden servir como vehículos aceptables para uso farmacéutico son azúcares tales como lactosa, glucosa y sacarosa; almidones tales como almidón de maíz y almidón de papa; celulosa y sus derivados, tales como carboximetilcelulosa sódica, etilcelulosa y acetato de celulosa; goma tragacanto en polvo; malta; gelatina; talco; excipientes tales como manteca de cacao y ceras para supositorios; aceites tales como aceite de maní, aceite de algodón; aceite de cártamo; aceite de sésamo; aceite de oliva; aceite de maíz y aceite de soja; glicoles; tales como propilenglicol; ésteres tales como oleato de etilo y laurato de etilo; agar; agentes reguladores del pH tales como hidróxido de magnesio e hidróxido de aluminio; ácido algínico; agua libre de pirógenos; solución salina isotónica; solución de Ringer; alcohol etílico, y soluciones amortiguadoras de pH de fosfato, así como otros lubricantes compatibles no tóxicos tales como laurilsulfato de sodio y estearato de magnesio, así como agentes colorantes, agentes desmoldantes, agentes de recubrimiento, agentes endulzantes, saborizantes y aromatizantes, en la composición también pueden estar presentes conservantes y antioxidantes, de acuerdo con el juicio de quién la formule. Las composiciones farmacéuticas de esta invención se pueden administrar a humanos y otros animales por vía oral, rectal, parenteral, intracisternal, intravaginal, intraperitoneal, tópica (por ejemplo como polvos, ungüentos o gotas), bucal, o como atomizado oral o nasal.

Las composiciones farmacéuticas de esta invención se pueden administrar en forma oral, parenteral, por atomizado e inhalación, tópica, rectal, nasal, bucal, vaginal o a través de un reservorio implantado, preferiblemente por medio de administración oral o por inyección. Las composiciones farmacéuticas de esta invención pueden contener cualquier vehículo, adyuvante o transportador no tóxico aceptable para uso farmacéutico. En algunos casos, el pH de la formulación se puede ajustar con ácidos, bases o amortiguadores aceptables para uso farmacéutico para potenciar la estabilidad del compuesto formulado o de su forma de presentación. El término parenteral tal como se usa en la presente documentación incluye inyección o técnicas de infusión subcutánea, intracutánea, intravenosa, intramuscular, intraarticular, intraarterial, intrasinovial, intraesternal, intratecal, intralesional e intracraneal.

Las formas de dosificación líquidas para administración oral incluyen emulsiones, microemulsiones, soluciones, suspensiones, jarabes y elixires aceptables para uso farmacéutico. Además de los compuestos activos, las formas de dosificación líquidas pueden contener diluyentes inertes que se usan comúnmente en el arte tales como, por ejemplo, agua u otros solventes, agentes solubilizantes y emulsionantes tales como alcohol etílico, alcohol isopropílico, carbonato de etilo, acetato de etilo, alcohol bencílico, benzoato de bencilo, propilenglicol, 1,3-butilenglicol, dimetilformamida, aceites (en particular, aceites de semilla de algodón, de maní, de maíz, de germen, de oliva, de ricino, y de sésamo), glicerol, alcohol tetrahidrofurfurílico, polietilenglicoles y ésteres de ácido graso de sorbitan, y mezclas de los mismos. Junto con los diluyentes inertes, las composiciones orales también pueden incluir coadyuvantes tales como agentes humectantes, emulsionantes y agentes de suspensión, agentes endulzantes, saborizantes, y aromatizantes.

Los preparados inyectables, por ejemplo, suspensiones estériles inyectables acuosas o al aceite se pueden formular de acuerdo con el arte conocido usando agentes dispersantes o humectantes y agentes de suspensión apropiados. La preparación estéril inyectable también puede ser una solución, suspensión o emulsión estéril inyectable en un diluyente o solvente aceptable para uso parenteral, no tóxico, por ejemplo, como una solución en 1,3-butanodiol. Entre los vehículos y solventes aceptables que se pueden emplear figuran agua, solución de Ringer, solución de cloruro de sodio U.S.P. e isotónica. Además, convencionalmente se emplean aceites fijos estériles como solventes o medios de suspensión. Para este propósito, se puede emplear cualquier aceite fijo suave entre los que se incluye a mono o diglicéridos sintéticos. Además, en la preparación de los inyectables se usan ácidos grasos tales como ácido oleico.

Las formulaciones inyectables se pueden esterilizar, por ejemplo, por filtración a través de un filtro que retiene bacterias, o incorporando agentes de esterilización en la forma de composiciones sólidas estériles que se pueden disolver o dispersar en agua estéril u otro medio inyectable estéril antes de usar.

Para prolongar el efecto de una droga, frecuentemente es deseable hacer más lenta la absorción de la droga a partir de una inyección subcutánea o intramuscular.Esto se puede conseguir usando una suspensión líquida de material cristalino o amorfo con baja solubilidad en agua. La tasa de absorción de la droga depende entonces de su tasa de disolución, lo que, a la vez, puede depender del tamaño del cristal y de la forma cristalina. De forma alternativa, la absorción con retraso de una droga administrada en forma parenteral se lleva a cabo por medio de la disolución o dispersión de la droga en un vehículo oleoso. Las formas de depósito inyectables se preparan formando matrices microencapsuladas de la droga en

polímeros biodegradables, tales como poliláctido-poliglicólido. Dependiendo de la relación de droga a polímero y de la naturaleza del polímero en particular que se emplee, se puede controlar la velocidad de liberación de la droga. Entre los ejemplos de otros polímeros biodegradables se incluyen poli(ortoésteres) y poli(anhídridos). Las formulaciones inyectables de depósito también se preparan por atrapamiento de la droga en liposomas o microemulsiones que son compatibles con los tejidos corporales.

Las composiciones para administración rectal o vaginal son preferiblemente supositorios, que se pueden preparar mezclando los compuestos de la presente invención con excipientes o vehículos no irritantes apropiados tales como manteca de cacao, polietilenglicol o una cera para supositorios que sean sólida a temperatura ambiente pero líquida a la temperatura del cuerpo y que por lo tanto se funda en la pocillo rectal o vaginal y libere el compuesto activo.

Las formas de dosificación sólidas para administración oral incluyen a cápsulas, tabletas, píldoras, polvos, y gránulos. En dichas formas sólidas de dosificación, el compuesto activo se mezcla con al menos un excipiente o vehículo inerte, aceptable para uso farmacéutico, tal como citrato de sodio o fosfato de calcio y/o: a) rellenos o extendedores tales como almidones, lactosa, sacarosa, glucosa, manitol, y ácido silícico, b) aglutinantes tales como, por ejemplo, carboximetilcelulosa, alginatos, gelatina, polivinilpirrolidinona, sacarosa, y acacia, c) humectantes tales como glicerol, d) agentes desintegrantes tales como agar-agar, carbonato de calcio, almidón de papa o tapioca, ácido algínico, ciertos silicatos, y carbonato de sodio, e) agentes retardantes de solución tales como parafina, f) aceleradores de absorción tales como compuestos de amonio cuaternario, g) agentes humectantes tales como, por ejemplo, alcohol cetílico y glicerol monostearato, h) absorbentes tales como

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caolina y arcilla bentonita, y i) lubricantes tales como talco, estearato de calcio, estearato de magnesio, polietilenglicoles sólidos, lauril sulfato de sodio, y mezclas de los mismos. En el caso de cápsulas, tabletas y píldoras, la forma de dosificación puede comprender también agentes reguladores del pH.

También se pueden emplear composiciones sólidas de un tipo similar como cargas en cápsulas de gelatina blandas y duras usando excipientes tales como lactosa o azúcar de leche así como polietilenglicoles de alto peso molecular, etcétera.

Los compuestos activos también pueden estar en una forma microencapsulada con uno o más de los excipientes que se acaban de mencionar. Las formas de dosificación sólidas de tabletas, grageas, cápsulas, píldoras y gránulos se pueden preparar con recubrimientos y revestimientos tales como recubrimientos entéricos, recubrimientos para controlar la liberación y otros recubrimientos bien conocidos en el arte de la formulación farmacéutica. En dichas formas de dosificación sólidas, el compuesto activo se puede mezclar con por lo menos un diluyente inerte como por ejemplo sacarosa, lactosa o almidón. Dichas formas de dosificación también pueden comprender, al igual que en la práctica normal, sustancias adicionales diferentes a diluyentes inertes, por ejemplo, lubricantes para formación de tabletas y otros coadyuvantes para formación de tabletas tales como estearato de magnesio y celulosa microcristalina. En el caso de cápsulas, tabletas y píldoras, las formas de dosificación pueden comprender también agentes reguladores del pH. Opcionalmente, estos pueden contener agentes opacificantes y también pueden estar hechos por completo de una composición que libera el(los) ingrediente(s) activo(s), o preferentemente, en ciertas partes del tracto intestinal, opcionalmente, de una manera retardada. Los ejemplos de composiciones de embebido que se pueden usar incluyen sustancias poliméricas y ceras.

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Las formas de dosificación para administración tópica o transdérmica de un compuesto de la presente invención incluyen ungüentos, pastas, cremas, lociones, geles, polvos, soluciones, atomizados, inhalantes o parches. El componente activo se mezcla en condiciones estériles con un vehículo aceptable para uso farmacéutico y cualquier conservante o solución amortiguadora de pH que puedan ser necesarios. También se encuentran contempladas, dentro del alcance de esta invención, las formulaciones oftálmicas, gotas oculares, ungüentos, polvos y soluciones para ojos.

Los ungüentos, pastas, cremas y geles pueden contener, además de un compuesto activo de la presente invención, excipientes tales como grasas animales y vegetales, aceites, ceras, parafinas, almidón, goma tragacanto, derivados de celulosa, polietilenglicoles, silicatos, bentonitas, ácido silícico, talco y óxido de cinc, o mezclas de los mismos.

Los polvos y aerosoles pueden contener, además de los compuestos de esta invención, excipientes tales como lactosa, talco, ácido silícico, hidróxido de aluminio, silicatos de calcio y polvo de poliamida, o mezclas de estas sustancias. Los atomizados pueden contener adicionalmente los propelentes acostumbrados tales como clorofluorohidrocarburos.

Los parches transdérmicos tienen la ventaja adicional de proveer al cuerpo una administración controlada de un compuesto. Dichas formas de dosificación se pueden hacer disolviendo o dosificando el compuesto en el medio adecuado. También se pueden utilizar mejoradores de absorción para aumentar el flujo del compuesto a través de la piel. La velocidad se puede controlar o bien proporcionando una membrana controladora de la velocidad o bien dispersando el compuesto en una matriz de polímero o gel.

Actividad antiviral

Una cantidad o dosis inhibitoria de los compuestos de la presente invención puede oscilar entre aproximadamente 0,01 mg/Kg y aproximadamente 500 mg/Kg, como alternativa entre aproximadamente 1 y aproximadamente 50 mg/Kg. Las cantidades o dosis inhibitorias también dependerán de la vía de administración, así como de la posibilidad de coadministración con otros agentes.

De acuerdo a los métodos de tratamiento de la presente invención, las infecciones virales se tratan o previenen en un sujeto, tal como un humano o mamífero inferior, administrando al sujeto una cantidad eficaz de un compuesto de la presente invención como agente anti hepatitis C, en dichas cantidades y durante dichos tiempos como sea necesario para conseguir el resultado deseado. Un método adicional de la presente invención es el tratamiento de las muestras biológicas con una cantidad inhibitoria de un compuesto de la composición de la presente invención en cantidades tales y durante un tiempo tal como sea necesario para lograr el resultado deseado.

El término "cantidad eficaz como agente anti-hepatitis C" de un compuesto de la invención, tal como se usa en la presente documentación, designa a una cantidad suficiente del compuesto de modo de disminuir la carga viral en una muestra biológica o en un sujeto (por ejemplo, para que resulte en al menos 10%, preferentemente al menos 50%, más preferentemente al menos 80%, y más preferentemente al menos 90% ó 95%, de reducción en la carga viral). Como está bien entendido en las artes médicas, una cantidad eficaz como agente anti-hepatitis C de un compuesto de esta invención estará en una relación razonable de beneficio/riesgo aplicable a cualquier tratamiento médico.

El término "cantidad inhibitoria" de un compuesto de la presente invención designa a una cantidad suficiente para disminuir la carga viral de hepatitis C en una muestra biológica o un sujeto (por ejemplo, para que resulte en al menos 10%,

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preferentemente al menos 50%, más preferentemente al menos 80%, y más preferentemente al menos 90% o 95%, de reducción de la carga viral). Queda entendido que cuando dicha cantidad inhibitoria de un compuesto de la presente invención se administra a un sujeto, lo será con una relación de riesgo/beneficio aplicable a cualquier tratamiento médico según lo determine un médico. El término "muestra(s) biológica(s)" tal como se usa en la presente documentación, significa una sustancia de origen biológico que se usa para administrar a un sujeto. Entre los ejemplos de muestras biológicas se incluye a, pero sin carácter taxativo, sangre y componentes de la misma tales como plasma, plaquetas, subpoblaciones de células sanguíneas y similares; órganos tales como riñón, hígado, corazón, pulmón, y similares; esperma y óvulos; médula ósea y componentes de la misma; o células madre. Por consiguiente, otra realización de la presente invención es un método para tratar una muestra biológica haciendo contactar dicha muestra biológica con una cantidad inhibitoria de un compuesto o composición farmacéutica de la presente invención.

Ante la mejora de la condición del sujeto, se puede administrar una dosis de mantenimiento de un compuesto, composición o combinación de esta invención, si es necesario. Posteriormente, se pueden reducir la dosis o la frecuencia de administración, o ambas, en función de los síntomas, del nivel al que se detuvo la condición mejorada en donde se han aliviado los síntomas a un nivel deseado, o si el tratamiento se debería interrumpir. El sujeto puede, sin embargo, requerir tratamiento intermitente a largo plazo ante cualquier recurrencia de los síntomas de la enfermedad.

Se comprenderá, sin embargo, que el uso diario total de los compuestos y composiciones de la presente invención será decidido por el médico a cargo dentro del

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alcance del buen juicio médico. La dosis inhibitoria específica para un paciente en particular dependerá de una variedad de factores que incluyen el trastorno que se está tratando y la gravedad del trastorno; la actividad del compuesto específico que se está empleando; la composición específica que se está empleando; la edad, peso corporal, estado general de salud, sexo y dieta del paciente; el momento de la administración, la ruta de administración, y la tasa de excreción del compuesto específico que se está empleando; la duración del tratamiento; las drogas que se utilizan en combinación o de manera coincidente con el compuesto específico que se está empleando; y otros factores bien conocidos en la ciencia médica.

La dosis inhibitoria diaria total de los compuestos de esta invención se administra a un sujeto en una única dosis o en dosis divididas que pueden tener cantidades de, por ejemplo, entre 0,01 y 50 mg/kg de peso corporal o más usualmente entre 0,1 y 25 mg/kg de peso corporal. Las composiciones de dosis única pueden contener dichas cantidades o submúltiplos de las mismas para llegar a la dosis diaria. En general, los regímenes de tratamiento de acuerdo con la presente invención comprenden la administración a un paciente que necesita dicho tratamiento de entre aproximadamente 10 mg y aproximadamente 1.000 mg del o de los compuestos de la presente invención por día en dosis únicas o múltiples.

A menos que se defina de otra forma, todos los términos científicos y técnicos que se usan en la presente están de acuerdo con el significado comúnmente conocido para una persona con experiencia en la materia. Todas las publicaciones, patentes, solicitudes de patentes publicadas, y otras referencias que se mencionan en la presente documentación se encuentran incorporadas a modo de referencia en su totalidad a la presente documentación.

Abreviaturas

Las abreviaturas que se han utilizado en las descripciones de los esquemas y los ejemplos siguientes son:

ACN para acetonitrilo;

BME para 2-mercaptoetanol;

BOP para hexafluorofosfato benzotriazol-1-iloxi-tris(dimetilamino)fosfonio;

COD para ciclooctadieno;

DAST para trifluoruro de dietilaminoazufre;

DABCILO para 6-(*N*-4'-carboxi-4-(dimetilamino)azobenceno)-aminohexil-1-O-(2-cianoetil)-(*N*,*N*-diisopropil)-fosforamidita;

DCM para diclorometano;

DIAD para diisopropilazodicarboxilato;

DIBAL-H para hidruro de diisobutilaluminio;

DIEA para diisopropiletilamina;

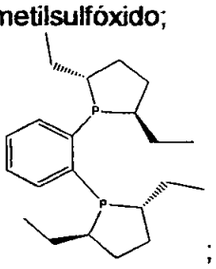
DMAP para *N*,*N*-dimetilaminopiridina;

DME para éter dimetílico de etilenglicol;

DMEM para Medio Eagles Modificado por Dulbecco;

DMF para *N*,*N*-dimetil formamida;

DMSO para dimetilsulfóxido;

DUPHOS para  ;

EDANS para ácido 5-(2-amino-etilamino)-naftaleno-1-sulfónico;

EDCI o EDC para clorhidrato de 1-(3-dietilaminopropil)-3-etilcarbodiimida;

EtOAc para acetato de etilo;

HATU para hexafluorofosfato de O-(7-Azabenzotriazol-1-il)-*N*,*N*,*N*',*N*'–tetrametiluronio;

Hoveyda's Cat. para Dicloro(o-isopropoxifenilmetilen) (triciclohexilfosfina)rutenio(II);

KHMDS para bis(trimetilsilil) amida de potasio;

Ms para mesilo;

NMM para N-4-metilmorfolina;

PiBrOP para hexafluorofosfato de bromo-*tri*-pirolidino-fosfonio;

F para fenilo;

RCM para metátesis de cerrado de anillo;

RT para transcripción inversa;

RT-PCR para reacción en cadena de la polimerasa de transcripción inversa;

TEA para trietilamina;

TFA para ácido trifluoroacético;

THF para tetrahidrofurano;

TLC para cromatografía en capa delgada.

TPP o PPh_3 para trifenilfosfina;

tBOC o Boc para *tert*-butiloxicarbonilo; y

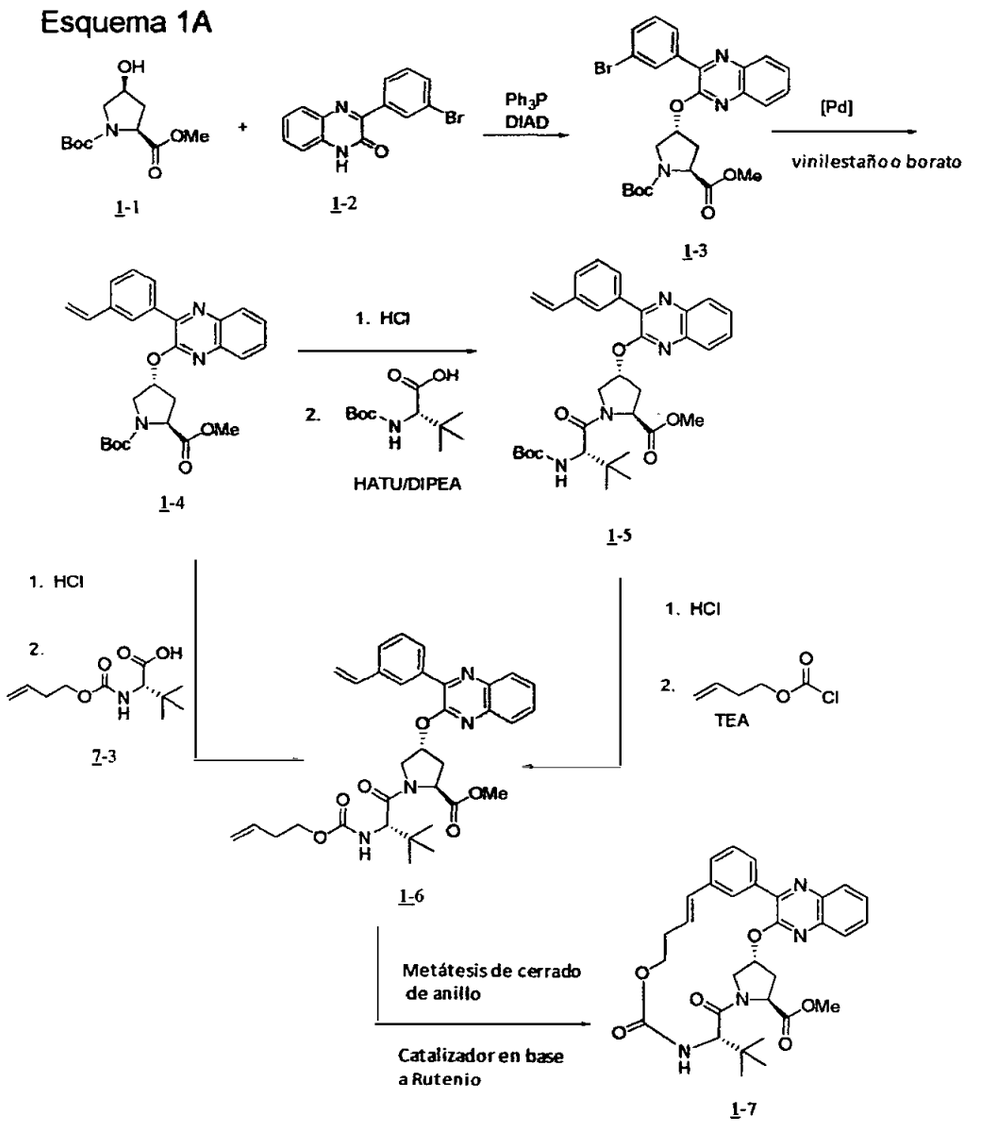
Xantphos para 4,5-bis-difenilfosfanil-9,9-dimetil-9H-xanteno.

<u>Métodos de síntesis</u>

Los compuestos y procesos de la presente invención se comprenderán mejor en conexión con los siguientes esquemas de síntesis que ilustran los métodos mediante los que se pueden preparar los compuestos de la invención, los cuales solo tienen la intención de ser ilustrativos y no limitantes del alcance de la invención. Para las personas con experiencia en la materia serán evidentes diferentes cambios y

modificaciones de las realizaciones expuestas y entre dichos cambios y modificaciones se incluye a, sin limitación, aquellos que se relacionan con estructuras químicas, sustituyentes, derivados y/o métodos de la invención, que se pueden hacer sin alejarse del espíritu de la invención y del alcance de la reivindicaciones adjuntas.

Esquema 1A

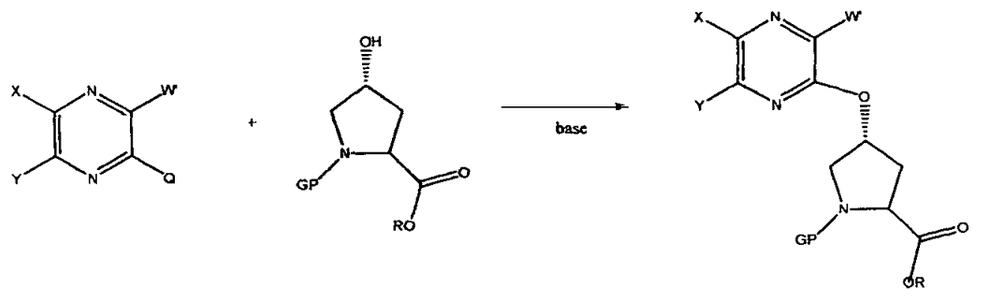


1-1 1-2 1-3 1-4 1-5 7-3 1-6 1-7

La preparación de compuestos con núcleo de quinoxalinilo macrocíclico se ejemplifica en el esquema 1A. Se acopló Boc-hidroxiprolina 1-1 disponible

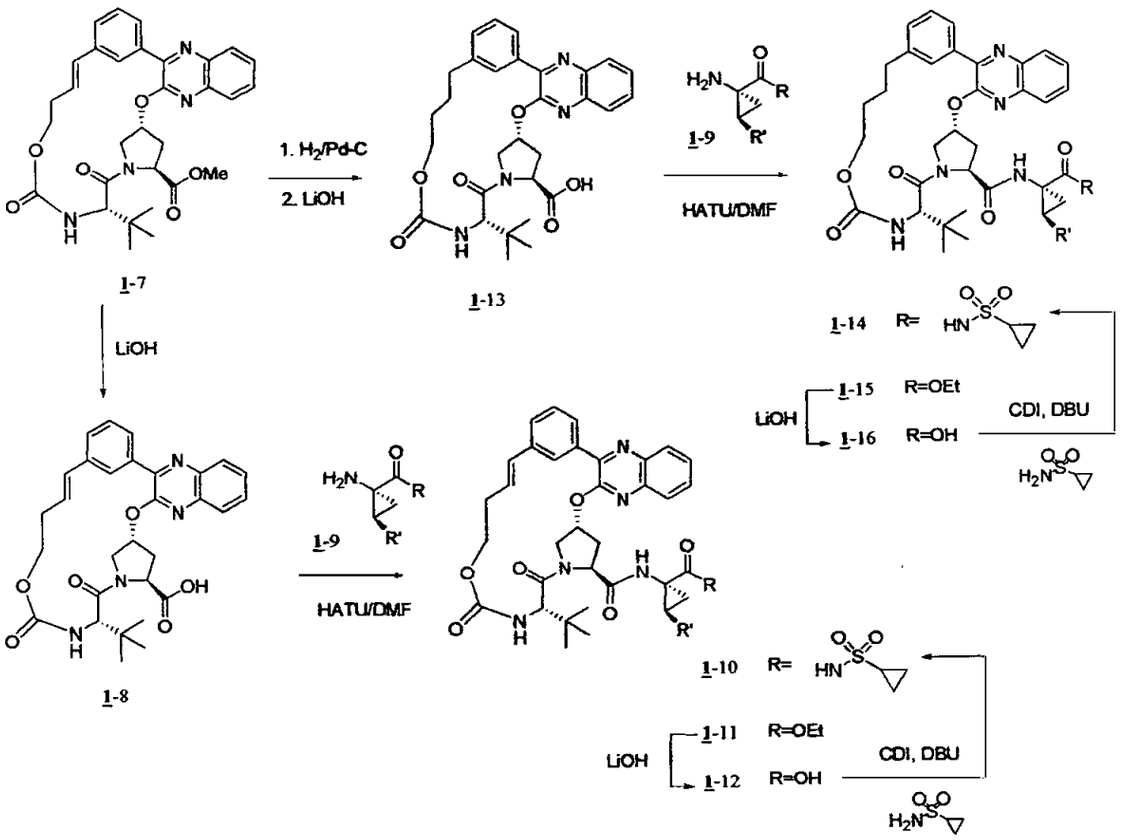
comercialmente con derivado de quinoxalina 1-2 (para la preparación de análogos de quinoxalina, véanse los esquemas 3-6) bajo condiciones de Mitsunobu dando el compuesto 1-3. Se observó unión al oxígeno carbonílico para formar el compuesto deseado. En los ejemplos de la presente documentación aparece una discusión detallada acerca de la identificación y caracterización del inesperado producto de adición oxo de Mitosunobu. Para mayores detalles sobre la reacción de Mitsunobu, véase O. Mitsunobu, *Synthesis* 1981, 1-28; D. L. Hughes, Org. React. 29, 1-162 (1983); D. L. Hughes, *Organic Preparations and Procedures Int.* 28, 127-164 (1996); y J. A. Dodge, S. A. Jones, *Recent Res. Dev. Org. Chem.* 1, 273-283 (1997). La introducción del grupo vinilo se llevó a cabo a través de reacción de Suzuki (vinilborato/paladio) o de Still (vinilestaño/Paladio) para dar el compuesto 1-4. La desprotección de 1-4 con HCl seguida por reacción de acoplamiento (HATU/DMF) con Boc-L-tert.-leucina dio el compuesto 1-5. La desprotección de 1-5 con HCl seguida por reacción con 3-butenilcloroformioato resultó en el precursor del compuesto macrocíclico 1-6. Como alternativa, el compuesto 1-6 se puede preparar a partir de acoplamiento directo del intermediario 1-4 (luego de la desprotección del grupo Boc) con el correspondiente aminoácido carbamato 7-3 (para la preparación de los derivados de aminoácidos carbamato véase el esquema 7). La metátesis de cerrado de anillo del compuesto 1-6 con un catalizador en base a rutenio da el intermediario macrocíclico deseado 1-7 (para más detalles sobre metátesis de cerrado de anillo véanse las recientes revisiones: Grubbs et al., *Acc. Chem. Res.*, **1995**, *28*, 446; Shrock et al., *Tetrahedron* **1999**, *55*, 8141; Furstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012; Trnka et al., *Acc. Chem. Res.* **2001**, *34*, 18, y Hoveyda et al., *Chem. Eur. J.* **2001**, *7*, 945).

Esquema 1B



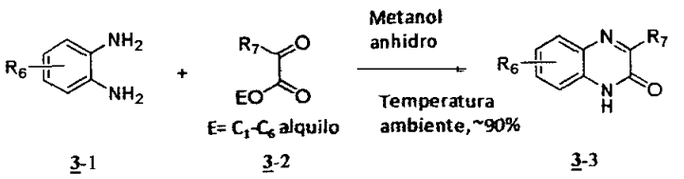
Una ruta alternativa par alas estructuras con núcleo de quinoxalina es la que se presenta en el Esquema 1B, que ilustra la reacción de desplazamiento de un haluro de quinoxalina sustituido con hidroxiprolina amino-protegida en la presencia de una base, tal como NaH o NaO^{t}Bu. En este esquema, PG es un grupo protector de amino, Q es un halógeno, preferentemente bromo, cloro o yodo, X e Y tienen los valores que se dan por estas variables en la Fórmula I, , W' tiene los valores que se dan para L_{101}-W_{101}- en la Fórmula I y Z-W- en la Fórmula II y R es hidrógeno o alquilo.

Esquema 2



La *síntesis de compuestos macrocíclicos de quinoxalinilo como inhibidores de* proteasa de VHC se ejemplifica en el esquema 2. La hidrólisis del compuesto 1-7 da el correspondiente ácido carboxílico 1-8, que se acopla con amino sulfinimida o éster de aminoácido 1-9 (para la preparación, véanse los Esquemas 8 y 9) para dar el compuesto 1-10 o el éster 1-11. La hidrólisis de 1-11 da 1-12. El compuesto 1-10 también se puede preparar a partir del ácido 1-12 como se muestra en el esquema 2. La hidrogenación de 1-7 da el compuesto 1-13, que se transforma en los compuestos 1-14 y 1-16 usando la misma química que en la preparación de los compuestos 1-10 y 1-12.

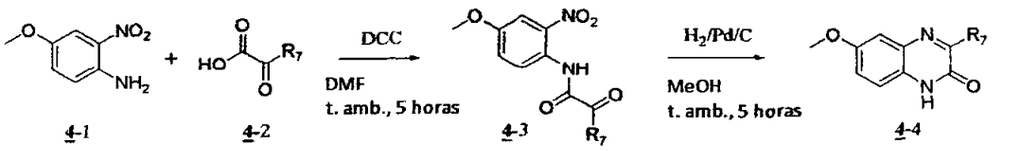
Esquema 3



3-1 3-2 3-3

Se pueden hacer diferentes derivados de quinaxolina del compuesto 1-2 (o sea de fórmula 3-3) a través de la condensación de fenildiaminas de fórmula 3-1, en donde R_6 se definió previamente, con cetoácido o ésteres de fórmula 3-2, en donde R_7 es W-Z como se definió previamente, en metanol anhidro a temperatura ambiente (véase Bekerman et al., *J. Heterocycl. Chem.* **1992**, *29*, 129-133 para más detalles sobre esta reacción). Entre los ejemplos de fenildiaminas apropiadas para crear los derivados de quinaxolina de fórmula 3-3 se incluye a, pero sin carácter taxativo, 1,2-diamino-4-nitrobenceno, o–fenilenediamina, 3,4-diaminotolueno, 4-cloro-1,2-fenilenediamina, 3,4-diaminobenzoato de metilo, benzo[1,3]dioxol-5,6-diamina, 1,2-diamino-4,5-metilendioxibenceno, 4-cloro-5-(trifluorometil)-1,2-bencenodiamina, y similares. Entre los ejemplos de cetoácidos apropiados para la reacción que se describe en el esquema 3 se incluye a, pero sin carácter taxativo, ácido benzoilfórmico, ácido fenilpirúvico, ácido indol-3-glioxílico, ácido indol-3-pirúvico, ácido nitrofenilpirúvico, ácido (2-furil)glioxílico y similares. Entre los ejemplos de cetoésteres apropiados ara la reacción que se describe en el esquema 3 se incluye a, pero sin carácter taxativo, etiltiofeno-2-glioxilato, 2-oxo-4-fenilbutirato de etilo, 2-(formilamino)-4-tiazolilglioxilato de etilo, 2-amino-4-tiazolilglioxilato de etilo, 2-oxo-4-fenilbutirato de etilo, (5-bromotien-2-il)glioxilato de etilo, 3-indolilglioxilato de etilo, 2-metilbenzoilformiato de etilo, 3-etilbenzoilformiato de etilo, 3-etilbenzoilformiato de etilo, 4-ciano-2-oxobutirato de etilo, (1-metilindolil)-3-glioxilato de metilo, y similares.

Esquema 4

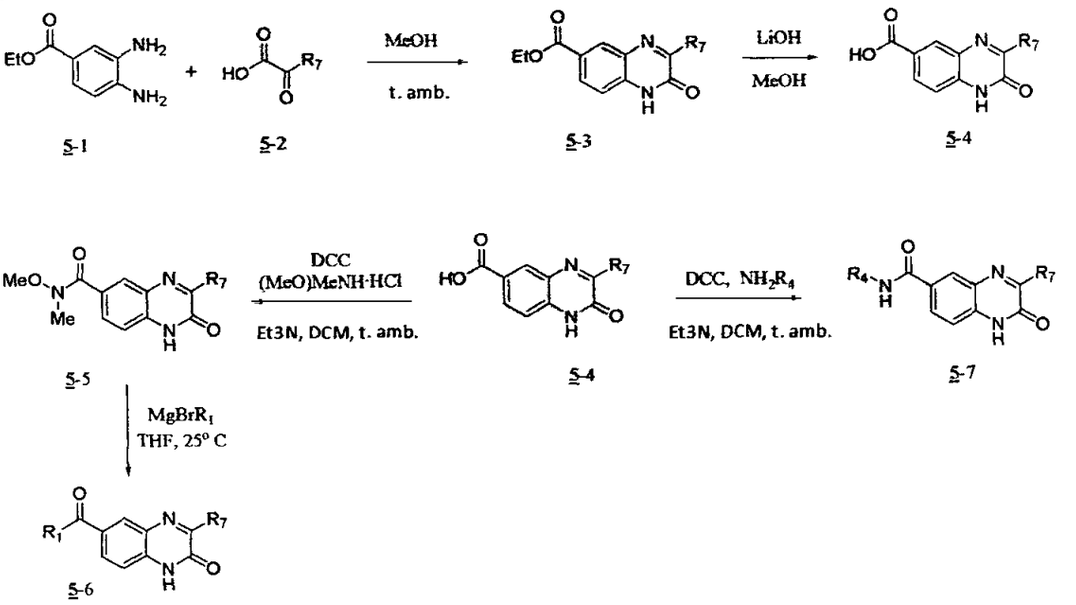


4-1 4-2 4-3 4-4

Las quinoxalin-2-onas 3,6-sustituidas de fórmula 4-4, en donde R_7 es W-Z como se definió previamente, se pueden preparar en modo regioselectivo para favorecer la sustitución en la posición 6 comenzando con el acoplamiento de amida de 4-metoxi-2-nitro anilina 4-1 y ácido glioxílico sustituido 4-2 para dar el compuesto 4-3. La quinoxalin-2-ona 3,6-sustituida 4-4 se creó a través de reducción catalítica del nitro del compuesto 4-3 seguido por condensación. Se pueden introducir otros sustituyentes en 4-4 a través del uso de otras 2-nitroanilinas. Entre los ejemplos de cetoácidos apropiados para la reacción que se describe en el esquema 4 se incluye a, pero sin carácter taxativo, ácido benzoilfórmico, ácido fenilpirúvico, ácido indol-3-glioxílico, ácido indol-3-pirúvico, ácido nitrofenilpirúvico, ácido (2-furil)glioxílico y similares. Entre los ejemplos de 2-nitro anilinas apropiadas para la reacción que se describe en el esquema 4 se incluye a, pero sin carácter taxativo, 4-etoxi-2-nitroanilina, 4-amino-3-nitrobenzotrifluoruro, 4,5-dimetil-2-nitroanilina, 4-fluoro-2-nitroanilina, 4-cloro-2-nitroanilina, 4-amino-3-nitrometilbenzoato, 4-benzoil-2-nitroanilina, 3-bromo-4-metoxi-2-nitroanilina, 3'-amino-4'-metil-2-nitroacetofenona, 5-etoxi-4-fluoro-2-nitroanilina, 4-bromo-2-nitroanilina, 4-(trifluorometoxi)-2-nitroanilina, 4-amino-3-nitrobenzoato de etilo, 4-bromo-2-metil-6-nitroanilina, 4-propoxi-2-nitroanilina, 5-(propiltio)-2-nitroanilina, y similares.

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Esquema 5



El ácido 2-oxo-1,2-dihidro-quinoxalina-6-carboxílico intermediario 3-sustituido **5**-4 se puede preparar a través de la condensación de 3,4-diaminobenzoato de etilo (**5**-1) con ácido oxoacético de fórmula **5**-2, en donde R_7 = W-Z como se definió previamente, usando el método que se describió previamente en el esquema 3 (véase Bekerman et al., *J. Heterocycl. Chem.* **1992**, *29*, 129-133 para más detalles). El éster etílico resultante **5**-3 se hidroliza entonces con LiOH en MeOH a temperatura ambiente para dar el ácido carboxílico intermediario **5**-4.

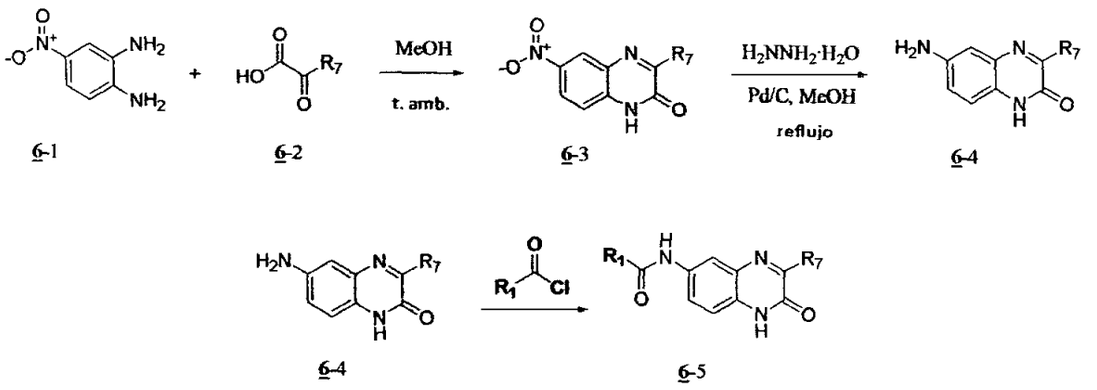
El ácido carboxílico **5**-4 se puede convertir entonces a cetona sustituida **5**-6 (en donde R_1 es como se definió previamente) mediante la amida de Weinreb **5**-5 y posterior tratamiento con diferentes Reactivos de Grignard (véase Weinreb et al. *Tetrahedron Lett.* **1977**, 33, 4171; Weinreb et al, *Synth. Commun.* **1982**, *12*, 989 para detalles en la formación y uso de la amida de Weinreb; y véase B.S. Furniss, A.J. Hannaford, P.W.G. Smith, A.R. Tatchell, Vogel's Textbook of Practical Organic Chemistry, 5ta ed., Longman, 1989). El agregado se llevó a cabo en un solvente inerte, por lo general a bajas temperaturas. Entre los solventes apropiados se incluye a, pero

sin carácter taxativo, tetrahidrofurano, éter dietílico, 1,4-dioxano, 1,2-dimetoxietano, y hexanos. Preferentemente el solvente fue tetrahidrofurano o dietiléter. Preferentemente la reacción se llevó a cabo a entre –78°C y 0°C.

Como alternativa, el ácido carboxílico 5-4 se puede usar para formar diferentes amidas de fórmula 5-7, en donde R_4 es como se definió previamente, en una forma que se describe en general en el esquema 5. Los diferentes compuestos de quinoxalin-2-ona que se describen en el esquema 5 se acoplan adicionalmente al precursor macrocíclico mediante condiciones de Mitsunobu que se describieron previamente.

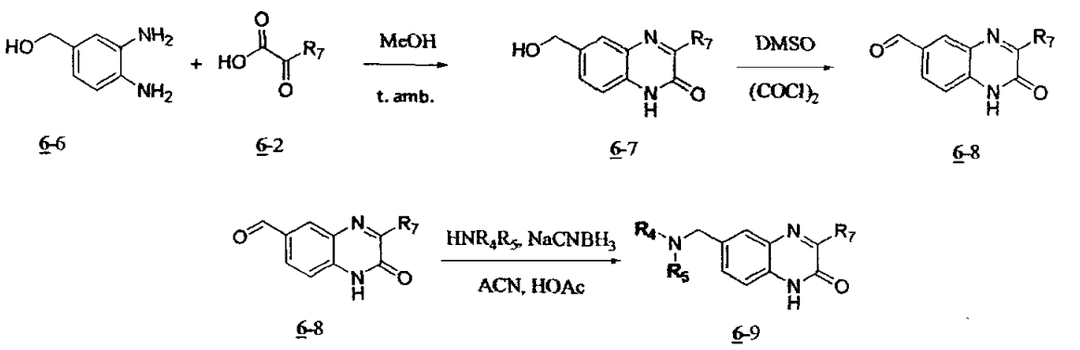
Esquema 6

A



6-1 6-2 6-3 6-4 6-4 6-5

B



6-6 6-2 6-7 6-8 6-8 6-9

Se pueden hacer otros compuestos de quinoxalin-2-ona 6-sustituidos mediante los procedimientos generales que se establecen en el esquema 6.

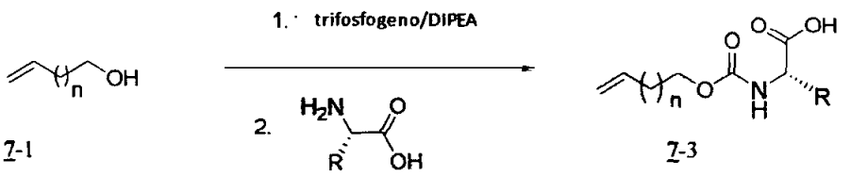
A. Reducción de 6-nitro y Formación de Amida

La 6-nitro-1H-quinoxalin-2-ona (**6**-3) se puede preparar mediante el camino descrito previamente a partir de 3,4-diaminonitrobenceno y el ácido oxoacético de fórmula **6**-2, en donde R_7 = W-Z es como se describió previamente. La reducción del grupo nitro en la posición 6 se puede conseguir mediante Pd/C con $H_2NNH_2 \bullet H_2O$ en reflujo de MeOH. La posición 6- de la amina **6**-4 se puede tratar entonces con un amplio rango de cloruros ácidos para dar diferentes amidas de fórmula **6**-5 en donde R_1 es como se definió previamente.

B. Oxidación de Alcohol Bencílico y Aminación Reductiva

La quinoxalin-2-ona de fórmula 6-7 se puede preparar a través de la condensación de alcohol 3,4-diaminobecílico y diferentes ácidos oxoacéticos de fórmula 6-2, en donde R_7 = W-Z es como se describió previamente. El alcohol bencílico resultante 6-7 se puede oxidar entonces bajo condiciones de Swern, o cualquier otra condición de oxidación, para generar el aldehído de fórmula 6-8. Para más detalles respecto a la reacción de Swern véase A. J. Mancuso, D. Swern, *Synthesis* **1981**, 165-185 *passim;* T. T. Tidwell, *Org. React.* **1990**, *39*, 297-572 *passim.* Para otras condiciones de oxidación véase B.S. Furniss, A.J. Hannaford, P.W.G. Smith, A.R. Tatchell, Vogel's Textbook of Practical Organic Chemistry, 5ta ed., Longman, 1989. Subsiguientes reacciones de aminación reductiva con aminas primarias o secundarias en presencia de $NaCNBH_3$ y ácido acético pueden dar compuestos de fórmula 6-9, en donde R_4 and R_5 son como se definió previamente.

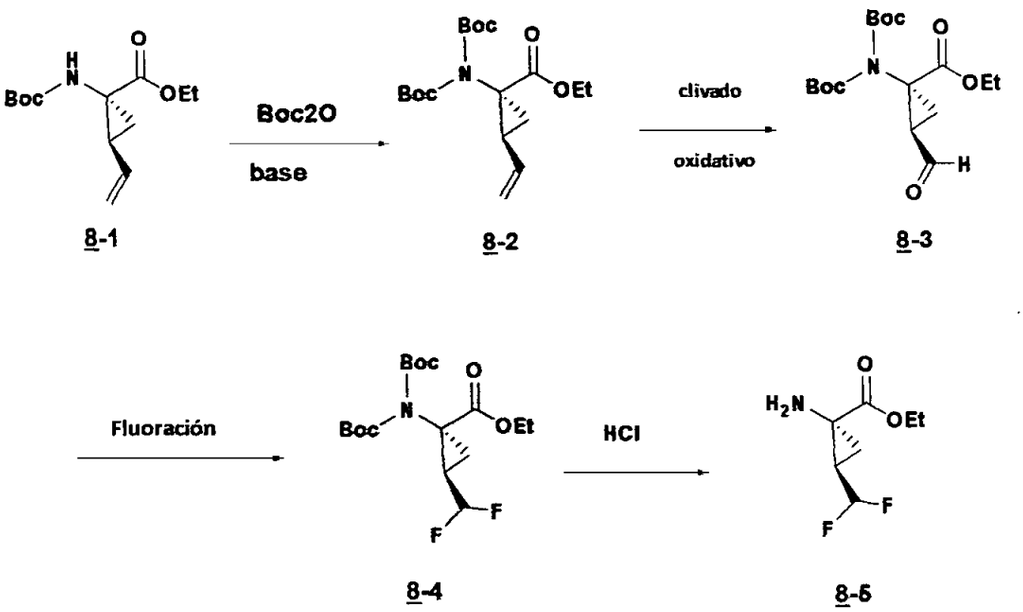
Esquema 7



7-1 7-2 7-3

La preparación de aminoácidos de carbamato 7-3 se muestra en el esquema 7; n es un número entero entre 0 y 5. El alcohol olefínico correspondiente reacciona con trifosfogeno en presencia de DIPEA, seguido por el agregado de los aminoácidos apropiados 7-2 para dar los aminoácidos de carbamato deseados 7-3.

Esquema 8



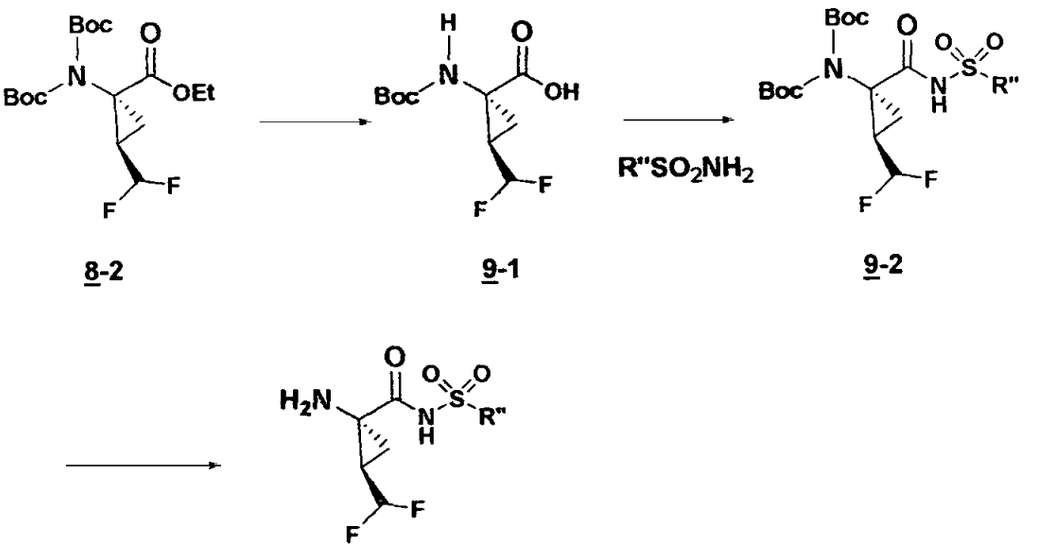
8-1 8-2 8-3

8-4 8-5

La síntesis de derivados de difluorometil P1 aminoácido 8-5 (o sea 1-9 con R=OEt y R'=CF_2H) se representa en el esquema 8. El éster de mono-Boc aminoácido se protegió además como éster de bis-Boc aminoácido 8-2. El clivaje oxidativo del compuesto 8-2 resultó en el aldehído 8-3, que luego se convirtió al compuesto de difluorometilo 8-4 usando derivados de trifluoruro de aminoazufre tales como trifluoruro de dietilaminoazufre (DAST). La desprotección de 8-4 con HCl dio el compuesto de difluorometil P1 deseado 8-5.

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Esquema 9



8-2 9-1 9-2

9-3

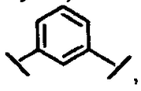
El derivado de difluorometil P1 sulfonamida 9-3 (o sea 1-9 con R=NHS(O)$_2$R" y R'=CF_2H) se preparó como se muestra en el esquema 9. La hidrólisis del compuesto 8-2 dio el ácido 9-1, que se convirtió a 9-2 usando CDI/R"SO_2NH_2/DBU o EDC/DMAP/ R"SO_2NH_2. La desprotección de 9-2 dio el intermediario deseado 9-3.

Todas las referencias que se citan en la presente documentación, ya sean impresas, electrónicas, en medio de almacenamiento accesible por computadora u otra forma, se incorporan expresamente a modo de referencia en su totalidad, incluyendo, pero sin carácter taxativo, resúmenes, artículos, revistas, publicaciones, textos, tratados, sitios web en Internet, bases de datos, patentes, y publicaciones de patentes.

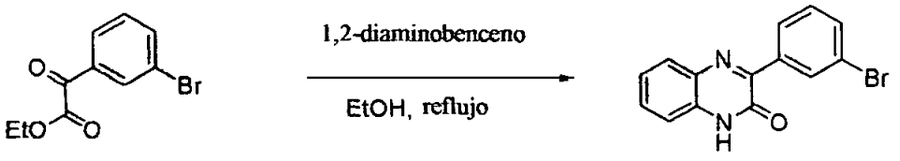
Ejemplos

Los compuestos y procesos de la presente invención se comprenderán mejor en conexión con los siguientes ejemplos, los que tienen la intención de ser sólo una

ilustración y no de limitar el alcance de la invención. Para las personas con experiencia en la materia resultarán evidentes diferentes cambios y modificaciones de las realizaciones expuestas y entre dichos cambios y modificaciones se incluye a, sin limitación, aquellos que se relacionan con estructuras químicas, sustituyentes, derivados, formulaciones y/o métodos de la invención, que se pueden hacer sin alejarse del espíritu de la invención y del alcance de la reivindicaciones adjuntas.

Ejemplo 1. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=CF_2H, G =OH

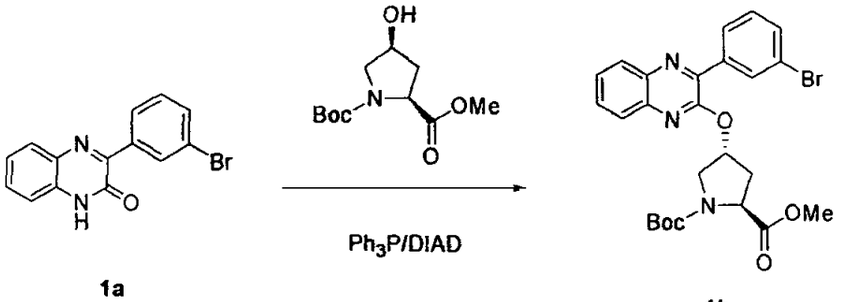
Paso 1A



1a-1 **1a**

Una mezcla del compuesto **1a-1** (0,84g, 7,77mmol), 1,2-diaminobenceno (2g, 7,77mmol) y etanol (10m) se calentó bajo reflujo durante 2h, se enfrió a temperatura ambiente, se filtró, se lavó con etanol frío y se secó bajo presión reducida para dar compuesto **1a** (2,12g) directamente se usó en el paso siguiente.

Paso **1B**

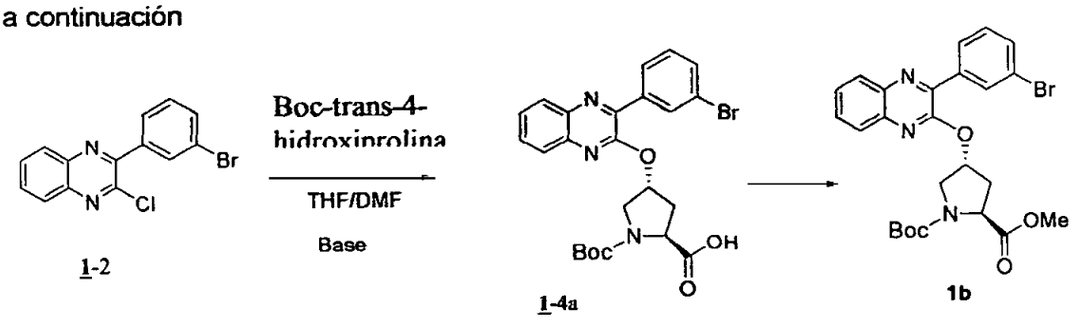


1a **1b**

A una mezcla del **1a** precedente (1,02g, 3,39mmol), éster metílico de Boc-L-cis-hidroxiprolina (0,831g, 3,38mmol) y trifenilfosfina (1,8g, 6,86mmol) en THF a 0°C

se agregó por goteo DIAD (1,33ml, 6,76mmol). La mezcla resultante se mantuvo a 0°C durante 15 min. antes de calentarse a temperatura ambiente. Después de 18 horas, la mezcla se concentró bajo vacío y el residuo se purificó por cromatografía (Hexano/EtOAC = 1:0 a 4:1) para dar **1b** (1,74g). MS(ESI): m/e 528,02 (M+H).

Como alternativa, el intermediario **1b** se prepara a partir de 1-2 como se indica a continuación



1-2

1-4a

1b

Se cargó un balón de 12L con Boc-trans-4-hidroxiprolina (141g, 0.61 mol), THF (3.3L). La mezcla se enfrió a 0°C, se agregó lentamente una solución de NaOtBu (175.9g, 1.83 mol) en DMF (0.8L) a través de un embudo de adición mientras la temperatura interna no excedía los 10°C. Se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 1.5h. El recipiente de reacción se colocó nuevamente a 0°C, y se agregó compuesto 1-2 (195g, 0.61 mol) por porciones. La cromatografía en capa delgada indicó que no quedaba material de partida remanente después de las 2h. La mezcla de reacción se neutralizó con agua (2L) y se concentró para eliminar la mayor parte del THF. Se agregaron otros 2 L de agua y la mezcla se extrajo con t-butimetiléter dos veces (4L+3L). Se agregaron 4L de EtOAc a la capa acuosa. Se agregó lentamente ácido cítrico al 10% para ajustar el pH a 4-5. Se separaron las dos fases, la capa acuosa se extrajo con EtOAc (2X 3L). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ y se concentraron para dar un aceite marrón (356g). Este material crudo se disolvió en $MeOH/CH_2Cl_2$

(1.5L/1.6L), se enfrió a 0°C, y se agregó $Me_3SiCH_2N_2$ (2M en hexano, 640mL, 1.28 mol) por goreo. Después de 3.5h se completó la adición y la cromatografía en capa delgada indicó material de partida remanente. . La mezcla de reacción se concentró y el residuo se cristalizó a partir de MeOH (~500mL) para dar 275g del compuesto **1b**. El licor madre se purificó en una columna de gel de sílice para dar 22g más del producto. (rendimiento combinado: 88% a partir de **1**-2).

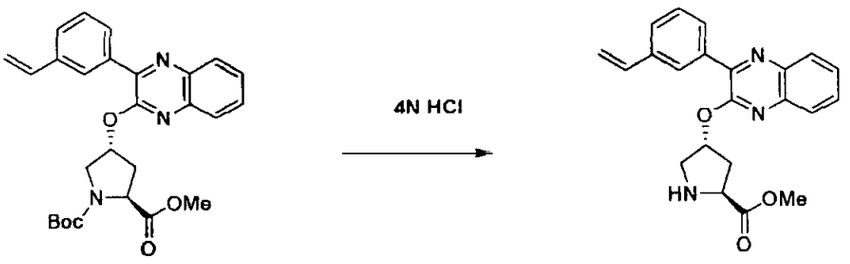
Paso **1C**



1b **1c**

A una mezcla del compuesto **1b** (0,6g, 1mmol), viniltrfluoroborato de potasio (0,52g, 2mmol), trietilamina (0,55ml) y etanol (20ml) se agregó complejo cloruro de 1,1'-bis(difenilfosfino)ferroceno paladio (II) con CH_2Cl_2(40mg, 0,048mmol). La mezcla resultante se agitó a 75°C durante 15h, se enfrió a temperatura ambiente, se detuvo con solución acuosa al 10% de KHSO4, se extrajo con acetato de etilo (3x). Las capas orgánicas combinadas se secaron (MgSO4), se concentraron bajo vacío, y el residuo se purificó por cromatografía (Hexano/EtOAC = 1:0 a 4:1) para dar **1c** (0,49g). MS(ESI): m/z 476,21(M+H).

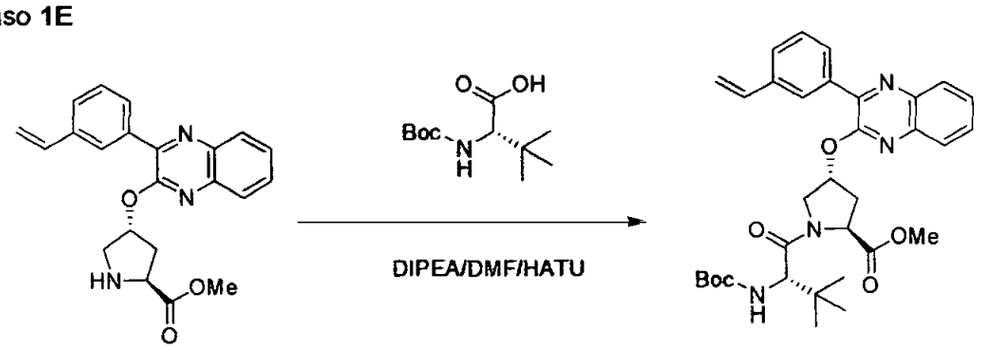
Paso **1D**



1c 1d

Una solución del compuesto **1c** (1mmol) en diclorometano (2ml) se trató con HCl 4M/dioxano (4ml, 16mmol). La mezcla resultante se agitó a temperatura ambiente durante 1 hora, y se concentró al vacío a sequedad para dar la sal de HCl del compuesto **1d** (100%). MS (ESI): m/e 376,15 (M+H).

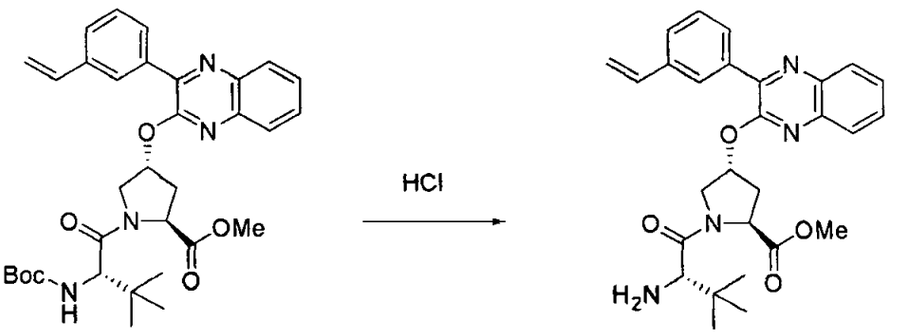
Paso **1E**



1d 1e

A una solución del compuesto **1d** (sal de HCl, 100mg, 0,223mmol), Boc-L-t-leucina (67mg, 0,29mmol) y DIPEA (0,24ml, 1,37mmol) en DMF (3ml) a 0 °C se agregó HATU (110mg, 0,29mmol). La mezcla se agitó a temperatura ambiente durante 18h, se diluyó con EtOAc y se lavó con NaCl acuoso semisaturado cuatro veces. La fase orgánica se secó sobre $MgSO_4$ anhidro, se filtró, y luego se concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (Hexano/EtOAC = 9 : 1 a 4 : 1) para dar compuesto **1e** (128mg). MS (ESI): m/e 589,44 (M+H), 489,36 (M-Boc).

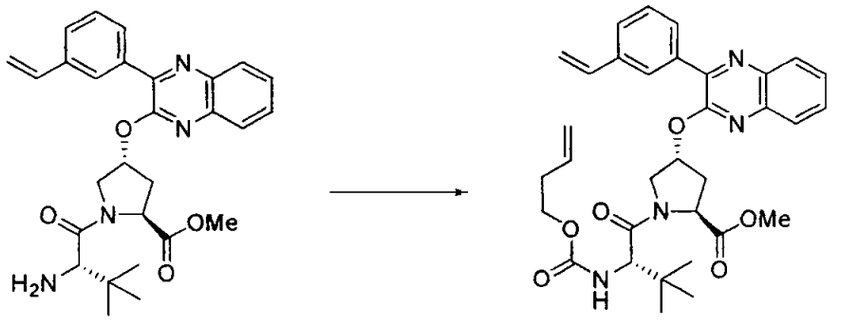
Paso **1F**



1e **1f**

Una solución del compuesto **1e** (117mg, 0,2mmol) en diclorometano (1ml) se trató con HCl 4M/dioxano (3ml, 12mmol). La mezcla resultante se agitó a temperatura ambiente durante 1 hora, y se concentró al vacío a sequedad para dar la sal de HCl del compuesto **1f** (100%). MS (ESI): m/z 489,45(M+H).

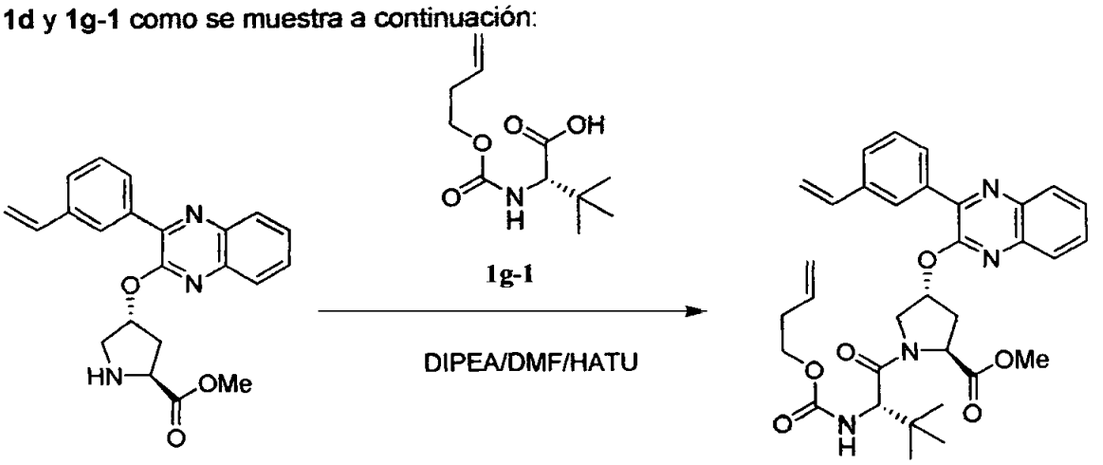
Paso **1G**



1f **1g**

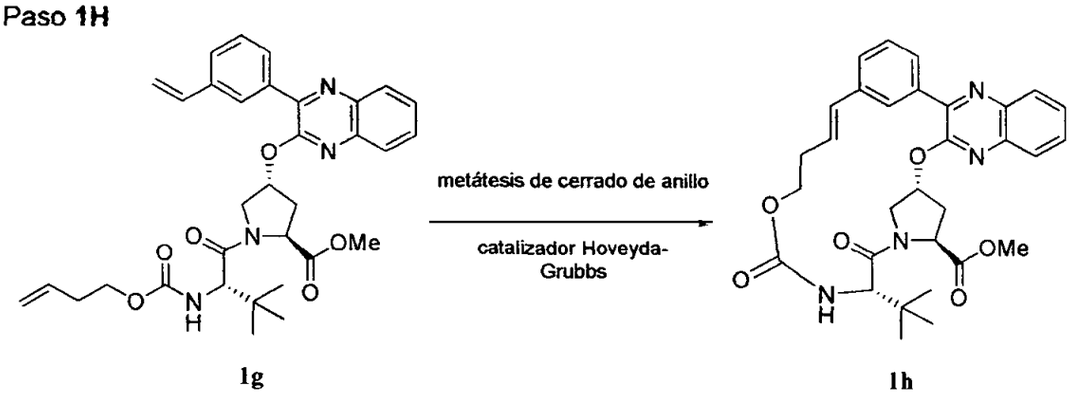
El compuesto **1f** (0,198mmol) se disolvió en diclorometano (3m), se enfrió a 0°C, se trató con trietilamina (120ul, 4eq.) seguido por cloroformato de 3-butenilo (0,041ml, 0,33mmol). La mezcla se agitó a temperatura ambiente durante 0,5 a 1 hora, se diluyó con acetato de etilo, se lavó con NaCl acuoso semisaturado dos veces, se secó (MgSO4) y se concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (Hexanos/ EtOAc = 6 : 1 a 4: 1) para dar compuesto **1g** (95mg). MS(ESI): m/z 587,47 (M+H).

Como alternativa, el compuesto **1g** se preparó a partir del acoplamiento del compuesto **1d** y **1g-1** como se muestra a continuación:



A una solución del compuesto **1d** (sal de HCl, 10,78mmol), **1g-1** (2,97g, 13,12mmol) y DIPEA (5,6ml, 32,3mmol) en DMF (30ml) a 0 °C se agregó en porciones HATU (5,12g, 13,5mmol). La mezcla se agitó a temperatura ambiente durante 18h, se diluyó con EtOAc y se lavó con NaCl acuoso semisaturado cuatro veces. La fase orgánica se secó sobre $MgSO_4$ anhidro, se filtró, y luego se concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (Hexano/EtOAC = 9 : 1 a 4 : 1) para dar compuesto **1g** (6,1g).

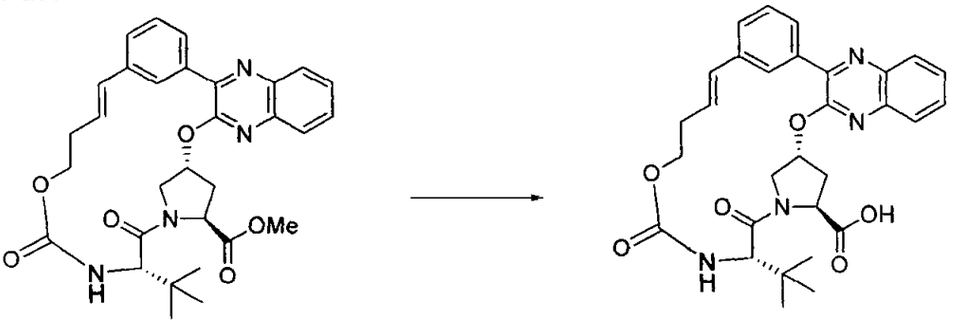
Paso **1H**



000486

A una solución del compuesto **1g** (95mg, 0,16mmol) en diclorometano (20ml) se agregó catalizador Hoveyda-Grubbs de primera generación o un catalizador similar (5 mol% eq.). La mezcla de reacción se agitó a 40°C durante 20h. El solvente luego se evaporó y el residuo se purificó por cromatografía flash en gel de sílice usando un gradiente de elución (Hexano/EtOAC = 9 : 1 a 7 : 3) para dar el compuesto macrocíclico **1h** (58mg). MS (ESI) m/z 559,30 (M+H).

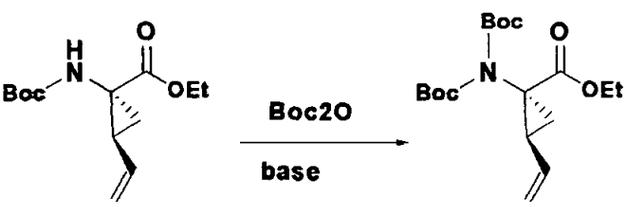
Paso **1I**



1h **1i**

A una solución del compuesto **1h** (58mg, 0,103mmol) en THF/MeOH (3ml/1,5ml) se agregó hidruro de litio 1N (1,5ml, 1,5mmol). La mezcla se agitó a temperatura ambiente durante 20 horas. La mayor parte de los solventes orgánicos se evaporaron al vacío, y el residuo resultante se diluyó con agua y se acidificó a entre pH 5 y 6. La mezcla se extrajo con EtOAc tres veces. Los extractos orgánicos combinados se secaron ($MgSO_4$), se filtró y se concentró al vacío para dar **1i** (100%). MS(ESI): m/z 545,24 (M+H), 551,25 (M+Li).

Paso **1J**

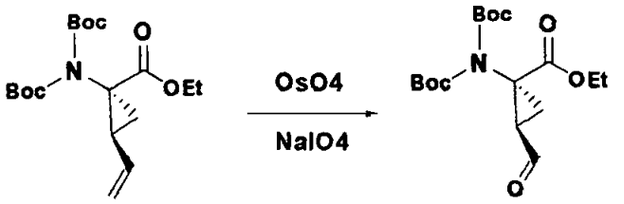


1j-1 **1j**

000457

A una solución del compuesto **1j**-1 (6,6g, 25,85mmol) en THF (115ml) a -78°C se agregó lentamente NaHMDS (1,0M en THF, 28,5ml, 28,5mmol). Después de la mezcla se agitó a -78°C durante una hora, se agregó Boc2O (6,8g, 1,2 eq.) en THF (15ml). La mezcla resultante se agitó, y se dejó levantar temperatura gradualmente a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con EtOAc, se lavó con salmuera (2x), se secó (MgSO4) y se concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (Hexano/EtOAc = 1 : 0 a 85 : 15) para dar **1j** (8,05g).

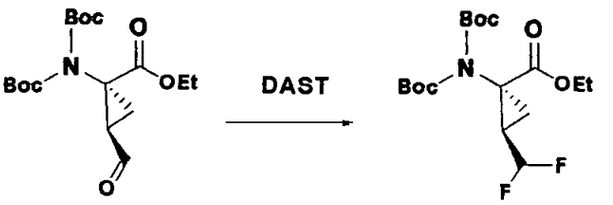
Paso **1K**



1j **1k**

A una solución del compuesto **1j** (0,5g, 1,4mmol) en iso-propanol (5ml) se agregó NaIO4 (0,9g, 4,2mmol), seguido por agua (5ml). A esta mezcla en agitación fuerte se agregó OsO4 (solución acuosa al 0,4%, 0,22m, 2,5% eq.). La mezcla resultante se agitó a temperatura ambiente durante 4h, se diluyó con EtOAc, se lavó con NaHCO3 acuoso, Na2S2O3 acuoso, salmuera, se secó (MgSO4) y se concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (Hexano/EtOAc = 1:0 a 85:15) para dar **1k** (0,37g).

Paso **1L**

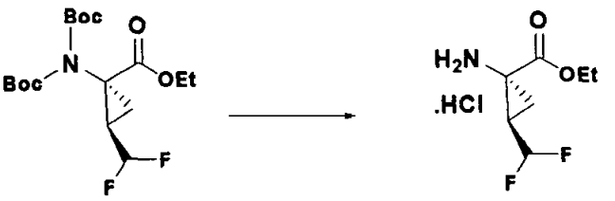


1k **1l**

000453

A una solución del compuesto **1k** (2,9g, 8,1mmol) en diclorometano (25ml) a -78°C se agregó trifluoruro de dietilaminoazufre (DAST) (2,7ml, 20,25mmol). La mezcla resultante se agitó a -78°C durante una hora, luego se dejó levantar la temperatura gradualmente a temperatura ambiente durante 6h, se diluyó con EtOAc, se lavó con NaHCO3 acuoso (2x), salmuera, se secó (MgSO4) y se concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (Hexano/EtOAc = 1 : 0 a 85 : 15) para dar **1l** (1,49g). Material de partida recuperado **1k** (1,2g).

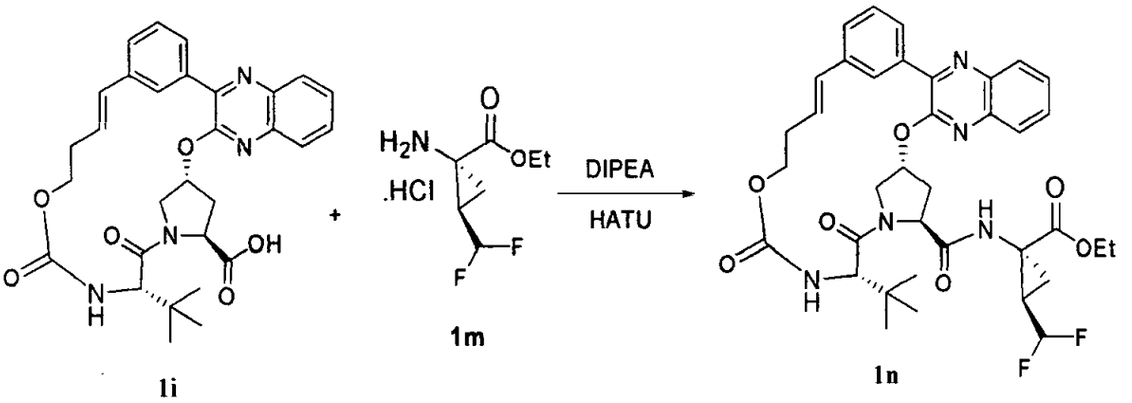
Paso **1M**



1l **1m**

Una solución de compuesto **1l** (491mg, 1,29mmol) en diclorometano (1ml) se trató con HCl 4N en 1, 4-dioxano (6ml, 24mmoL). La mezcla se agitó a temperatura ambiente durante una hora, se concentró a sequedad para dar **1m** (~100%).

Paso **1N**



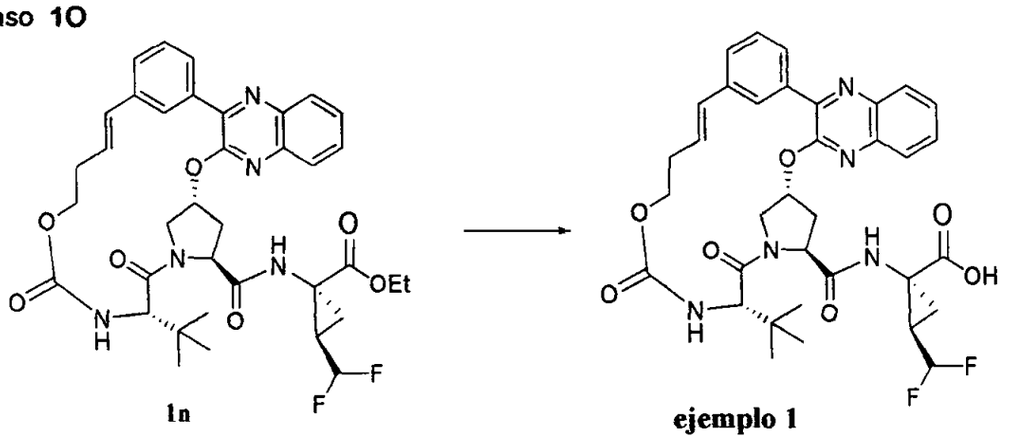
1i **1m** **1n**

A una solución de **1i** (5,28mmol), compuesto **1m** (5,808mmol) y DIPEA (3,6ml, 3,9eq.) en DMF (22ml) a 0 °C se agregó HATU (2,31g, 6,07mmol). La mezcla se agitó a

000459

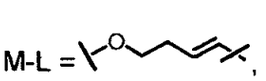
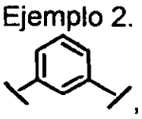
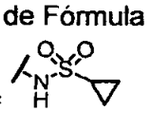
temperatura ambiente durante 4h, se diluyó con EtOAc y se lavó con NaCl acuoso semisaturado cuatro veces. La fase orgánica se secó sobre $MgSO_4$ anhidro, se filtró, y luego se concentró al vacío. El residuo se purificó por columna de gel de sílice (Hexano/EtOAc = 9 : 1 a 6 : 4) para dar compuesto **1n** (2,85g). MS (ESI): m/z 706,53 (M+H).

Paso **1O**



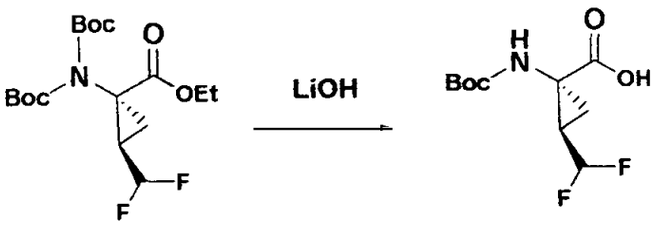
1n **ejemplo 1**

A una solución del compuesto **1n** (2,85g, 4,04mmol) en THF/MeOH (28ml-12ml) a 0°C se agregó hidróxido de litio monohidratado (1,02g, 24,2mmol) seguido por agua (12ml). La mezcla se agitó a temperatura ambiente durante 2 horas, se enfrió a 0°C, se acidificó con HCl 1N a entre pH 5 y 6. Algunos solventes orgánicos se eliminaron al vacío, y la mezcla resultante se extrajo con EtOAc tres veces (3x 150ml). Los extractos orgánicos combinados se lavaron con salmuera (30ml), se secó ($MgSO_4$), se filtró y se concentró al vacío para dar el compuesto del título (~100%). MS(ESI): m/z 678,41 (M+H).

Ejemplo 2. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=CF_2H, G = 

Método I

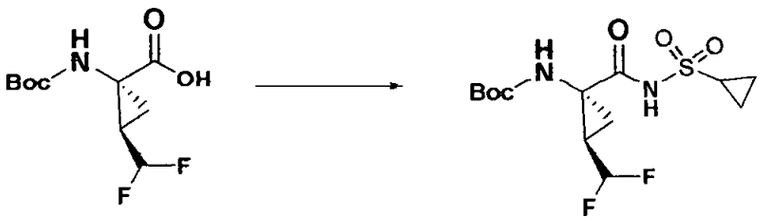
Paso **2A**



1l **2a**

Se disolvió éster etílico **1l** (50 g, 132 mmol) en THF (400 mL), luego se diluyó con MeOH (160 mL) y agua (160 mL). Se agregó $LiOH \cdot H_2O$ (27,6 g, 660 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. La solución se acidificó a pH ~ 2 usando HCl 1 M, y luego se extrajo con DCM (3 x 500 mL). Las porciones orgánicas combinadas se secaron (Na_2SO_4), se filtró, y se concentró. El ácido carboxílico crudo **2a** se llevó adelante directamente sin ninguna purificación adicional.

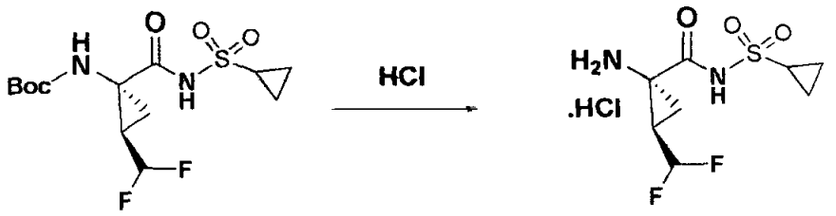
Paso **2B**



2a **2b**

Se disolvió ácido carboxílico **2a** (~ 132 mmol) en DCM (400 mL) luego se enfrió a 0 °C. Se agregó DMAP (40,3 g, 330 mmol), sulfonamida (16,0 g, 132 mmol), y EDC (63,3 g, 330 mmol) y la reacción se agitó a 0 °C durante 1 h, se dejó a temperatura ambiente, luego se agitó otras 48 h. La reacción se diluyó con EtOAC (1,5 L) y se extrajo con HCl 1N (2 x 750 mL). Las capas acuosas combinadas se extrajeron con EtOAc, y las capas de EtOAc combinadas se lavaron con salmuera (1 L). Las porciones orgánicas se secaron (Na_2SO_4), se filtró, y se concentró. El aceite crudo se purificó mediante cromatografía SiO_2 usando EtOAc al 60%/hexanos para dar la sulfonimida deseada **2b** (40 g, 85%, dos pasos).

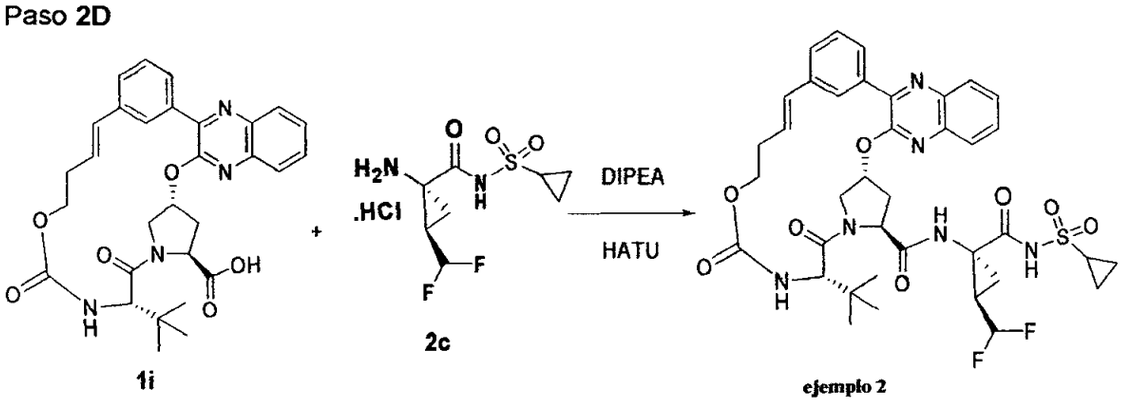
Paso **2C**



2b **2c**

Se cargó sulfonimida **2b** (40 g, 112 mmol) directamente con una solución 4M de HCl en dioxano (282 mL, 1,13 mol), y la solución resultante se agitó a temperatura ambiente durante 1,5 h. La mezcla de reacción se concentró al vacío, y el aceite crudo se disolvió en una cantidad mínima de DCM, y se trituró con hexano (hexano/DCM = 3,5/1,5). El sólido luego se filtró y se secó para dar 32,4 g del compuesto buscado **2c**.

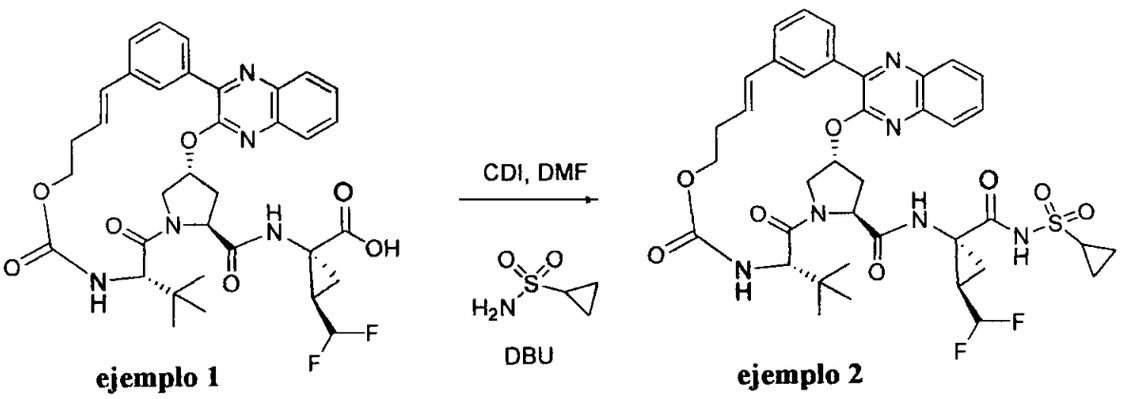
Paso **2D**



1i **2c** **ejemplo 2**

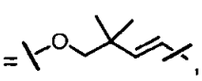
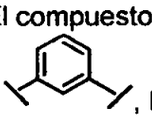
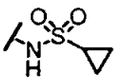
A una solución del compuesto **1i** (11mg, 0,02mmol), 2c (1 eq.) y DIPEA (0,05ml, 0,287mmol) en DMF (1ml) a 0 °C se agregó HATU (24mg, 0,063mmol). La mezcla se agitó a temperatura ambiente durante 18h, se diluyó con EtOAc y se lavó con NaCl acuoso semisaturado cuatro veces. La fase orgánica se secó sobre $MgSO_4$ anhidro, se filtró, y luego se concentró al vacío. El residuo se purificó por HPLC preparativa para dar el compuesto del título (6mg). MS(ESI); m/z 781,20 (M+H).

Método II

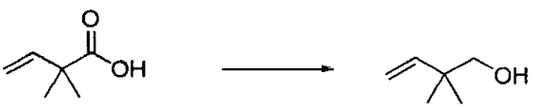


ejemplo 1 **ejemplo 2**

El compuesto de ejemplo 1 (2,78g, 4,04 mmol) y carbonildiimidazol (1,11g, 6,85mmol) se disolvieron en 22 ml de DMF anhidro y la solución resultante se agitó a 40°C durante 1 hora. Se agregó ciclopropilsulfonamida (1,22g, 10,06mmol) a la reacción seguido por DBU (0,96ml, 6,4mmol). La mezcla de reacción se agitó a 40°C durante 5 horas. La mezcla de reacción se diluyó con acetato de etilo (400ml), se lavó con agua (2x50ml), 0,5M KH_2PO_4 (2x50ml), solución acuosa saturada de NaCl (50ml), se secó sobre (MgSO4) anhidro y se concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (Hexano/ EtOAc = 1 : 1 a 0 : 1) para dar el compuesto del título (2,4g). MS(ESI); m/z 781,20 (M+H).

Ejemplo 3. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=  , G = 

Paso **3A**

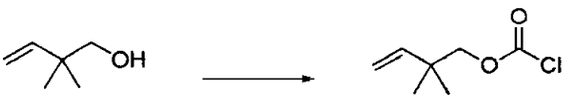


3a-1 **3a**

A una solución del compuesto **3a-1** (21,7g, 0,19mole) en dietiléter (100ml) a 5-10°C se agregó por goteo LAH (1M en éter, 200ml, 0,2mol). La mezcla luego se agitó a temperatura ambiente durante 1h, se enfrió a 0-5°C. Se agregó EtOAc (5ml)

lentamente, seguido por la adición cuidadosa de HCl 6N (200ml), agua (50ml) y éter (50ml). La fase acuosa separada luego se extrajo con éter (2x250ml). las capas orgánicas combinadas se lavaron con salmuera (75ml), se secó (sulfato de sodio) y se concentró a 0°C para eliminar el éter. La destilación bajo presión reducida dio compuesto **3a** (10,5g).

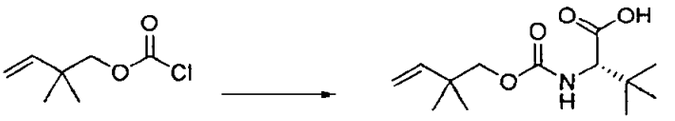
Paso 3B



3a **3b**

A una solución de solución de fosgeno en tolueno (20% en peso 100ml, 188mmol) a 10°C se agregó por goteo compuesto **3a** durante 20min. La mezcla se agitó a temperatura ambiente durante 3h, se coevaporó con cloruro de metileno (5x40ml) para dar compuesto **3b** (15,6g, 77% de pureza).

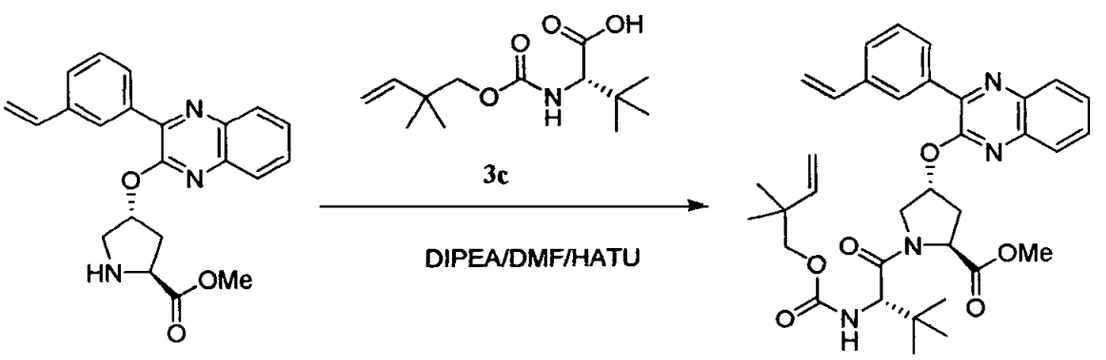
Paso 3C



3b **3c**

A una mezcla de L-tert-leucina (5,36g, 40,8mmol) y 1,4-dioxano (22m) se agregó lentamente NaOH 2N mientras la temperatura interna se mantuvo por debajo de los 30°C. La mezcla se enfrió a 10-15°C, se agregó compuesto **3b** (10,6g, 77%, 49mmol) lentamente. La mezcla se agitó a temperatura ambiente durante 15h, luego a 60°C durante 3h, se enfrió a temperatura ambiente, se lavó con cloruro de metileno (3x35ml), La fase acuosa se ajustó a entre pH 2 y 3 con HCl 6N, se extrajo con EtOAc (3x70ml). Las capas de EtOAc combinadas se lavaron con salmuera (20ml), se secó (sulfato de sodio) y se concentró a sequedad para dar compuesto **3c** (8,3g).

Paso **3D**

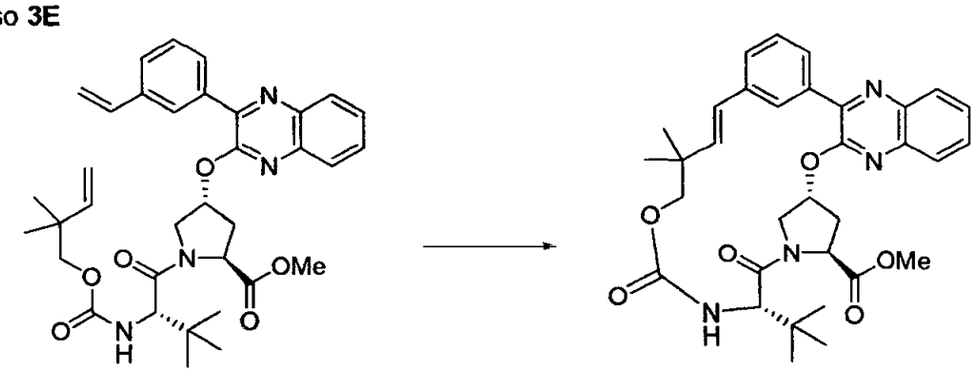


1d

3d

A una solución del compuesto **1d** (sal de HCl, 13,57mmol), **3c** (3,84g, 14,9mmol) y DIPEA (7,1ml, 40,7mmol) en DMF (45ml) a 0 °C se agregó en porciones HATU (5,95g, 15,6mmol). La mezcla se agitó a temperatura ambiente durante 18h, se diluyó con EtOAc (400m) y se lavó con agua, NaCl acuoso semisaturado cuatro veces. La fase orgánica se secó sobre Na_2SO_4 anhidro, se filtró, y luego se concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (Hexano/EtOAC = 9 : 1 a 4 : 1) para dar compuesto **3d** (8,6g).

Paso **3E**



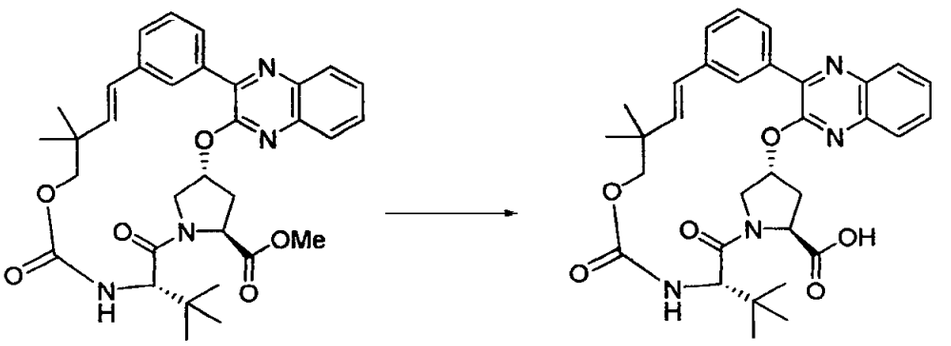
3d

3e

Una solución del compuesto **3d** (4,04g, 6,75mmol) en tolueno (1200ml) se purgó con nitrógeno por 0,5h y se agregó catalizador Zhan basado en rutenio 1B (0,5g 0,675mmol). La mezcla se agitó a 110°C durante 8h, se enfrió a temperatura ambiente,

se agregó ácido 2-mercaptonicotínico (1,014g, 6,7mmo) y DIPEA (1,2ml, 6,75mmol). La mezcla se agitó a temperatura ambiente durante 16h, se filtró y se concentró. El residuo se disolvió en EtOAc, se lavó con $NaHCO_3$ acuoso, salmuera, se secó (sulfato de sodio). El solvente luego se evaporó y el residuo se purificó por cromatografía flash en gel de sílice usando un gradiente de elución (EtOAc/Hexano 0% a 25%) para dar compuesto **3e** (2,6g). MS (ESI) m/z 587,30 (M+H).

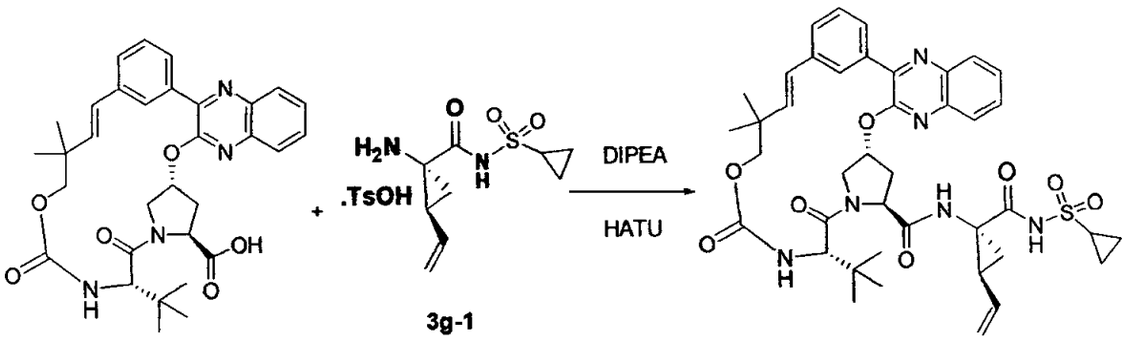
Paso **3F**



3e **3f**

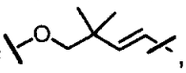
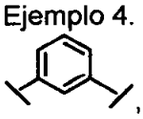
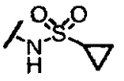
A una solución del compuesto **3e** (3,1g, 5,28mmol) en THF/MeOH (32ml/14ml) a 0°C se agregó hidrato de hidróxido de litio (1,11g, 26,45mmol), seguido por agua (14ml). La mezcla se agitó a temperatura ambiente durante una hora, se colocó a 0°C, se agregó HCl 1N (~ 29ml) por goteo hasta que el pH de la mezcla = ~5. La mezcla se extrajo con EtOAc (3x80ml). Las capas orgánicas combinadas se lavaron con salmuera (30ml), se secó (Na_2SO_4), se filtró y se concentró al vacío para dar **3f** (~100%). MS(ESI): m/z 573,39 (M+H).

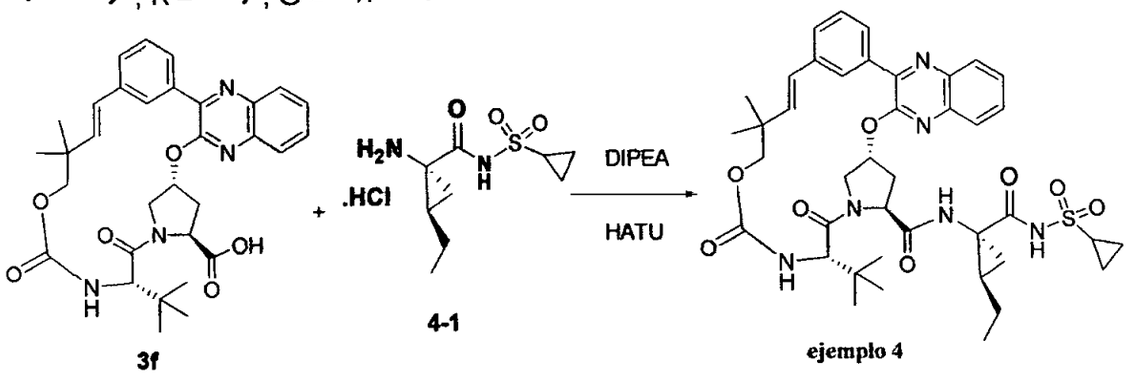
Paso **3G**



3f 3g-1 ejemplo 3

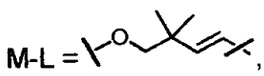
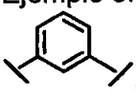
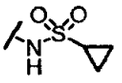
A una solución del compuesto **3f** (16mg, 0,028mmol), **3g-1** (14mg, 0,034.) y DIPEA (0,025ml, 0,14mmol) en DMF (1,8ml) a 0 °C se agregó HATU (15mg, 0,039mmol). La mezcla se agitó a temperatura ambiente durante 2h, y se purificó por HPLC preparativa para dar el compuesto del título (16mg). MS(ESI): m/z 785,26 (M+H).

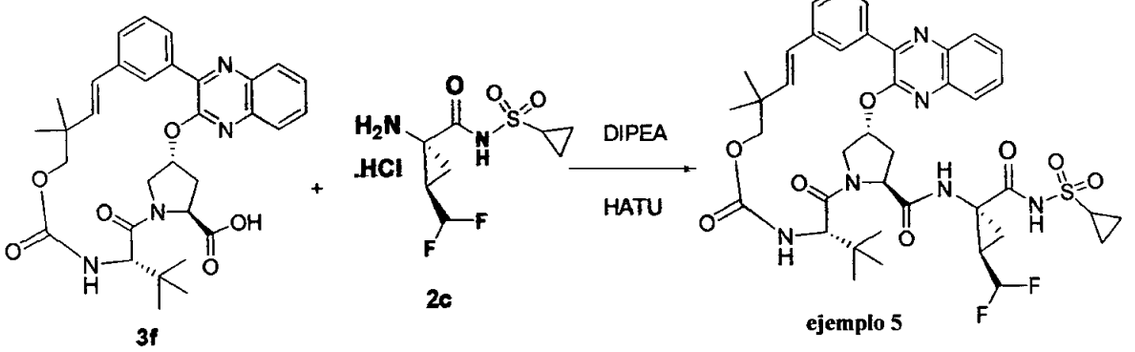
Ejemplo 4. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=  , G = 



3f 4-1 ejemplo 4

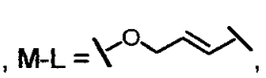
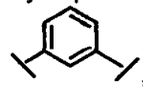
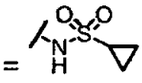
A una solución del compuesto **3f** (15mg, 0,026mmol), **4-1** (8,4mg, 0,031.) y DIPEA (0,025ml, 0,14mmol) en DMF (1,8ml) a 0 °C se agregó HATU (15mg, 0,039mmol). La mezcla se agitó a temperatura ambiente durante 2h, y se purificó por HPLC preparativa para dar el compuesto del título (15mg). MS(ESI): m/z 787,39 (M+H).

Ejemplo 5. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'= CF_2H, G = 

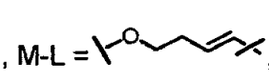
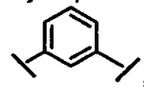
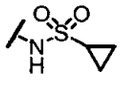


3f 2c ejemplo 5

A una solución del compuesto **3f** (1,284g, 2,07mmol), **2c** (0,681g, 2,34mmol) y DIPEA (1,1ml, 3eq.) en DMF (16ml) a 0 °C se agregó en porciones HATU (0,914g, 2,4mmol). La mezcla se agitó a temperatura ambiente durante 1h, se diluyó con EtOAc (180ml), y se lavó con agua (20ml), NaCl acuoso semisaturado (20ml), KH_2PO_4 acuoso 0,5M (2x20ml), salmuera (20ml). La fase orgánica se secó sobre sulfato de sodio anhidro, se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (EtOAc/Hexano 25% a 50%) para dar el compuesto del título (1,3g). MS(ESI); m/z 809,55 (M+H).

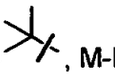
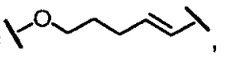
Ejemplo 6. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'= CF_2H, G = 

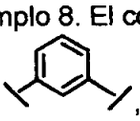
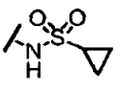
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 2 o Ejemplo 5. MS (ESI): m/e 767,35 (M+H).

Ejemplo 7. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'= , G = 

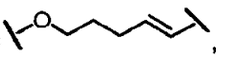
000468

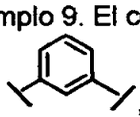
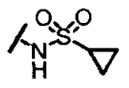
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 3. MS (ESI): m/e 757,51 (M+H).

Ejemplo 8. El compuesto de Fórmula XV, en donde R =  , M-L =  ,

Ar=  , R'=  , G = 

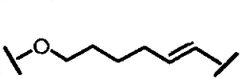
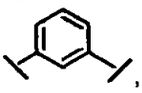
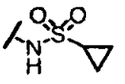
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 3. MS (ESI): m/z 771,23 (M+H).

Ejemplo 9. El compuesto de Fórmula XV, en donde R =  , M-L =  ,

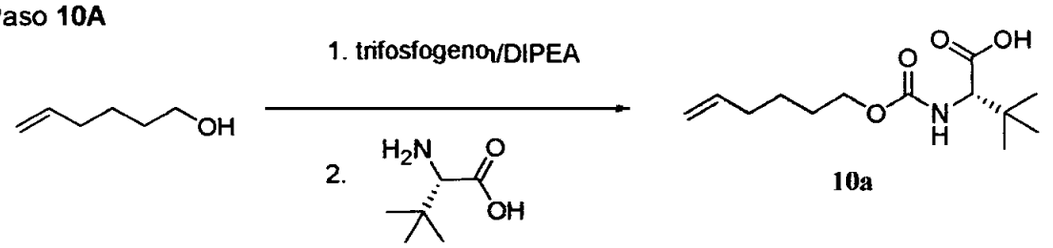
Ar=  , R'= CF_2H, G = 

Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 2 o Ejemplo 5. MS (ESI): m/z 795,34 (M+H).

Ejemplo 10. El compuesto de Fórmula XV, en donde R =  , M-L

=  , Ar=  , R'=  , G = 

Paso **10A**



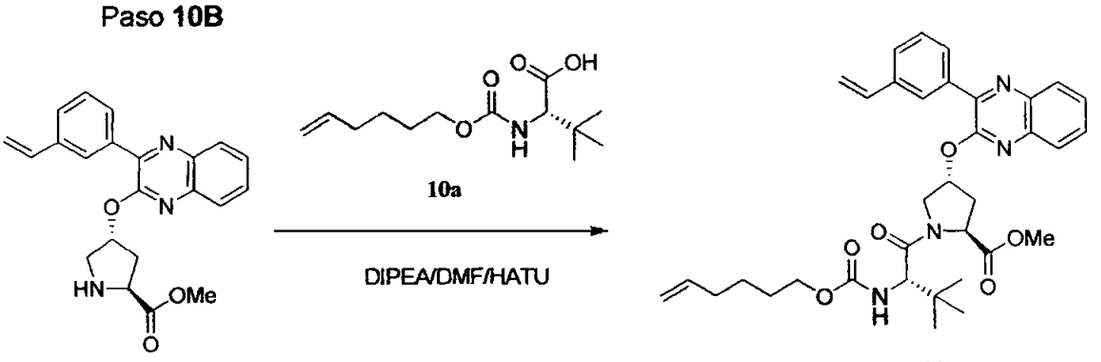
10a

A una solución de hex-5-en-1-ol (1,3ml, 10,9mol), trifosfogeno (1,46g, 4,92mmol) en 1,4-dioxano (21ml) a 0°C se agregó por goteo DIPEA (1,7ml, 9,72mmol). La mezcla se agitó a temperatura ambiente durante una hora, se enfrió a 0°C. A esto se agregó lentamente L-t-leucina (1,28g, 9,72mmol) disuelta en NaOH 1N (9,8ml). La mezcla resultante se agitó a temperatura ambiente durante la noche, se concentró para eliminar la mitad del volumen de dioxano, se trató con NaOH 1N (25ml), se lavó con éter (3x30ml). La fase acuosa se acidificó a pH 2~3 con HCl 6N, y luego se extrajo con

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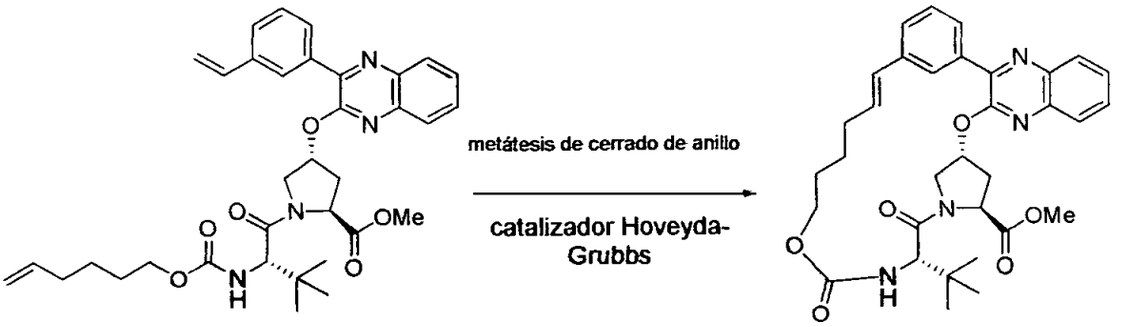
diclorometano (3x30ml). Las capas orgánicas combinadas se secaron (MgSO4), se concentró a sequedad para dar compuesto **10a** (2,5g) directamente se usó en el paso siguiente.

Paso **10B**



A una solución del compuesto **1d** (sal de HCl, 98mg, 0,218mmol), compuesto **10a** (90mg, 0,35mmol) y DIPEA (0,24ml, 1,37mmol) en DMF (3ml) a 0 °C se agregó HATU (133mg, 0,35mmol). La mezcla se agitó a temperatura ambiente durante 18h, se diluyó con EtOAc y se lavó con NaCl acuoso semisaturado cuatro veces. La fase orgánica se secó sobre $MgSO_4$ anhidro, se filtró, y luego se concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (Hexano/EtOAC = 6 : 1 a 4 : 1) para dar compuesto **10b** (119mg). MS (ESI): m/e 615,45 (M+H).

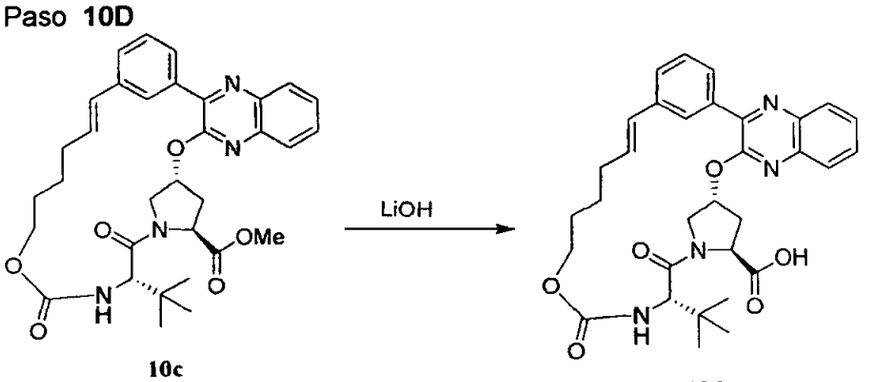
Paso **10C**



10b **10c**

A una solución del compuesto **10b** (119mg, 0,19mmol) en diclorometano (20ml) se agregó catalizador Hoveyda-Grubbs de primera generación (5 mol% eq.). La mezcla de reacción se agitó a 40°C durante 20h. El solvente luego se evaporó y el residuo se purificó por cromatografía flash en gel de sílice usando un gradiente de elución (Hexano/EtOAC = 9 : 1 a 7 : 3) para dar el compuesto macrocíclico **10c** (58mg). MS (ESI) m/z 587,44 (M+H).

Paso **10D**

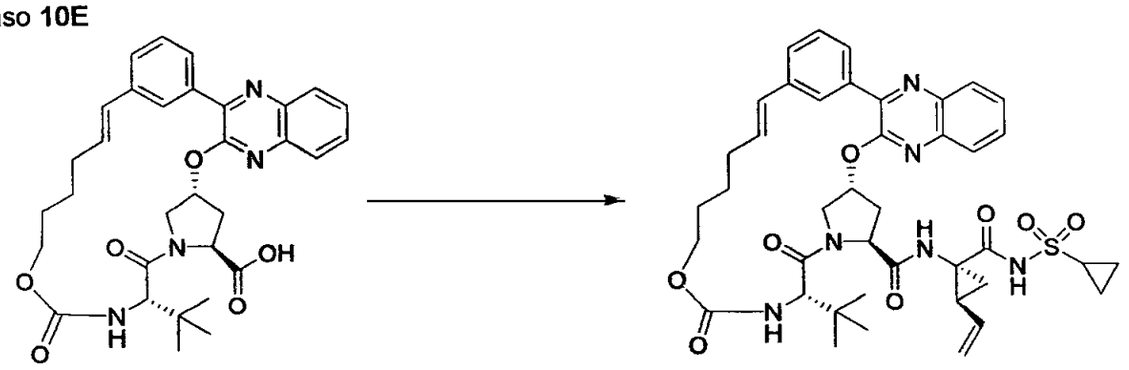


10c **10d**

A una solución del compuesto **10c** (58mg, 0,099mmol) en THF/MeOH (3ml/1,5ml) se agregó hidróxido de litio 1N (1,5ml, 1,5mmol). La mezcla se agitó a temperatura ambiente durante 20 horas. La mayor parte de los solventes orgánicos se evaporaron al vacío, y el residuo resultante se diluyó con agua y se acidificó entre pH 5 y 6. La mezcla se extrajo con EtOAc tres veces. Los extractos orgánicos combinados

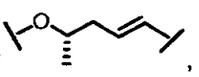
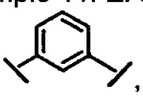
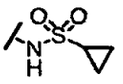
se secaron ($MgSO_4$), se filtró y se concentró al vacío para dar **10d** (100%). MS(ESI): m/z 573,31 (M+H), 579,32 (M+Li).

Paso **10E**

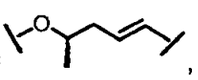
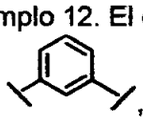
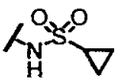


10d **ejemplo 10**

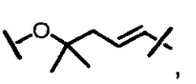
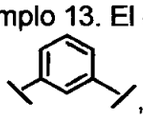
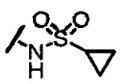
Este compuesto se preparó a partir del **10d** mediante el mismo procedimiento que se describe en Ejemplo 3. MS (ESI): m/z 785,31 (M+H).

Ejemplo 11. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'= CF_2H, G = 

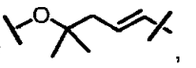
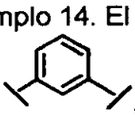
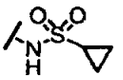
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 2 o Ejemplo 5. MS (ESI): m/z 795,53 (M+H).

Ejemplo 12. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'= CF_2H, G = 

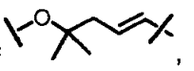
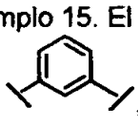
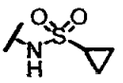
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 2 o Ejemplo 5. MS (ESI): m/z 795,58 (M+H).

Ejemplo 13. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=  , G = 

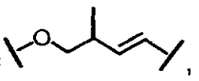
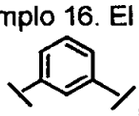
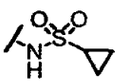
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 3. MS (ESI): m/z 785,29 (M+H).

Ejemplo 14. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=  , G = 

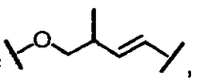
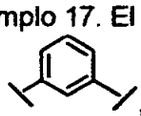
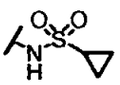
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 4. MS (ESI): m/z 787,39 (M+H).

Ejemplo 15. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=CF_2H, G = 

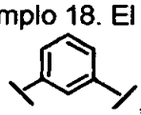
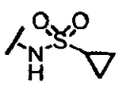
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 2 o Ejemplo 5. MS (ESI): m/e 809,28 (M+H).

Ejemplo 16. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=  , G = 

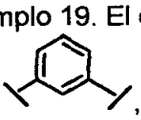
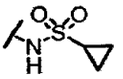
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 3. MS (ESI): m/e 771,11 (M+H).

Ejemplo 17. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=CF_2H, G = 

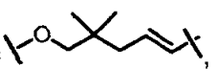
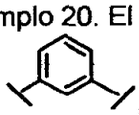
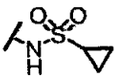
Este compuesto se preparó mediante el mismo procedimiento que se describe en Ejemplo 2 o Ejemplo 5. MS (ESI): m/z 795,21 (M+H).

Ejemplo 18. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=  , G = 

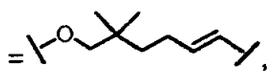
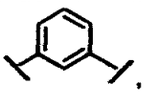
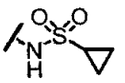
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 3. MS (ESI): m/z 799,25 (M+H).

Ejemplo 19. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=  , G = 

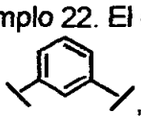
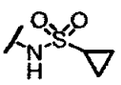
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 4. MS (ESI): m/z 801,22 (M+H).

Ejemplo 20. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=CF_2H, G = 

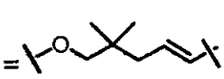
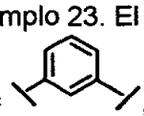
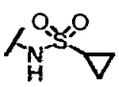
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 2 o Ejemplo 5. MS (ESI): m/z 823,21 (M+H).

Ejemplo 21. El compuesto de Fórmula XV, en donde R =  , M-L
=  , Ar=  , R'=  , G = 

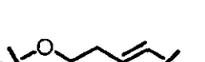
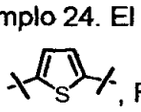
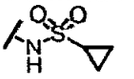
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 3. MS (ESI): m/z 813,42 (M+H).

Ejemplo 22. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=  , G = 

Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 4. MS (ESI): m/z 815,43 (M+H).

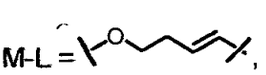
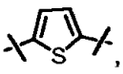
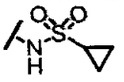
Ejemplo 23. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=CF_2H, G = 

Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 2 o Ejemplo 5. MS (ESI): m/z 837,41 (M+H).

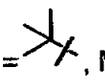
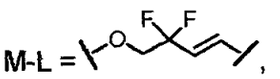
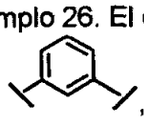
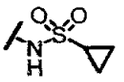
Ejemplo 24. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=  , G = 

000474

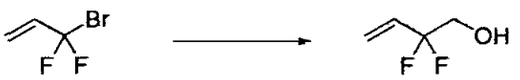
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 3. MS (ESI): m/z 763,25 (M+H).

Ejemplo 25. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=CF_2H, G = 

Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 2 o Ejemplo 5. MS (ESI): m/z 787,22 (M+H).

Ejemplo 26. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=  , G = 

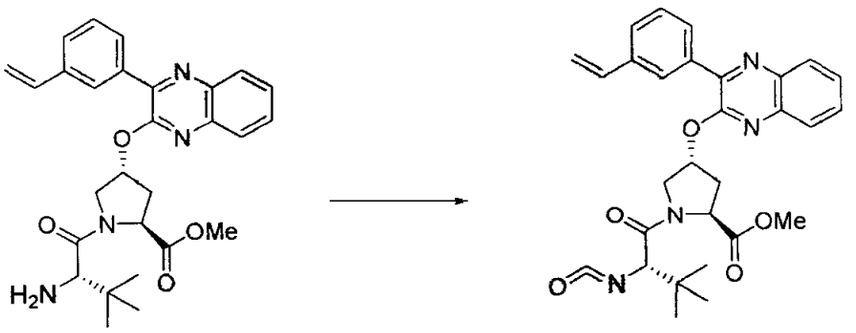
Paso **26A**



26a-1 **26a**

A una solución de **26a-1** (3,4g, 21,6mmol), HCOOEt (3,5ml, 43,2mmol) en THF (100ml)-éter (30ml)-pentano (30ml) a -95°C (baño de N2 líquido y tolueno) se agregó por goteo n-BuLi (2,5 M en hexano, 10ml, 25mmol). La mezcla se agitó a esa temperatura durante 1,5h y la temperatura del baño se dejó elevar gradualmente a 0°C durante 2 -3h, se neutralizó con solución acuosa de NH4Cl (1,4g en 20ml de agua). La mezcla se agitó durante 15min. A la capa orgánica separada se agregó MeOH (50ml), seguido por la adición de $NaBH_4$ (1g) en porciones a 0°C. La mezcla se agitó a temperatura ambiente por 0,5h, se enfrió a 0°C, se neutralizó cuidadosamente con HCl 1N, a pH ~3, se extrajo con éter (3x). Las capas orgánicas combinadas se lavaron con NaHCO3 acuoso, salmuera, se secó (Na2SO4) y se concentró a 0°C. El residuo se purificó por destilación para dar **26a** (1,3g).

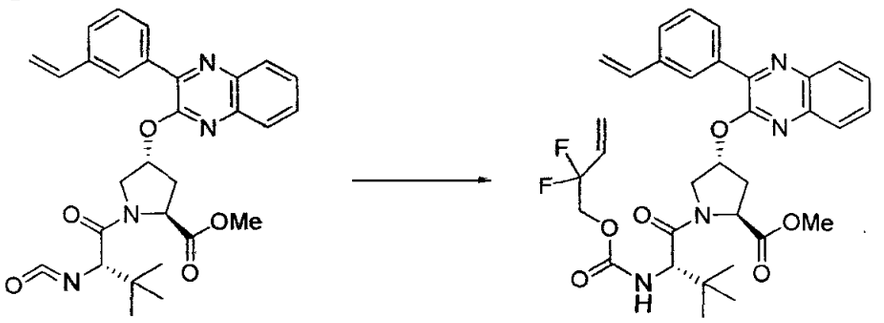
Paso **26B**



1f 26b

A una solución del compuesto **1f** (6,23g, 11,10mmol) en cloruro de metileno (100ml) a 0°C se agregó piridina (5,4ml, 67mmol), seguido por la adición por goteo de solución de fosgeno (20% en peso en tolueno, 17mmol) durante un periodo de 0,5h. la mezcla se agitó a temperatura ambiente por 0,5h, se diluyó con EtOAc (500ml), se lavó con agua (70ml), salmuera (2x70ml), se secó (sulfato de sodio), se filtró y se concentró a sequedad para dar compuesto **26b** (5,3g). MS(ESI): m/z 515,28 (M+H)

Paso **26C**

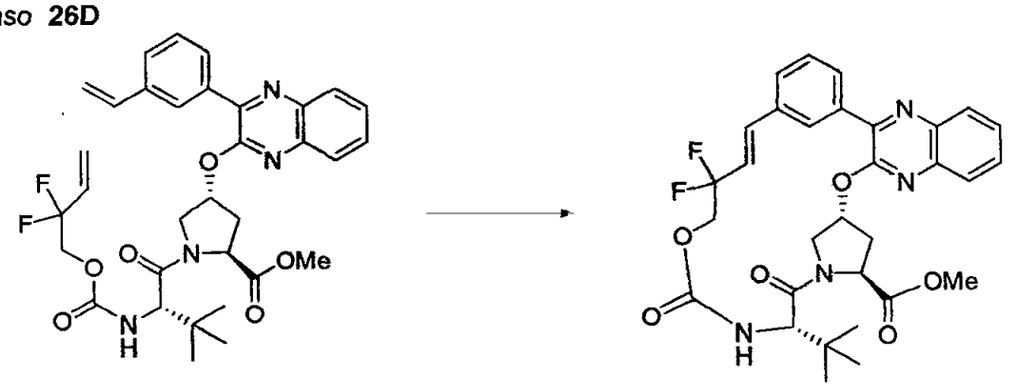


26b 26c

A una solución del compuesto **26b** (4,89g, 9,5mmol) y **26a** (~1,4eq.) en cloruro de metileno (65ml) se agregó filtro molecular (4A, 5g). Después de la mezcla se agitó a temperatura ambiente por 0,5h, se agregó DBU (2,1ml, 16=4mmol). La mezcla resultante se agitó a temperatura ambiente durante 2h y se concentró. El residuo se purificó por cromatografía flash en gel de sílice usando un gradiente de elución

(EtOAC/Hexano 0% a 25%) para dar compuesto **26c** (6,1g). MS (ESI) m/z 623,34 (M+H).

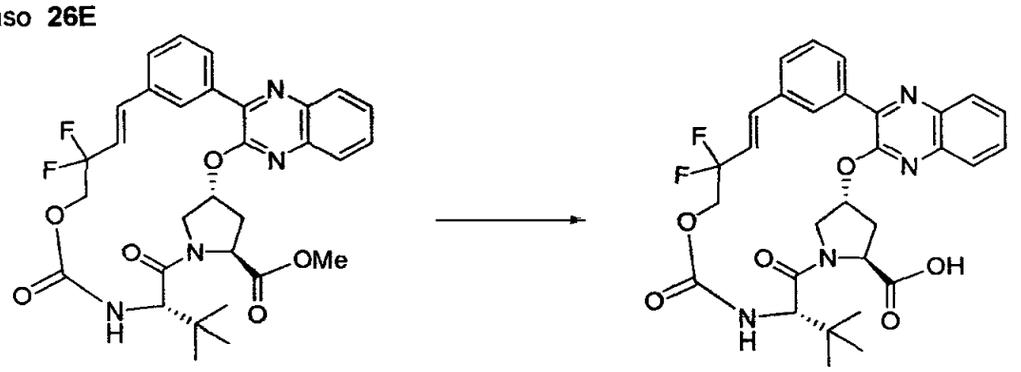
Paso **26D**



26c **26d**

El compuesto **26d** se preparó a partir del compuesto **26c** mediante el mismo procedimiento que se describe en Paso 3E de ejemplo 3. MS (ESI) m/z 595,01 (M+H).

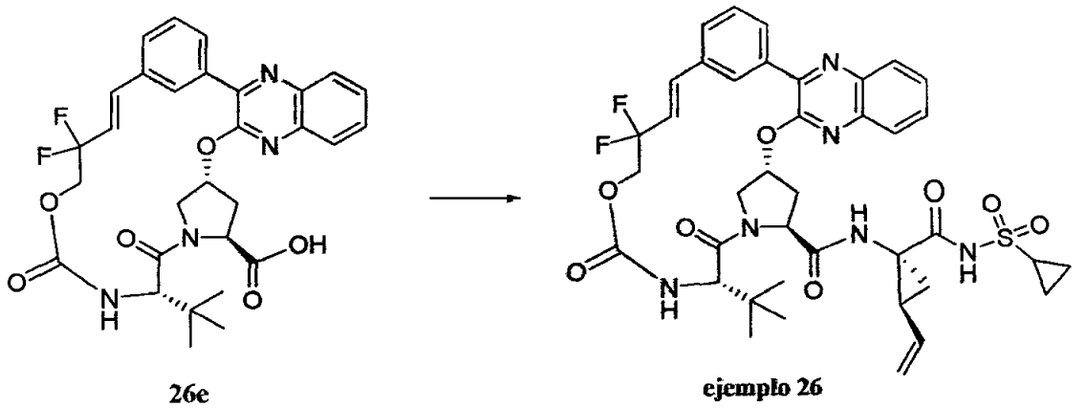
Paso **26E**



26d **26e**

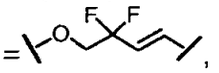
El compuesto **26e** se preparó a partir del compuesto **26d** mediante el mismo procedimiento que se describe en Paso 3F de ejemplo 3. MS (ESI) m/z 581,15 (M+H).

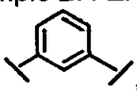
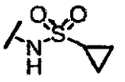
Paso **26F**



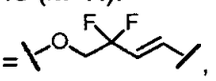
26e **ejemplo 26**

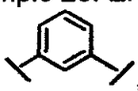
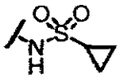
El compuesto ejemplo 26 se preparó a partir del **26e** mediante los mismos procedimientos que se describen en Ejemplo 3. MS (ESI): m/z 793,20 (M+H).

Ejemplo 27. El compuesto de Fórmula XV, en donde R =  , M-L =  ,

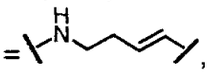
Ar=  , R'=  , G = 

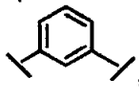
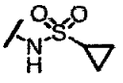
Este compuesto se preparó a partir del compuesto **26e** mediante los mismos procedimientos que se describen en Ejemplo 4. MS (ESI): m/z 795,43 (M+H).

Ejemplo 28. El compuesto de Fórmula XV, en donde R =  , M-L =  ,

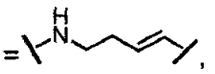
Ar=  , R'=CF_2H, G = 

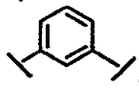
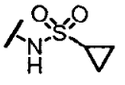
Este compuesto se preparó a partir del compuesto **26e** mediante los mismos procedimientos que se describen en Ejemplo 5. MS (ESI): m/z 817,27 (M+H).

Ejemplo 29. El compuesto de Fórmula XV, en donde R =  , M-L =  ,

Ar=  , R'=  , G = 

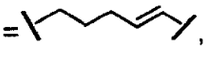
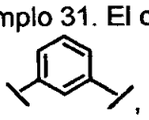
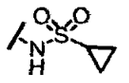
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 3. MS (ESI): m/z 756,23 (M+H).

Ejemplo 30. El compuesto de Fórmula XV, en donde R =  , M-L =  ,

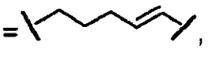
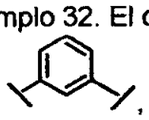
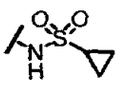
Ar=  , R'=CF_2H, G = 

000478

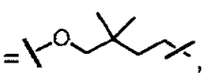
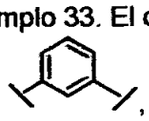
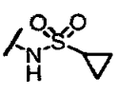
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 2 o Ejemplo 5. MS (ESI): m/z 780,19 (M+H).

Ejemplo 31. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=  , G = 

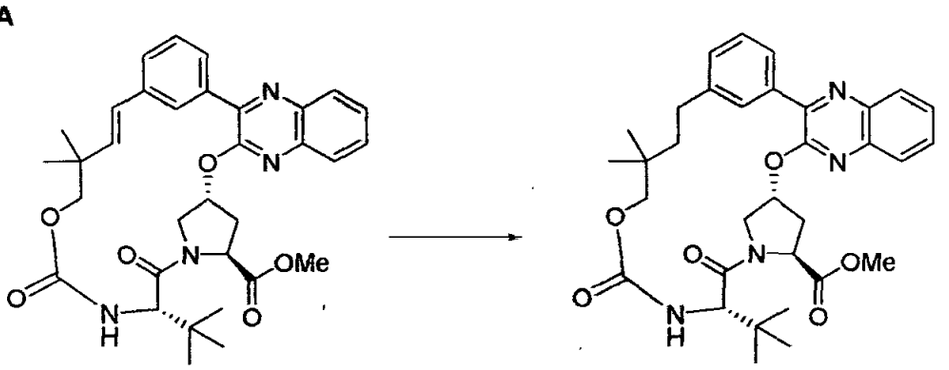
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 3. MS (ESI): m/z 755,13 (M+H).

Ejemplo 32. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=CF_2H, G = 

Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 2 o Ejemplo 5. MS (ESI): m/z 779,26 (M+H).

Ejemplo 33. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=  , G = 

Paso **33A**

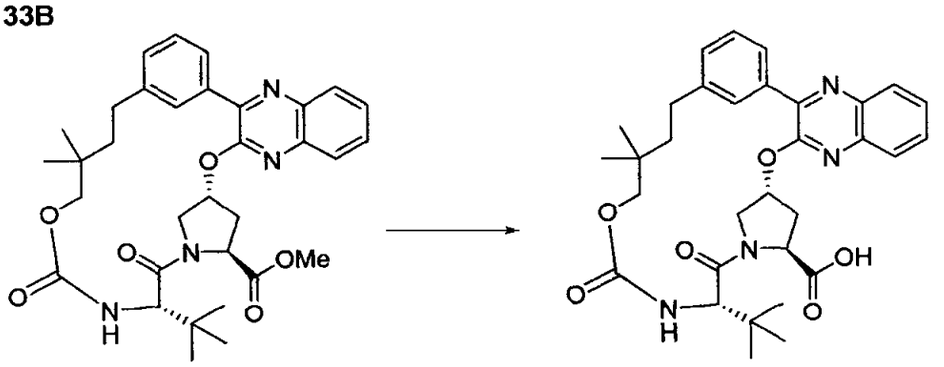


3e **33a**

Una mezcla de **3e** (1,52g, 2,59mmol), Pd-C (10% en peso 182mg) y EtOAc (38ml) se hidrogenó durante 10h, se filtró y se concentró. El residuo se purificó por cromatografía flash en gel de sílice usando un gradiente de elución (EtOAC/Hexano 0% a 25%) para dar compuesto **33a** (1,3g). MS (ESI): m/z 589,27 (M+H).

000479

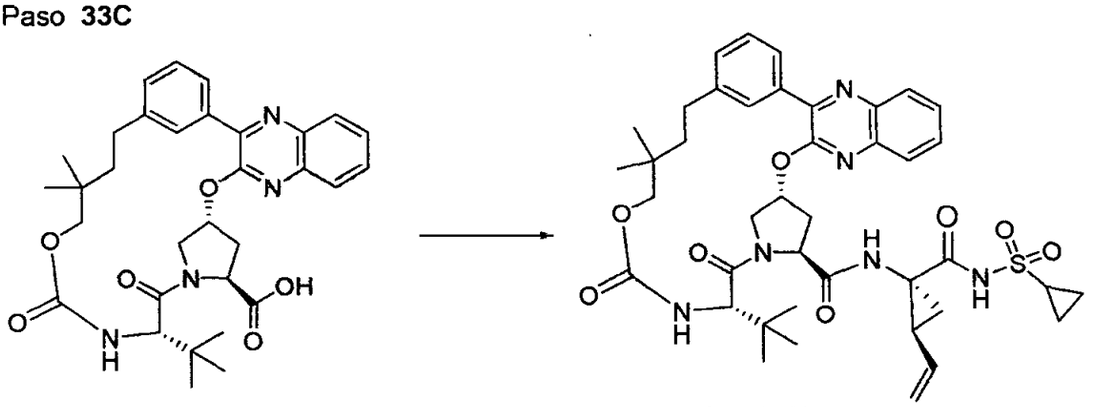
Paso **33B**



33a **33b**

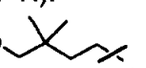
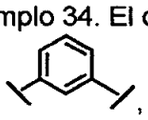
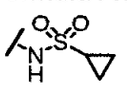
El compuesto **33b** se preparó a partir del **33a** mediante los mismos procedimientos que se describen en Paso 3F del Ejemplo 3. MS(ESI): m/z 575,15 (M+H).

Paso **33C**

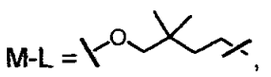
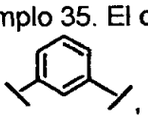
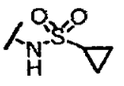


33b **ejemplo 33**

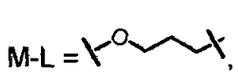
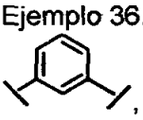
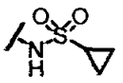
El compuesto de ejemplo 33 se preparó a partir del **33b** mediante los mismos procedimientos que se describen en Ejemplo 3. MS (ESI): m/z 778,39 (M+H).

Ejemplo 34. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=  , G = 

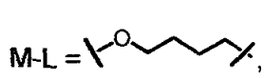
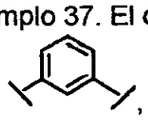
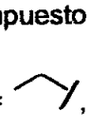
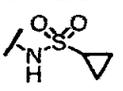
Este compuesto se preparó a partir del **33b** mediante los mismos procedimientos que se describen en Ejemplo 4. MS (ESI): m/z 789,37 (M+H).

Ejemplo 35. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=CF_2H, G = 

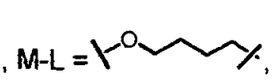
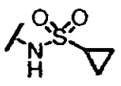
Este compuesto se preparó a partir del **33b** mediante los mismos procedimientos que se describen en Ejemplo 5. MS (ESI): m/z 811,26 (M+H).

Ejemplo 36. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=CF_2H, G = 

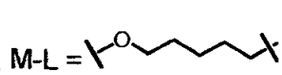
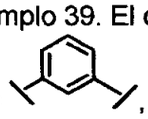
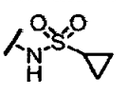
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 35. MS (ESI): m/z 769,35 (M+H).

Ejemplo 37. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=  , G = 

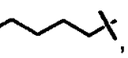
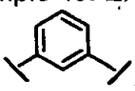
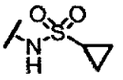
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 34. MS (ESI): m/z 761,62 (M+H).

Ejemplo 38. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=CF_2H, G = 

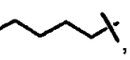
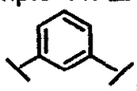
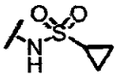
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 35. MS (ESI): m/z 783,38 (M+H).

Ejemplo 39. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=  , G = 

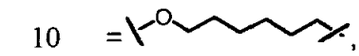
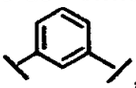
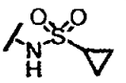
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 33. MS (ESI): m/z 773,49 (M+H).

Ejemplo 40. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=  , G = 

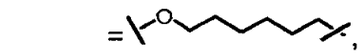
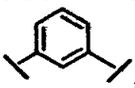
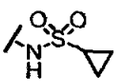
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 34. MS (ESI): m/z 775,36 (M+H).

Ejemplo 41. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=CF_2H, G = 

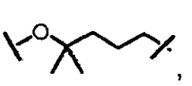
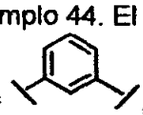
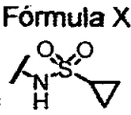
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 35. MS (ESI): m/z 797,34 (M+H).

Ejemplo 42. El compuesto de Fórmula XV, en donde R =  , M-L
=  , Ar=  , R'=  , G = 

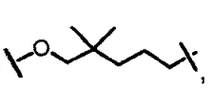
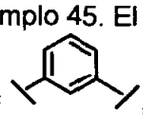
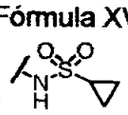
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 33. MS (ESI): m/z 787,41 (M+H).

Ejemplo 43. El compuesto de Fórmula XV, en donde R =  , M-L
=  , Ar=  , R'=  , G = 

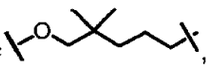
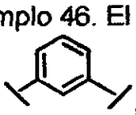
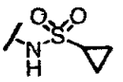
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 34. MS (ESI): m/z 789,26 (M+H).

Ejemplo 44. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=CF_2H, G = 

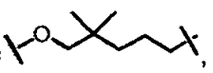
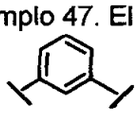
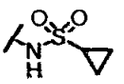
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 35. MS (ESI): m/z 811,28 (M+H).

Ejemplo 45. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=  , G = 

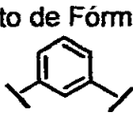
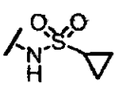
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 33. MS (ESI): m/z 801,57 (M+H).

Ejemplo 46. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=  , G = 

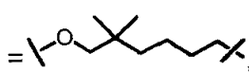
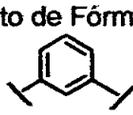
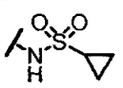
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 34. MS (ESI): m/z 803,57 (M+H).

Ejemplo 47. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=CF_2H, G = 

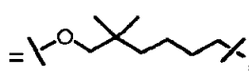
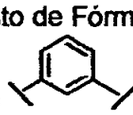
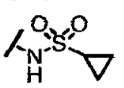
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 35. MS (ESI): m/z 825,50 (M+H).

Ejemplo 48. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=  , G = 

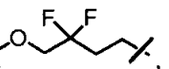
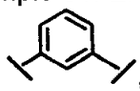
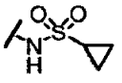
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 33. MS (ESI): m/z 815,46 (M+H).

Ejemplo 49. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=  , G = 

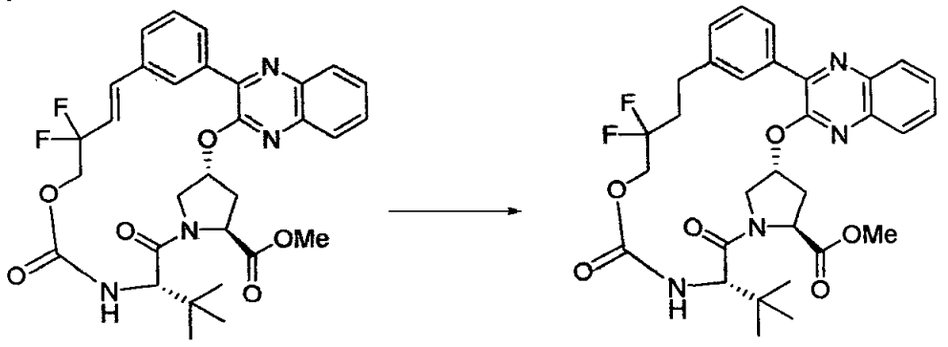
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 34. MS (ESI): m/z 817,46 (M+H).

Ejemplo 50. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=CF_2H, G = 

Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 35. MS (ESI): m/z 839,46 (M+H).

Ejemplo 51. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=  , G = 

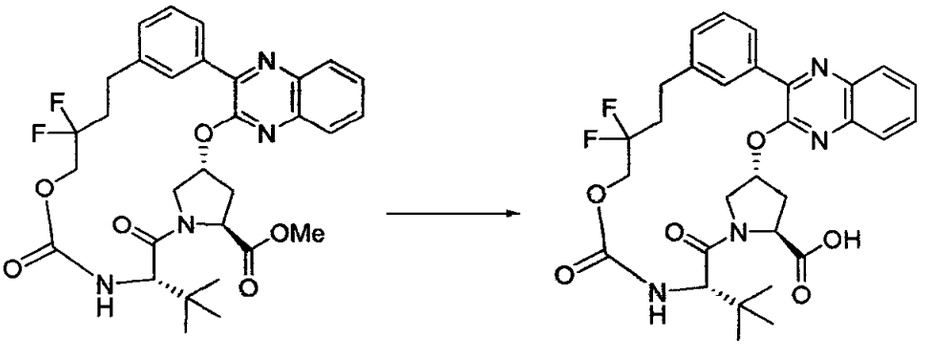
Paso **51A**



26d **51a**

Una mezcla de **26d** (2,55g, 4,286mmol), Pd-C (10% en peso 255mg), DIPEA (1,5ml) y EtOAc (65ml) se hidrogenó durante 4h, se filtró y se concentró. El residuo se purificó por cromatografía flash en gel de sílice usando un gradiente de elución (EtOAC/Hexano 0% a 25%) para dar compuesto **51a** (1,83g). MS (ESI): m/z 597,05 (M+H).

Paso **51B**

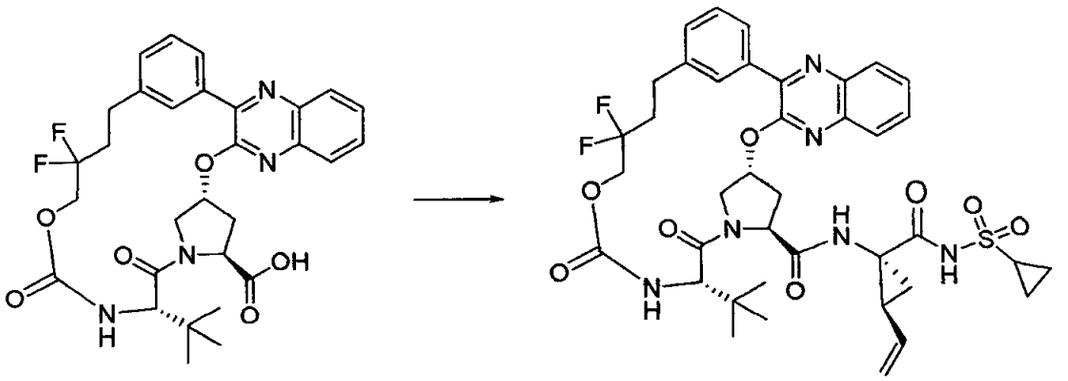


51a **51b**

El compuesto **51b** se preparó a partir del compuesto **51a** mediante el mismo procedimiento que se describe en Paso 3F de ejemplo 3. MS (ESI) m/z 583,04 (M+H).

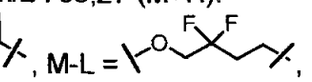
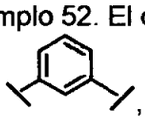
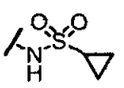
Paso **51C**

000484

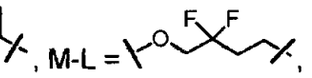
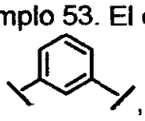
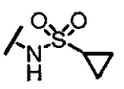


51b **ejemplo 51**

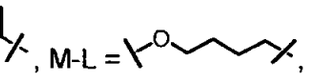
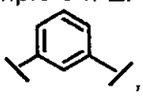
El compuesto de ejemplo 51 se preparó a partir del **51b** mediante los mismos procedimientos que se describen en Ejemplo 3. MS (ESI): m/z 795,27 (M+H).

Ejemplo 52. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=  , G = 

Este compuesto se preparó a partir del **51b** mediante los mismos procedimientos que se describen en Ejemplo 4. MS (ESI): m/z 797,43 (M+H).

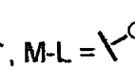
Ejemplo 53. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=CF_2H, G = 

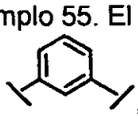
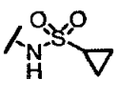
Este compuesto se preparó a partir del **51b** mediante los mismos procedimientos que se describen en Ejemplo 5. MS (ESI): m/z 819,43 (M+H).

Ejemplo 54. El compuesto de Fórmula XV, en donde R =  , M-L =  , Ar=  , R'=CF_2H, G = OH

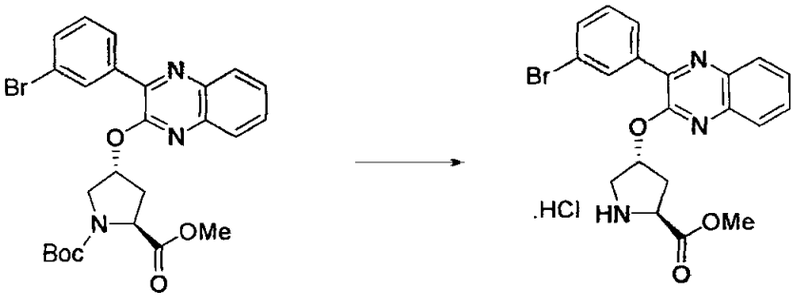
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 1. MS (ESI): m/z 680,46 (M+H).

000485

Ejemplo 55. El compuesto de Fórmula XV, en donde R =  , M-L =  ,

Ar=  , R'=  , G = 

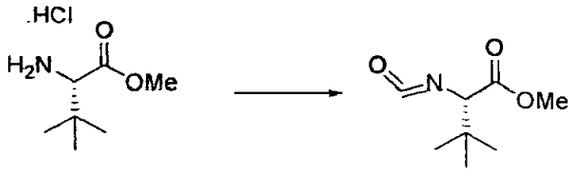
Paso **55A**



1b **55a**

Una solución del compuesto **1b** (1g, 1,9mmol) en diclorometano (1ml) se trató con HCl 4M/dioxano (6ml, 24mmol). La mezcla resultante se agitó a temperatura ambiente durante 2 horas, y se concentró al vacío a sequedad para dar la sal de HCl del compuesto **55a** (100%).

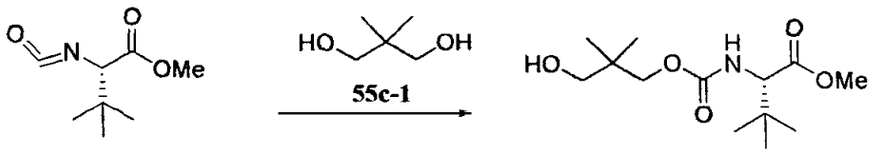
Paso **55B**



55b-1 **55b**

A una solución del compuesto **55b-1** (1,046g, 5,5mmol) en diclorometano (30ml) a 0°C se agregó piridina (2,23ml), seguido por la adición por goteo de solución de fosgeno (en tolueno, 20% en peso, 4,4ml, 8,3mmol). La mezcla se agitó a 0°C durante 2h, se diluyó con EtOAc, se lavó con HCl 1N, salmuera, se secó (sulfato de sodio) y se concentró a sequedad para dar **55b** (0,95g).

Paso **55C**



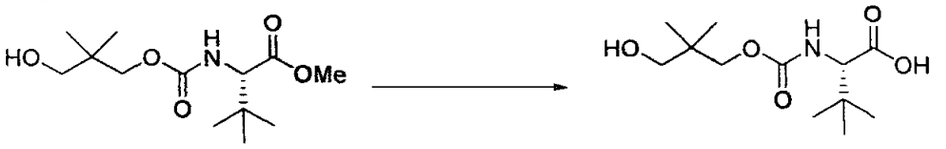
55b

55c-1

55c

A una solución del compuesto **55b** (0,228g, 1,33mmol) y **55c-1** (1,4g, 13,3mmol) en diclorometano (10ml) - DMF (2ml) a temperatura ambiente se agregó DBU (0,3ml, 2,18mmo). La mezcla se agitó a temperatura ambiente durante 16h, se diluyó con EtOAc, se lavó con agua, salmuera dos veces, HCl 1N, salmuera, se secó (sulfato de sodio) y se concentró. El residuo se purificó por cromatografía flash en gel de sílice usando un gradiente de elución (EtOAC/Hexano 0% a 30%) para dar compuesto **55c** (0,303g).

Paso **55D**

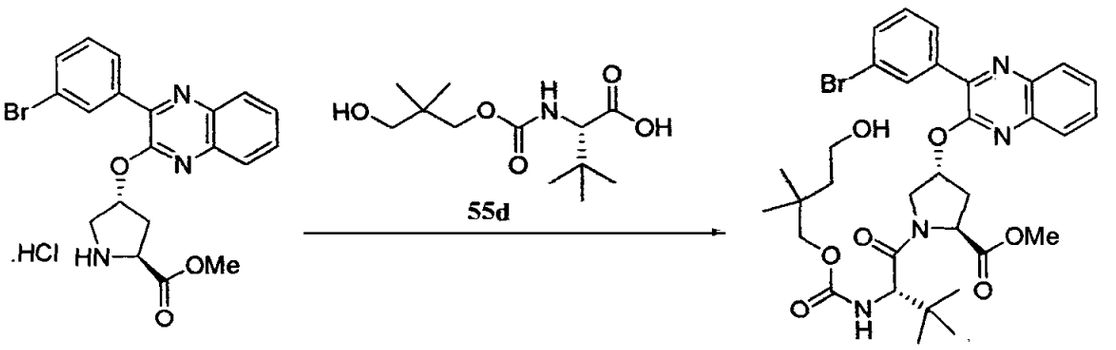


55c

55d

A una solución del compuesto **55c** (0,255g, 0,93mmol) en THF/MeOH (6ml/2,6ml) a 0°C se agregó hidrato de hidróxido de litio (0,195g, 4,6mmol), seguido por agua (2,6ml). La mezcla se agitó a temperatura ambiente durante 16h, se colocó a 0°C, se agregó HCl 1N por goteo hasta que el pH de la mezcla = ~3. La mezcla se extrajo con EtOAc tres veces. Las capas orgánicas combinadas se lavaron con salmuera, se secó (Na_2SO_4), se filtró y se concentró al vacío para dar **55d** (0,227g).

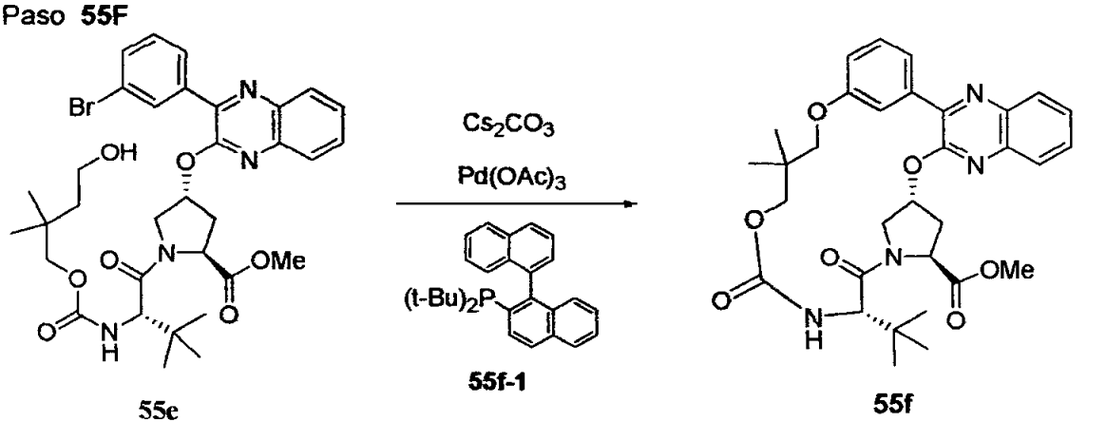
Paso **55E**



55a 55d 55e

A una solución del compuesto **55a** (0,52g, 1,1mmol), **55d** (0,93mmol) y DIPEA (0,81ml, 5eq.) en DMF (8ml) a 0 °C se agregó en porciones HATU (0,407g, 1,07mmol). La mezcla se agitó a temperatura ambiente durante 16h, se diluyó con EtOAc, se lavó con agua una vez, salmuera cuatro veces. La fase orgánica se secó sobre sulfato de sodio anhidro, se filtró, y se concentró al vacío. El residuo se purificó por cromatografía en gel de sílice (EtOAc/Hexano 0% a 40%) para dar **55e** (0,328g). MS(ESI); m/z 671,32, 673,32 (M+H).

Paso **55F**

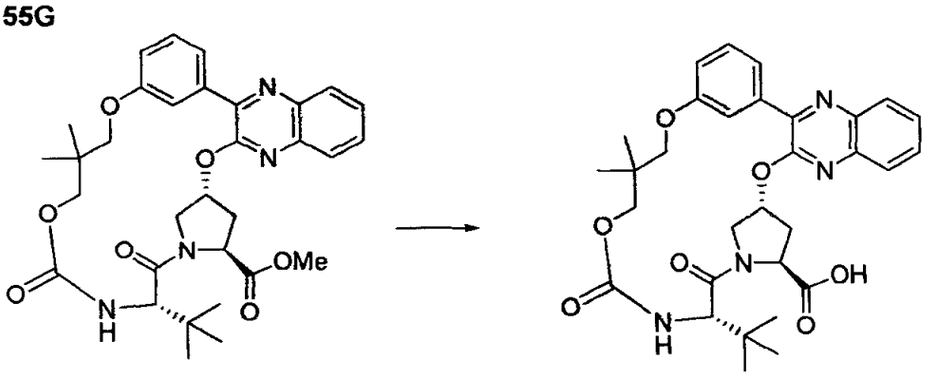


55e 55f-1 55f

una mezcla del compuesto **55e** (0,161g, 0,24mmol), carbonato de cesio (0,156g, 0,48mmol) y tolueno (10ml) se purgó con nitrógeno por 5min. Se agregó acetato de paladio (11mg, 0,049mmol) y ligando **55f-1** (24mg, 0,06mmol). La mezcla se agitó a

80°C durante 19h, se enfrió a temperatura ambiente, se filtró, se lavó con EtOAc y se concentró. El residuo se purificó por cromatografía en gel de sílice (EtOAc/Hexano 0% a 25%) para dar **55f** (0,035g). MS(ESI); m/z 591,61(M+H).

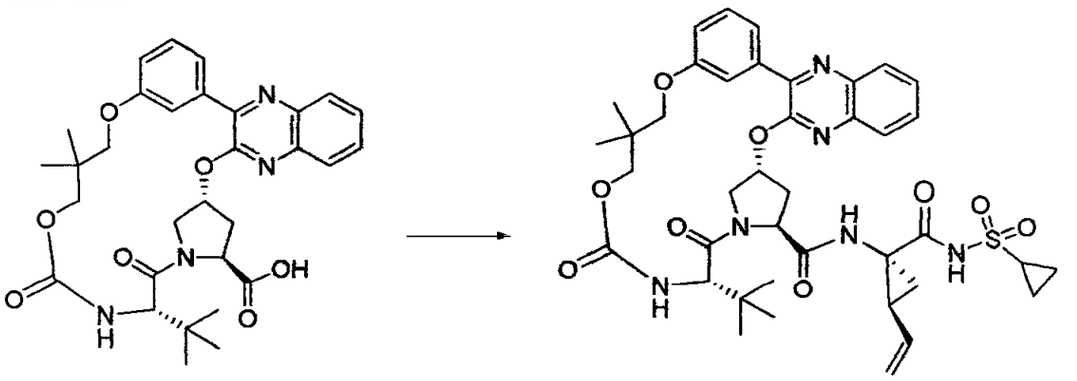
Paso **55G**



55f **55g**

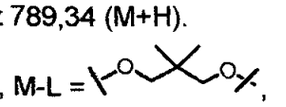
El compuesto **55g** se preparó a partir del compuesto **55f** mediante el mismo procedimiento que se describe en Paso 3F de ejemplo 3. MS(ESI): m/z 577,55 (M+H).

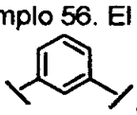
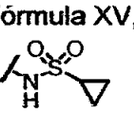
Paso **55H**



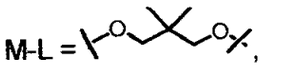
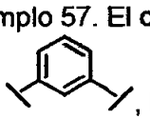
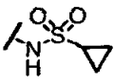
55g **ejemplo 55**

El compuesto de ejemplo 55 se preparó a partir del **55g** mediante los mismos procedimientos que se describen en Ejemplo 3. MS (ESI): m/z 789,34 (M+H).

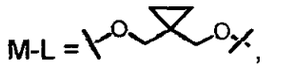
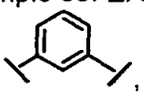
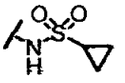
Ejemplo 56. El compuesto de Fórmula XV, en donde R =  , M-L =  ,

Ar=  , R'=  , G = 

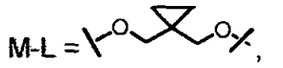
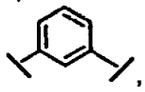
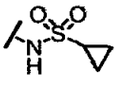
Este compuesto se preparó a partir del **55g** mediante los mismos procedimientos que se describen en Ejemplo 4. MS (ESI): m/z 790,92 (M+H).

Ejemplo 57. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=CF_2H, G = 

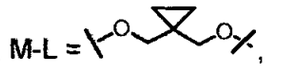
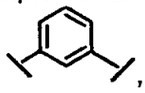
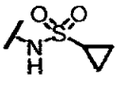
Este compuesto se preparó a partir del **55g** mediante los mismos procedimientos que se describen en Ejemplo 5. MS (ESI): m/z 813,74 (M+H).

Ejemplo 58. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=  , G = 

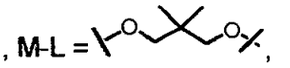
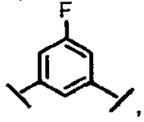
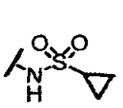
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 55. MS (ESI): m/z 787,20 (M+H).

Ejemplo 59. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=  , G = 

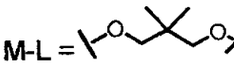
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 56. MS (ESI): m/z 789,22 (M+H).

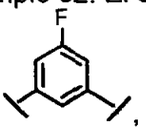
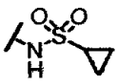
Ejemplo 60. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=CF_2H, G = 

Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 57. MS (ESI): m/z 811,59 (M+H).

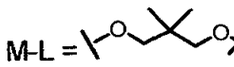
Ejemplo 61. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=  , G = 

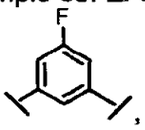
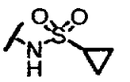
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 55. MS (ESI): m/z 807,17 (M+H).

Ejemplo 62. El compuesto de Fórmula XV, en donde R =  , M-L =  ,

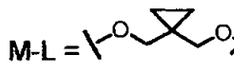
Ar=  , R'=  , G = 

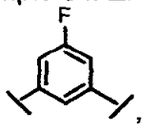
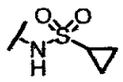
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 56. MS (ESI): m/z 809,10 (M+H).

Ejemplo 63. El compuesto de Fórmula XV, en donde R =  , M-L =  ,

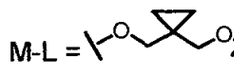
Ar=  , R'=CF_2H, G = 

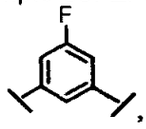
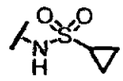
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 57. MS (ESI): m/z 831,24 (M+H).

Ejemplo 64. El compuesto de Fórmula XV, en donde R =  , M-L =  ,

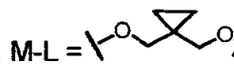
Ar=  , R'=  , G = 

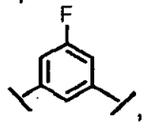
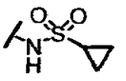
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 55. MS (ESI): m/z 805,14 (M+H).

Ejemplo 65. El compuesto de Fórmula XV, en donde R =  , M-L =  ,

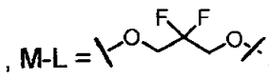
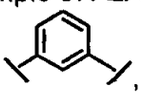
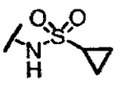
Ar=  , R'=  , G = 

Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 56. MS (ESI): m/z 807,03 (M+H).

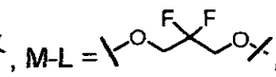
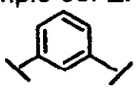
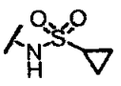
Ejemplo 66. El compuesto de Fórmula XV, en donde R =  , M-L =  ,

Ar=  , R'=CF_2H, G = 

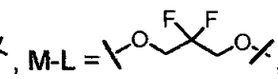
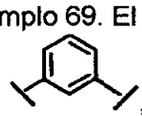
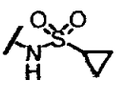
Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 57. MS (ESI): m/z 828,97 (M+H).

Ejemplo 67. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=  , G = 

Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 55. MS (ESI): m/z 797,11 (M+H).

Ejemplo 68. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=  , G = 

Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 56. MS (ESI): m/z 799,06 (M+H).

Ejemplo 69. El compuesto de Fórmula XV, en donde R =  , M-L =  ,
Ar=  , R'=CF_2H, G = 

Este compuesto se preparó mediante los mismos procedimientos que se describen en Ejemplo 57. MS (ESI): m/z 821,54 (M+H).

Los ejemplos 70 a 1506, compuestos de fórmula XV en la tabla 1, se preparan siguiendo los procedimientos que se describen en los ejemplos 1 a 69 y en la sección Métodos de Síntesis.

Los ejemplos 1507 a 1554, compuestos de fórmula XVI en la tabla 2, se preparan siguiendo los procedimientos que se describen en los ejemplos 1 a 69 y en la sección Métodos de Síntesis.

Los ejemplos 1555 a 1586, compuestos de fórmula XVII en la tabla 3, se preparan siguiendo los procedimientos que se describen en los ejemplos 1 a 69 y la sección Métodos de Síntesis.

Los compuestos de la presente invención exhiben potentes actividades inhibitorias contra la proteasa NS3 de VHC. Los siguientes ejemplos describen

ensayos en los que los compuestos de la presente invención se pueden probar para estudiar sus efectos anti-VHC.

Ejemplo 1587. Ensayo de Enzima Proteasa NS3/NS4a

La actividad anti-proteasa e inhibición de VHC se ensaya usando un sustrato fluorogénico que se extingue en forma interna. Un grupo DABCILO y un grupo EDANS están unidos en los extremos opuestos de un péptido corto. Se releva la extinción de la fluorescencia por EDANS por parte del grupo DABCILO ante el clivaje proteolítico. Se mide la fluorescencia con un Molecular Devices Fluoromax (o equivalente) usando una longitud de onda de excitación de 355 nm y una longitud de onda de emisión de 485 nm.

El ensayo se realiza en placas de 96 pocillos de media área blancas Corning (VWR 29444-312 [Corning 3693]) con la proteasa NS3 1b de VHC completa unida con el cofactor NS4A (concentración final de enzima entre 1 y 15 nM). El amortiguador de ensayo se complementa con 10 µM de cofactor NS4A Pep 4A (Anaspec 25336 o casero, PM 1424,8). Se usa RET S1 (Ac-Asp-Glu-Asp(EDANS)-Glu-Glu-Abu-[COO]Ala-Ser-Lys-(DABCIL)-NH_2, AnaSpec 22991, PM 1548,6) como sustrato peptídico fluorogénico. El amortiguador de ensayo contiene Hepes 50 mM a pH 7,5, NaCl 30 mM y BME 10 mM. La reacción enzimática se sigue durante un curso de tiempo de 30 minutos a temperatura ambiente en ausencia y presencia de inhibidores.

Los inhibidores peptídicos VHC *Inh* 1 (Anaspec 25345, PM 796,8) Ac-Asp-Glu-Met-Glu-Glu-Cys-OH, [-20°C] y VHC Inh 2 (Anaspec 25346, PM 913,1) Ac-Asp-Glu-Dif-Cha-Cys-OH, se usan como compuestos de referencia.

Se calculan los valores de IC50 usando XLFit en ActivityBase (IDBS) usando la ecuación 205: y = A + ((B – A)/(1 + ((C/x)^D))).

Ejemplo 1588 - Ensayo de Replicón Hecho en Células

La cuantificación de ARN del replicón VHC (Ensayo basado en células de VHC) se logra usando la línea de células Huh 11-7 (Lohmann, et al. Science 285:110-113, 1999). Las células se siembran a $4x10^3$ células/pocillo en placas de 96 pocillos y se alimentan con un medio que contiene DMEM (alta glucosa), 10% suero de neonato bovino, penicilina-estreptomicina y aminoácidos no esenciales. Las células se incuban en un incubador a 7,5% de CO_2 a 37°C. Al final del período de incubación, se extrae y se purifica el ARN total de las células usando el conjunto de elementos Ambion RNAqueous 96 (No. de Catálogo AM1812). Para amplificar el ARN de VHC de modo que se pueda detectar suficiente material mediante una sonda específica para VHC (ver más adelante), los cebadores específicos para VHC (ver más adelante) median tanto la transcripción inversa del ARN de VHC como la amplificación del ADNc mediante reacción en cadena de la polimerasa (PCR) usando TaqMan One-Paso RT-PCR Master Mix Kit (Applied Biosystems No. de Catálogo 4309169). La secuencia de nucleótidos de los cebadores para RT-PCR, los que se localizan en la región NS5B del genoma de VHC, son como sigue:

Cebador directo para VHC "RBNS5bfor"

5'GCTGCGGCCTGTCGAGCT (SEQ ID NO: 1):

Cebador inverso para VHC "RBNS5Brev"

5'CAAGGTCGTCTCCGCATAC (SEQ ID NO 2).

La detección del producto de la RT-PCR se lleva a cabo usando el Applied Biosystems (ABI) Prism 7500 Sequence Detection System (SDS) que detecta la fluorescencia que se emite cuando la sonda, que está marcada con una marca reportera fluorescente y una marca de extinción, se degrada durante la reacción de PCR. El incremento en la cantidad de fluorescencia se mide durante cada ciclo de PCR y refleja la cantidad de incremento de producto de RT-PCR. Específicamente, la

cuantificación se basa en el ciclo umbral, en donde el gráfico de amplificación cruza un umbral de fluorescencia definido. La comparación de los ciclos umbrales de la muestra con el de un estándar conocido provee una medida altamente sensible de la concentración relativa de molde en las diferentes muestras (ABI User Bulletin #2 Diciembre 11, 1997). Los datos se analizan usando el programa ABI SDS versión 1.7. La concentración relativa de molde se puede convertir a número de copias de ARN por medio del empleo de una curva estándar de estándares de ARN de VHC con número de copias conocido (ABI User Bulletin #2 Diciembre 11, 1997).

El producto de RT-PCR se detectó usando la siguiente sonda marcada:

5' FAM-CGAAGCTCCAGGACTGCACGATGCT-TAMRA (SEQ ID NO: 3)

FAM= Marca reportera de fluorescencia.

TAMRA:= Marca de extinción.

La reacción de RT se lleva a cabo a 48°C durante 30 minutos seguida de PCR. Los parámetros del ciclador térmico que se usaron para la reacción de PCR en el ABI Prism 7500 Sequence Detection System son: un ciclo a 95°C, 10 minutos seguido de 40 ciclos en donde cada uno incluyó una incubación a 95°C durante 15 segundos y una segunda incubación a 60°C durante 1 minuto.

Para normalizar los datos a una molécula de control interno dentro del ARN celular, se lleva a cabo una RT-PCR para el ARN mensajero de gliceraldehído-3-fosfato deshidrogenasa (GAPDH). El número de copias de GAPDH es muy estable en las líneas celulares que se usaron. La RT-PCR para GAPDH se lleva a cabo en la misma muestra de ARN extraída en la que se determina el número de copias de VHC. Los cebadores y sondas de GAPDH se obtienen del conjunto de elementos de ensayos ABI Pre-Developed TaqMan Assay Kit (Nro de Catálogo 4310884E). La

relación de ARN de VHC/GAPDH se usa para calcular la actividad de los compuestos que se evalúan para ver la inhibición de la replicación del ARN de VHC.

Actividad de los compuestos como inhibidores de replicación de VHC (Ensayo hecho en Células) en líneas celulares Huh-7 que contienen replicones.

Se determina el efecto de un compuesto anti-viral específico sobre los niveles de replicones de ARN de VHC en células Huh-11-7 mediante la comparación de la cantidad de ARN de VHC normalizado a GAPDH (por ejemplo la relación VHC/GAPDH) en las células expuestas a un compuesto versus células expuestas al vehículo de DMSO (control negativo). Específicamente, se siembran las células a 4x 10^3 células/pocillo en una placa de 96 pocillos y se incuban con uno de los siguientes: 1) medios que contienen 1% DMSO (control de inhibición 0%), o 2) medios/1%DMSO con una concentración fija del compuesto. Luego se incuban placas de 96 pocillos de la forma descrita y se incuba a 37°C durante 4 días (determinación de EC50). El porcentaje de inhibición se define como:

% de Inhibición= 100-100*S/C1

en donde

S= relación de número de copias de ARN de VHC/ número de copias de ARN de GAPDH en la muestra;

C_1= relación de número de copias de ARN de VHC/ número de copias de ARN de GAPDH en el control de inhibición de 0% (medio/1% de DMSO).

La curva de dosis-respuesta del inhibidor se genera mediante el agregado del compuesto en serie, en diluciones de tres veces sobre tres logs en los pocillos, comenzando con la concentración más alta de un compuesto específico a 1,5 µM y finalizando con la concentración más baja a 0,23 nM. Se realiza una serie de dilución adicional (entre 500 nM y 0,08 nM por ejemplo) si el valor de EC50 no se posiciona

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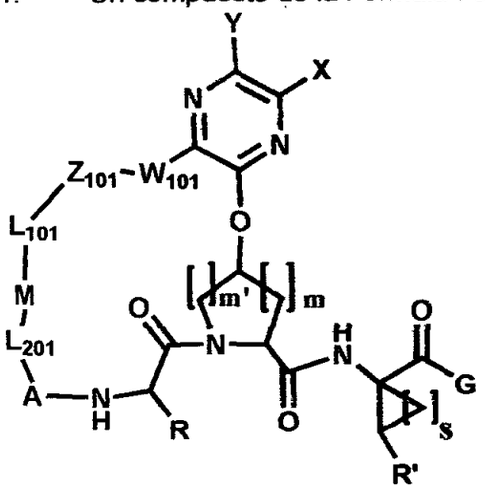
bien sobre la curva. La EC50 se determina con el programa IDBS Activity Base "XL Fit" usando un ajuste de regresión no lineal de 4 parámetros (modelo # 205 en la versión 4.2.1, *build* 16).

En tanto esta invención se ha demostrado y descrito con referencia a las realizaciones preferidas de la misma, los especialistas en el arte comprenderán que es posible efectuar diversos cambios en la forma y en los detalles sin apartarse del alcance de la invención comprendida por las reivindicaciones adjuntas.

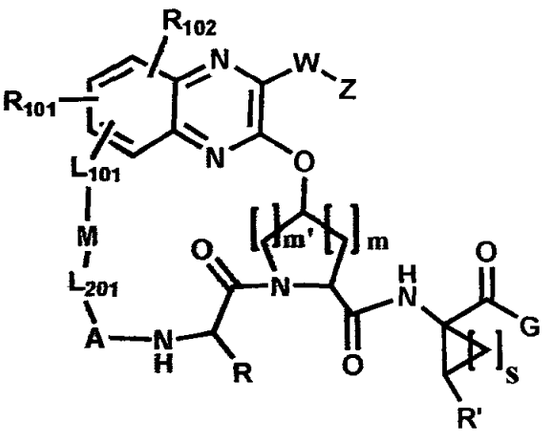
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REIVINDICACIONES:

1. Un compuesto de la Fórmula I o II:



(I)



(II)

en donde

A está ausente o se selecciona entre –(C=O)–, –S(O)$_2$, -C=N-OR$_1$ o –C(=N-CN);

L$_{201}$ está ausente o se selecciona entre -C$_1$-C$_8$ alquileno, –C$_2$-C$_8$ alquenileno, o –C$_2$-C$_8$ alquinileno cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C$_1$-C$_8$ alquileno sustituido, –C$_2$-C$_8$ alquenileno sustituido, o –C$_2$-C$_8$ alquinileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C$_3$-C$_{12}$ cicloalquileno, o–C$_3$-C$_{12}$ cicloalquileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C$_3$-C$_{12}$ cicloalquenileno, o–C$_3$-C$_{12}$ cicloalquenileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N;

M está ausente o se selecciona entre O, S, SO, SO$_2$ o NR$_1$; en donde R$_1$ se selecciona en cada oportunidad entre el grupo formado por:

(i) hidrógeno;

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(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(iii) heterocicloalquilo o heterocicloalquilo sustituido;

(iv) $-C_1$-C_8 alquilo, $-C_2$-C_8 alquenilo, o $-C_2$-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; $-C_1$-C_8 alquilo sustituido, $-C_2$-C_8 alquenilo sustituido, o $-C_2$-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; $-C_3$-C_{12} cicloalquilo, o $-C_3$-C_{12} cicloalquilo sustituido; $-C_3$-C_{12} cicloalquenilo, o $-C_3$-C_{12} cicloalquenilo sustituido;

L_{101} está ausente o se selecciona entre $-C_1$-C_8 alquileno, $-C_2$-C_8 alquenileno, o $-C_2$-C_8 alquinileno cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; $-C_1$-C_8 alquileno sustituido, $-C_2$-C_8 alquenileno sustituido, o $-C_2$-C_8 alquinileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; $-C_3$-C_{12} cicloalquileno, o $-C_3$-C_{12} cicloalquileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; $-C_3$-C_{12} cicloalquenileno, o $-C_3$-C_{12} cicloalquenileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N;

Z_{101} está ausente o se selecciona entre arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

W_{101} está ausente o se selecciona entre $-O-$, $-S-$, $-NR_1-$, $-C(O)-$ o $-C(O)NR_1-$;

X y Y se toman juntos con el átomo de carbono al cual se encuentran unidos para formar una porción carbocíclico o una porción heterocíclico seleccionados entre arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, heterocíclico, o heterocíclico sustituido;

o X y Y juntos forman un grupo C_2- C_8-alquileno o un grupo C_2-C_8-heteroalquileno;

R_{101} y R_{102}se seleccionan en forma independiente entre el grupo formado por:

(i) hidrógeno, halógeno, CN, CF_3, N_3, NO_2, OR_1, SR_1, SO_2R_2, $-NHS(O)_2-R_2$, $-NH(SO_2)NR_3R_4$, NR_3R_4, CO_2R_1, COR_1, $CONR_1R_2$, $N(R_1)COR_2$;

(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(iii) heterocicloalquilo o heterocicloalquilo sustituido;

(iv) $-C_1$-C_8 alquilo, $-C_2$-C_8 alquenilo, o $-C_2$-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; $-C_1$-C_8 alquilo sustituido, $-C_2$-C_8 alquenilo sustituido, o $-C_2$-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; $-C_3$-C_{12} cicloalquilo, o $-C_3$-C_{12} cicloalquilo sustituido; $-C_3$-C_{12} cicloalquenilo, o $-C_3$-C_{12} cicloalquenilo sustituido;

R_yR' se seleccionan en forma independiente entre sí entre el grupo formado por:

(i) $-C_1$-C_8 alquilo, $-C_2$-C_8 alquenilo, o $-C_2$-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; $-C_1$-C_8 alquilo sustituido, $-C_2$-C_8 alquenilo sustituido, o $-C_2$-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; $-C_3$-C_{12} cicloalquilo, o $-C_3$-C_{12} cicloalquilo sustituido; $-C_4$-C_{12} alquilcicloalquilo, o $-C_4$-C_{12} alquilcicloalquilo sustituido; $-C_3$-C_{12} cicloalquenilo, o $-C_3$-C_{12} cicloalquenilo sustituido; $-C_4$-C_{12} alquilcicloalquenilo, o $-C_4$-C_{12} alquilcicloalquenilo sustituido;

(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(iii) heterocicloalquilo o heterocicloalquilo sustituido;

(iv) hidrógeno; deuterio;

G se selecciona entre –OH, $-NHS(O)_2-R_2$, $-NH(SO_2)NR_3R_4$, y NR_3R_4;

R_2 se selecciona entre :

(i) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido

(ii) heterocicloalquilo; heterocicloalquilo sustituido;

(iii) $-C_1$-C_8 alquilo, $-C_2$-C_8 alquenilo, o $-C_2$-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N, $-C_1$-C_8 alquilo sustituido, $-C_2$-C_8 alquenilo sustituido, o $-C_2$-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; $-C_3$-C_{12} cicloalquilo, o $-C_3$-C_{12} cicloalquilo sustituido; $-C_3$-C_{12} cicloalquenilo, o $-C_3$-C_{12} cicloalquenilo sustituido; heterocíclico; heterocíclico sustituido;

R_3 y R_4 se seleccionan en forma independiente entre:

(i) hidrógeno;

(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(iii) heterocicloalquilo o heterocicloalquilo sustituido;

(iv) $-C_1$-C_8 alquilo, $-C_2$-C_8 alquenilo, o $-C_2$-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; $-C_1$-C_8 alquilo sustituido, $-C_2$-C_8 alquenilo sustituido, o $-C_2$-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; $-C_3$-C_{12} cicloalquilo, o $-C_3$-C_{12} cicloalquilo sustituido; $-C_3$-C_{12} cicloalquenilo, o $-C_3$-C_{12} cicloalquenilo sustituido; heterocíclico, o heterocíclico sustituido;

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como alternativa, R_3 y R_4 se toman juntos con el nitrógeno al cual se encuentran unidos para formar a heterocíclico o heterocíclico sustituido;

Z se selecciona entre los grupos que consisten en:

(i) hidrógeno;

(ii) CN;

(iii) N_3;

(iv) halógeno;

(v) $-NH-N=CHR_1$;

(vi) arilo, arilo sustituido;

(vii) heteroarilo, heteroarilo sustituido;

(viii) $-C_3-C_{12}$ cicloalquilo, $-C_3-C_{12}$ cicloalquilo sustituido, heterocicloalquilo, heterocicloalquilo sustituido;

(ix) $-C_1-C_6$ alquilo con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N, opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

(x) $-C_2-C_6$ alquenilo con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N, opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

(xi) $-C_2-C_6$ alquinilo con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N, opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

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W se encuentra ausente, o se selecciona entre alquileno, alquenileno, alquinileno, –O–, –S–, –NR_1-, -C(O)NR_1-, o -C(O)-;

m es 0, 1, 2 o 3;

m' es 0, 1, 2 o 3; y

s es 1, 2, 3 o 4.

2. Un compuesto de acuerdo con la reivindicación 1 en donde:

M está ausente o se selecciona entre O o NR_1;

Z_{101} es arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

W_{101} está ausente, o se selecciona entre –O–, –S–, –NH-, -N(Me)-, -C(O)NH-, o -C(O)N(Me)-;

X y Y se toman junto con los átomos de carbono a los cuales están unidos para formar una unidad cíclica que se selecciona entre arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo, o heterociclo sustituido;

R_{101} y R_{102} se seleccionan de forma independiente del grupo formado por:

(i) hidrógeno, halógeno, CN, CF_3, NO_2, OR_1, SR_1, –$NHS(O)_2$–R_2, -$NH(SO_2)NR_3R_4$, NR_3R_4, CO_2R_1, COR_1, $CONR_1R_2$, $N(R_1)COR_2$;

(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(iii) heterocicloalquilo o heterocicloalquilo sustituido;

(iv) –C_1-C_8 alquilo, –C_2-C_8 alquenilo, o –C_2-C_8 alquinilo cada uno conteniendo 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C_1-C_8 alquilo sustituido, –C_2-C_8 alquenilo sustituido, o –C_2-C_8 alquinilo sustituido cada uno conteniendo 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquilo, o –C_3-C_{12} cicloalquilo sustituido; –C_3-C_{12} cicloalquenilo, o –C_3-C_{12} cicloalquenilo sustituido;

R_3 y R_4 se seleccionan en forma independiente entre:

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(i) hidrógeno;

(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(iii) heterocicloalquilo o heterocicloalquilo sustituido;

(iv) $-C_1$-C_8 alquilo, $-C_2$-C_8 alquenilo, o $-C_2$-C_8 alquinilo cada uno conteniendo 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; $-C_1$-C_8 alquilo sustituido, $-C_2$-C_8 alquenilo sustituido, o $-C_2$-C_8 alquinilo sustituido cada uno conteniendo 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; $-C_3$-C_{12} cicloalquilo, o $-C_3$-C_{12} cicloalquilo sustituido; $-C_3$-C_{12} cicloalquenilo, o $-C_3$-C_{12} cicloalquenilo sustituido; heterociclo, o heterociclo sustituido;

W está ausente, o se selecciona entre alquileno, alquenileno, alquinileno, –O–, –S–, –NH-, -N(Me)-, -C(O)NH-, o -C(O)N(Me)-;

m = 0, 1, o 2;

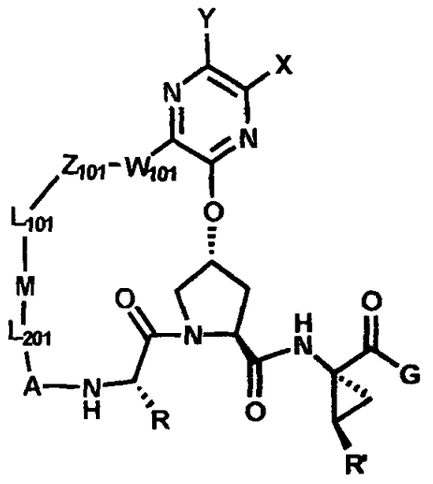
m' = 1 o 2; y

s es 1.

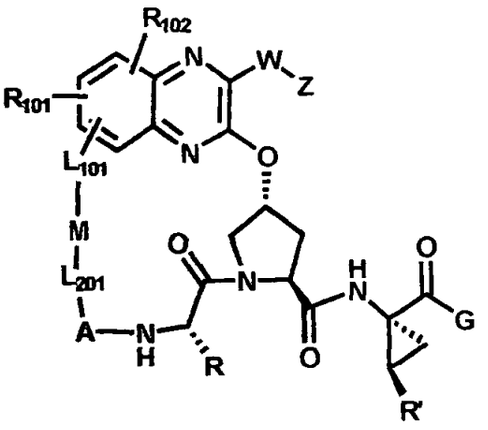
2. El compuesto de la reivindicación 1, donde R' es $-CHQ_1Q_2$, en donde Q_1 y Q_2 se seleccionan en forma independiente entre F, Cl y Br.

3. El compuesto de la reivindicación 1, de la Fórmula III o IV:

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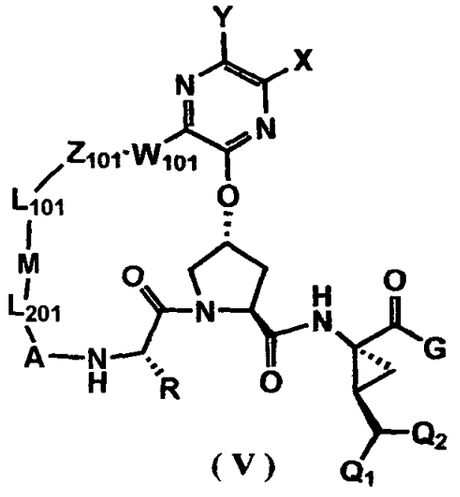
(III)



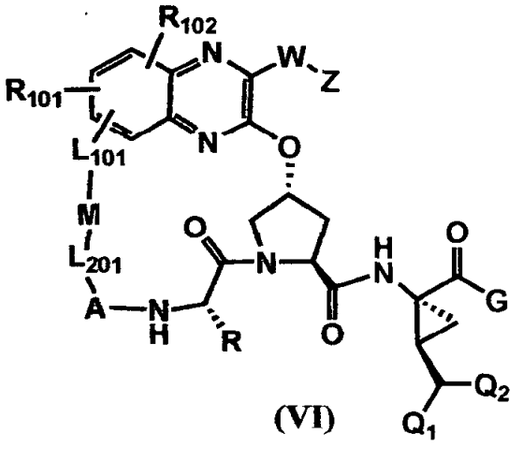
(IV)

o una sal farmacéuticamente aceptable, éster o prodroga del mismo, donde R, R', A, L_{201}, M, L_{101}, Z_{101}, W_{101}, X, Y, R_{101}, R_{102}, W, Z y G son como se define precedentemente en la reivindicación 1.

4. El compuesto de la reivindicación 1, de la Fórmula V o VI:



(V)



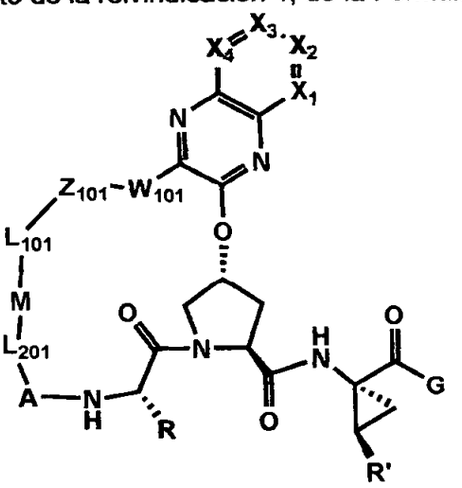
(VI)

o una sal farmacéuticamente aceptable, éster o prodroga del mismo, en donde Q_1 y Q_2 se seleccionan en forma independiente entre sí entre F, Cl y Br, y R, A, L_{201},

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M, L_{101}, Z_{101}, W_{101}, X, Y, R_{101}, R_{102}, W, Z y G son como se define precedentemente en la reivindicación 1.

5. El compuesto de la reivindicación 1, de la Fórmula VII:



(VII)

o una sal farmacéuticamente aceptable, éster o prodroga del mismo, donde X_1-X_4se seleccionan en forma independiente entre -CR_5 y N, en donde:

R_5 se selecciona en forma independiente entre:

(i) hidrógeno; halógeno; -NO_2; -CN; N_3; CF_3;

(ii) –M-R_4, M es O, S, NH;

(iii) NR_3R_4;

(iv) –C_1-C_8 alquilo, –C_2-C_8 alquenilo, o –C_2-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C_1-C_8 alquilo sustituido, –C_2-C_8 alquenilo sustituido, o –C_2-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquilo, o –C_3-C_{12} cicloalquilo sustituido; –C_3-C_{12} cicloalquenilo, o –C_3-C_{12} cicloalquenilo sustituido;

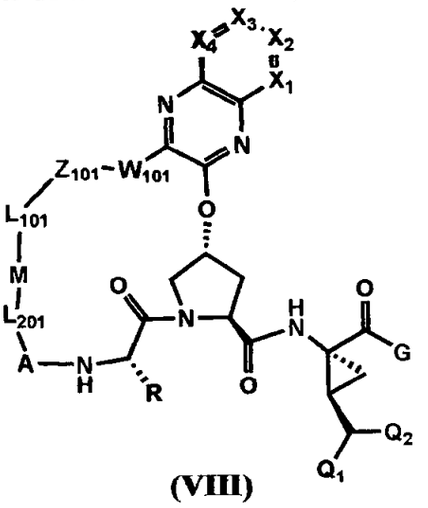
(v) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(vi) heterocicloalquilo o heterocicloalquilo sustituido; y

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R_3, R_4, R, R', A, L_{201}, M, L_{101}, Z_{101}, W_{101} y G son como se define precedentemente en la reivindicación 1.

6. El compuesto de la reivindicación 1, de la Fórmula VIII:



(VIII)

o una sal farmacéuticamente aceptable, éster o prodroga del mismo, donde X_1-X_4se seleccionan en forma independiente entre -CR_5 y N, en donde:

R_5 se selecciona en forma independiente entre:

(i) hidrógeno; halógeno; -NO_2; -CN; N_3; CF_3;

(ii) –M-R_4, M es O, S, NH;

(iii) NR_3R_4;

(iv) –C_1-C_8 alquilo, –C_2-C_8 alquenilo, o –C_2-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C_1-C_8 alquilo sustituido, –C_2-C_8 alquenilo sustituido, o –C_2-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquilo, o –C_3-C_{12} cicloalquilo sustituido; –C_3-C_{12} cicloalquenilo, o –C_3-C_{12} cicloalquenilo sustituido;

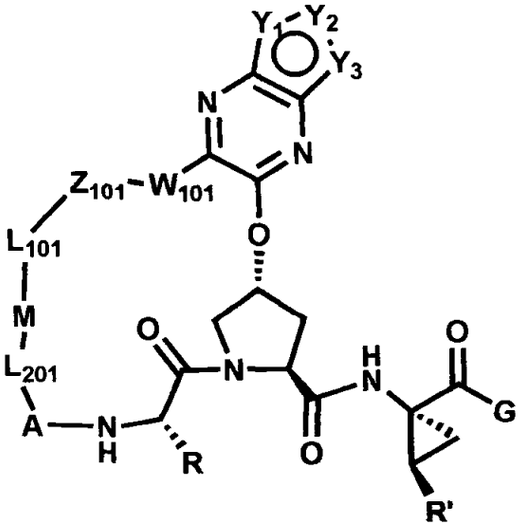
(v) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(vi) heterocicloalquilo o heterocicloalquilo sustituido;

Q_1 y Q_2 se seleccionan en forma independiente entre sí entre F, Cl y Br; y

R_3, R_4, R, A, L_{201}, M, L_{101}, Z_{101}, W_{101} y G son como se define precedentemente en la reivindicación 1.

7. El compuesto de la reivindicación 1, de la Fórmula IX:



(IX)

o una sal farmacéuticamente aceptable, éster o prodroga del mismo, en donde:

Y_1-Y_3se seleccionan en forma independiente entre CR_5, N, NR_5, S y O;

R_5 se selecciona en forma independiente entre:

(i) hidrógeno; halógeno; -NO_2; -CN; N_3; CF_3;

(ii) –M-R_4, M es O, S, NH;

(iii) NR_3R_4;

(iv) –C_1-C_8 alquilo, –C_2-C_8 alquenilo, o –C_2-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C_1-C_8 alquilo sustituido, –C_2-C_8 alquenilo sustituido, o –C_2-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquilo, o –C_3-C_{12} cicloalquilo sustituido; –C_3-C_{12} cicloalquenilo, o –C_3-C_{12} cicloalquenilo sustituido;

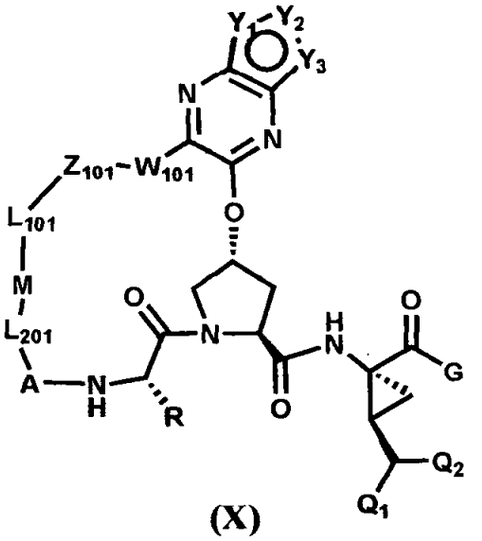
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(v) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(vi) heterocicloalquilo o heterocicloalquilo sustituido; y

R_3, R_4, R, R', A, L_{201}, M, L_{101}, Z_{101}, W_{101} y G son como se define precedentemente en la reivindicación 1.

8. El compuesto de la reivindicación 1, de la Fórmula X:



(X)

o una sal farmacéuticamente aceptable, éster o prodroga del mismo, en donde:

Y_1, Y_2 y Y_3 se seleccionan en forma independiente entre CR_5, N, NR_5, S y O;

R_5 se selecciona en forma independiente entre:

(i) hidrógeno; halógeno; $-NO_2$; -CN; N_3; CF_3;

(ii) $-M-R_4$, M es O, S, NH;

(iii) NR_3R_4;

(iv) $-C_1$-C_8 alquilo, $-C_2$-C_8 alquenilo, o $-C_2$-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; $-C_1$-C_8 alquilo sustituido, $-C_2$-C_8 alquenilo sustituido, o $-C_2$-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o

N; $-C_3$-C_{12} cicloalquilo, o $-C_3$-C_{12} cicloalquilo sustituido; $-C_3$-C_{12} cicloalquenilo, o $-C_3$-C_{12} cicloalquenilo sustituido;

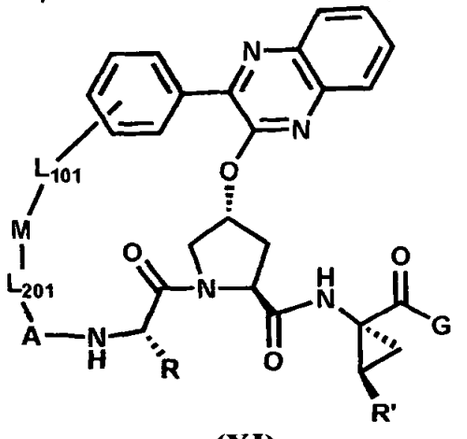
(v) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;

(vi) heterocicloalquilo o heterocicloalquilo sustituido;

Q_1 y Q_2 son en forma independiente entre sí flúor, cloro o bromo; y

R_3, R_4, R, A, L_{201}, M, L_{101}, Z_{101}, W_{101} y G son como se define precedentemente en la reivindicación 1.

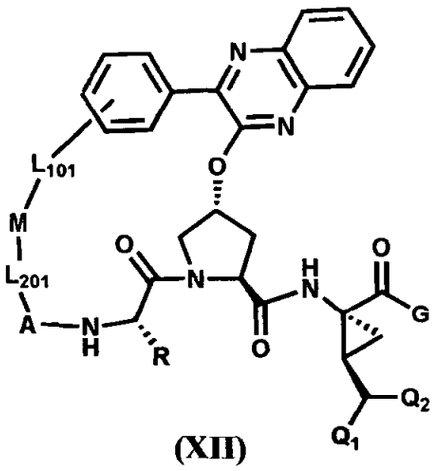
9. El compuesto de la reivindicación 1, de la Fórmula XI:



(XI)

o una sal farmacéuticamente aceptable, éster o prodroga del mismo, donde R, R', A, L_{201}, M, L_{101} y G son como se define precedentemente en la reivindicación 1.

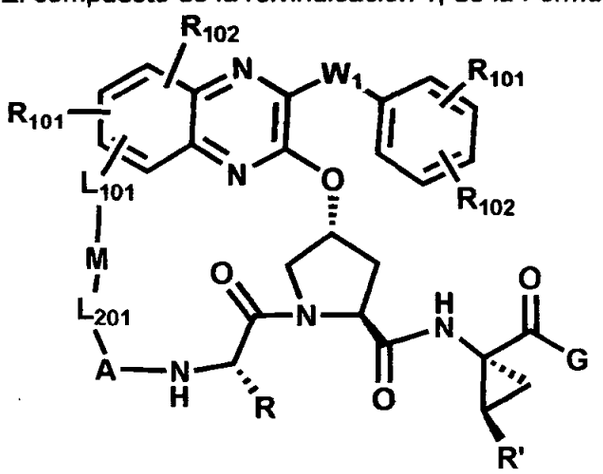
10. El compuesto de la reivindicación 1, de la Fórmula XII:



(XII)

o una sal farmacéuticamente aceptable, éster o prodroga del mismo, donde Q_1 y Q_2 son en forma independiente flúor, cloro o bromo y R, A, L_{201}, M, L_{101} y G son como se define precedentemente en la reivindicación 1.

11. El compuesto de la reivindicación 1, de la Fórmula XIII:

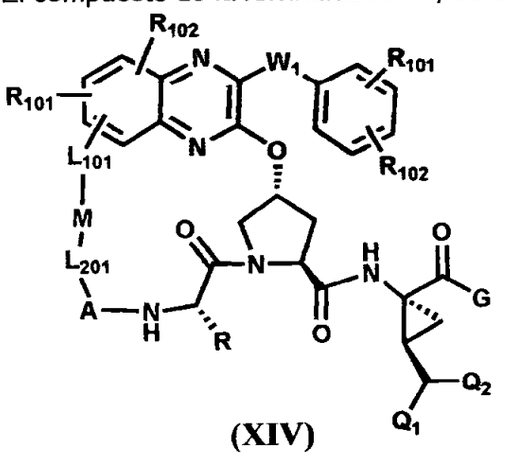


(XIII)

o una sal farmacéuticamente aceptable, éster o prodroga del mismo, en donde W_1 está ausente o se selecciona entre C_1-C_4 alquileno, C_2-C_4 alquenileno, y C_2-C_4 alquinileno; y

R, R', A, L_{201}, M, L_{101} , R_{101}, R_{102} y G son como se define precedentemente en la reivindicación 1.

12. El compuesto de la reivindicación 1, de la Fórmula XIV:



(XIV)

o una sal farmacéuticamente aceptable, éster o prodroga del mismo, en donde

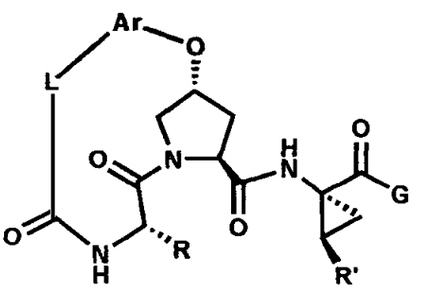
W_1 está ausente o se selecciona entre C_1-C_4 alquileno, C_2-C_4 alquenileno, y C_2-C_4 alquinileno;

Q_1 y Q_2 son en forma independiente flúor, cloro o bromo; y

R, A, L_{201}, M, L_{101}, R_{101}, R_{102} y G son como se define precedentemente en la reivindicación 1.

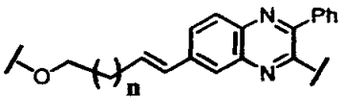
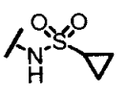
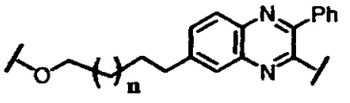
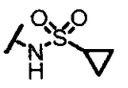
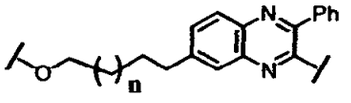
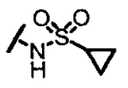
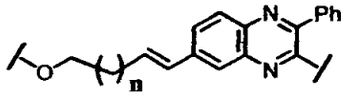
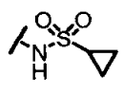
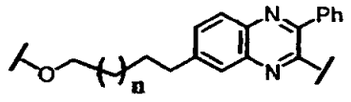
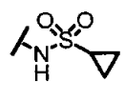
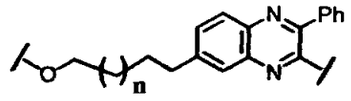
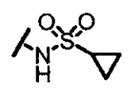
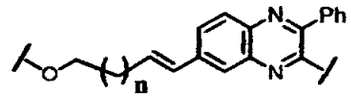
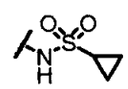
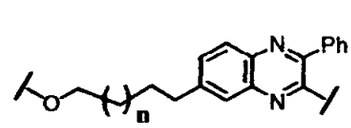
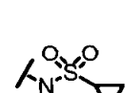
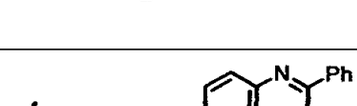
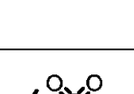
13. Un compuesto de acuerdo a la reivindicación 1 que es como se establece en la tabla 1 de la presente solicitud.

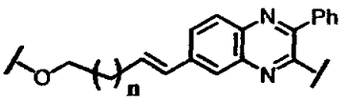
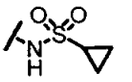
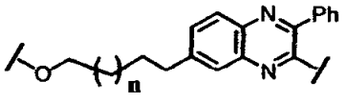
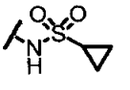
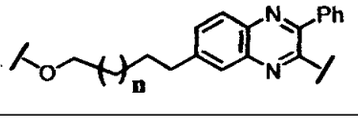
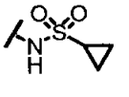
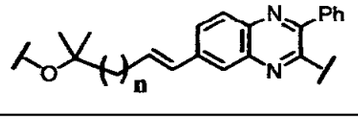
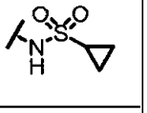
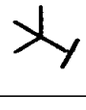
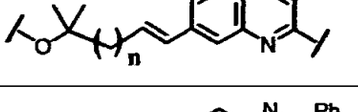
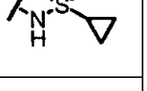
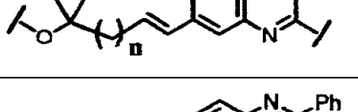
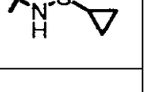
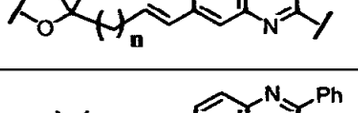
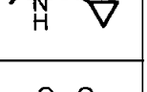
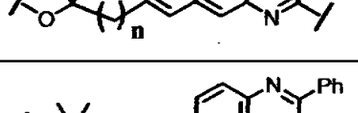
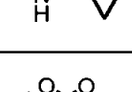
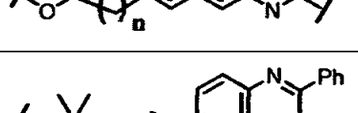
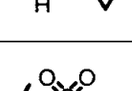
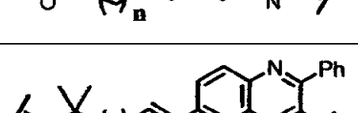
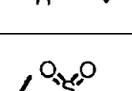
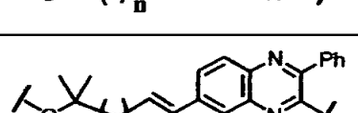
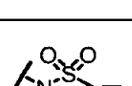
14. Un compuesto de acuerdo a la reivindicación 1 que se selecciona entre los compuestos de fórmula XVI en donde R, L-Ar, R' y G se indican para cada ejemplo en la tabla 2:

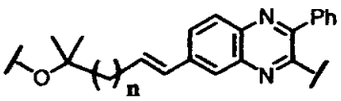
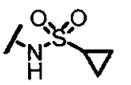
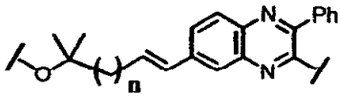
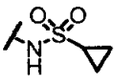
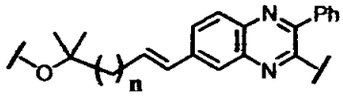
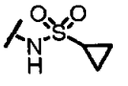
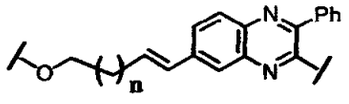
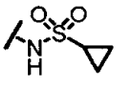
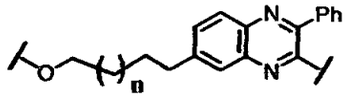
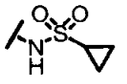
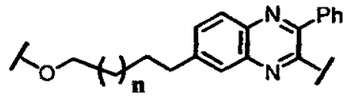
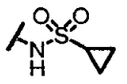
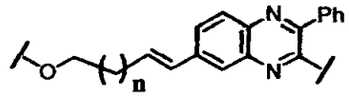
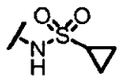
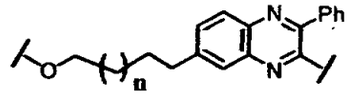
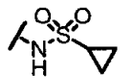
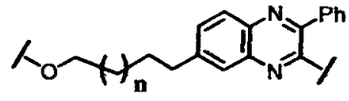
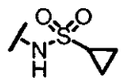
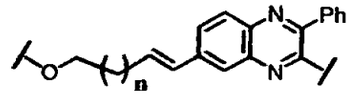
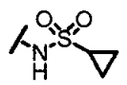
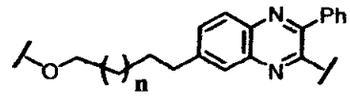
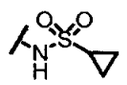
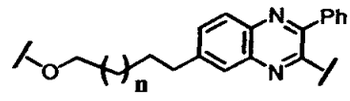
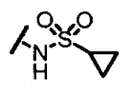


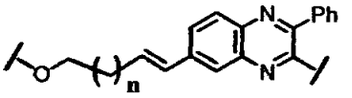
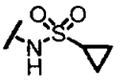
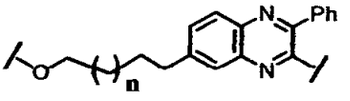
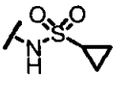
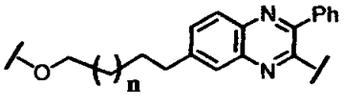
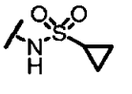
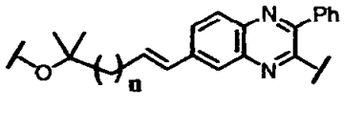
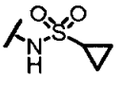
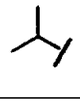
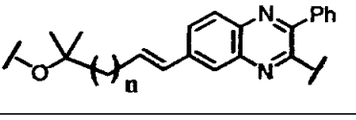
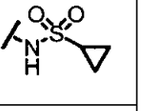
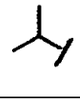
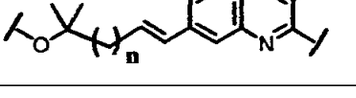
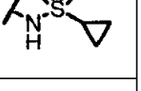
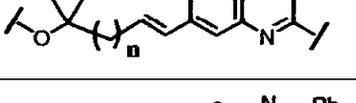
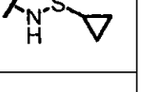
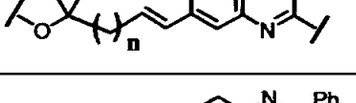
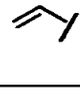
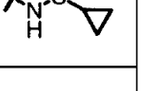
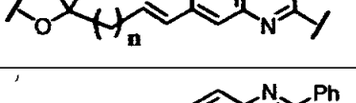
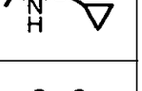
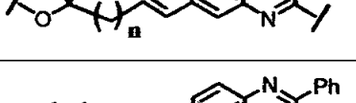
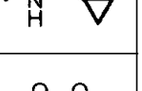
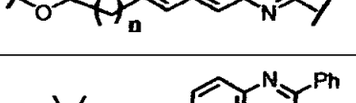
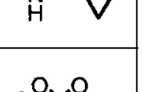
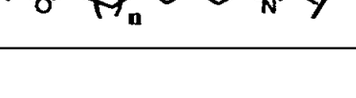
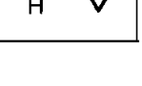
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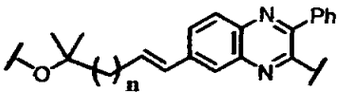
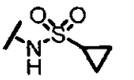
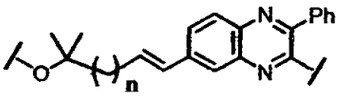
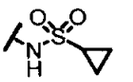
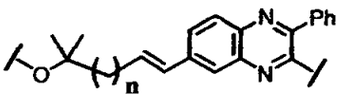
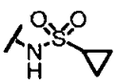
TABLA 2

Ejemplo #	R	L-Ar	n	R'	G
1507.			4		
1508.			4		
1509.			4		
1510.			3		
1511.			3		
1512.			3		
1513.			2		
1514.			2		
1515.			2		

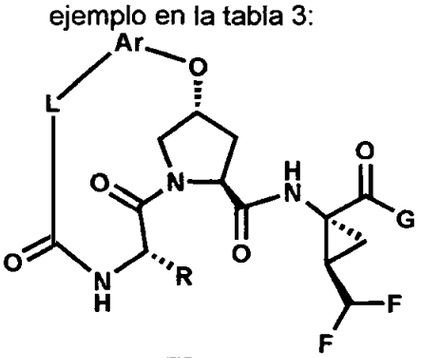
1516.			1		
1517.			1		
1518.			1		
1519.			4		
1520.			4		
1521.			4		
1522.			3		
1523.			3		
1524.			3		
1525.			2		
1526.			2		
1527.			2		

1528.			1		
1529.			1		
1530.			1		
1531.			4		
1532.			4		
1533.			4		
1534.			3		
1535.			3		
1536.			3		
1537.			2		
1538.			2		
1539.			2		

1540.			1		
1541.			1		
1542.			1		
1543.			4		
1544.			4		
1545.			4		
1546.			3		
1547.			3		
1548.			3		
1549.			2		
1550.			2		
1551.			2		

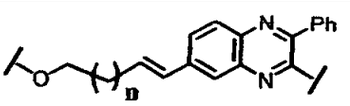
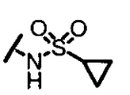
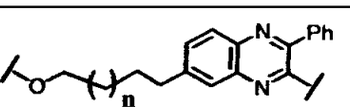
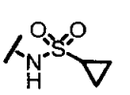
1552.			1		
1553.			1		
1554.			1		

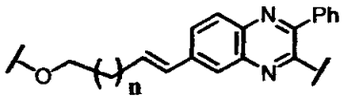
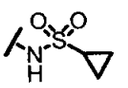
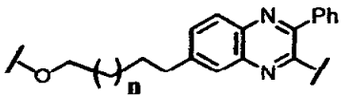
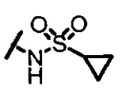
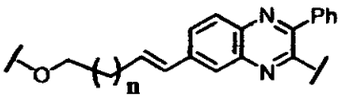
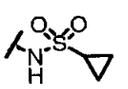
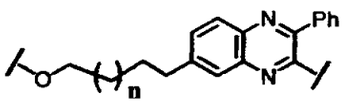
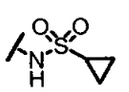
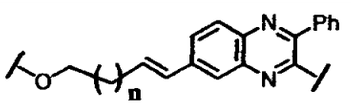
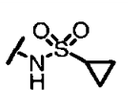
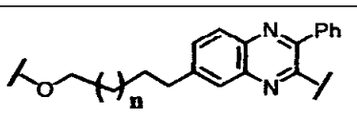
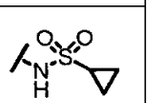
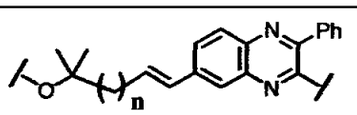
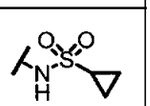
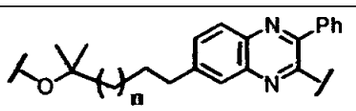
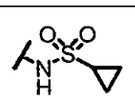
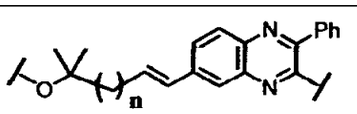
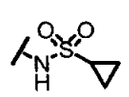
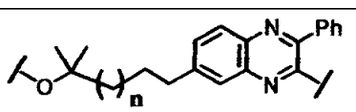
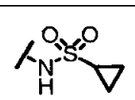
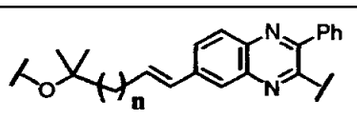
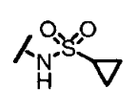
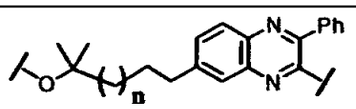
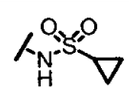
15. Un compuesto de acuerdo a la reivindicación 1, que se selecciona entre los compuestos de fórmula XVII en donde R, L-Ar, y G se indican para cada ejemplo en la tabla 3:



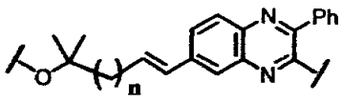
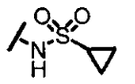
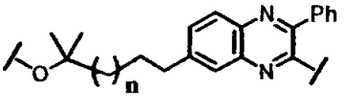
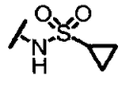
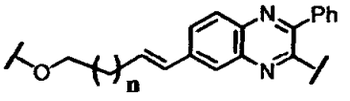
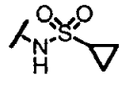
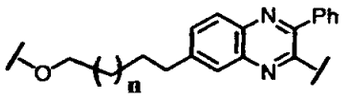
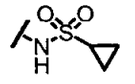
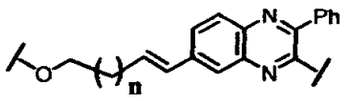
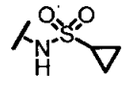
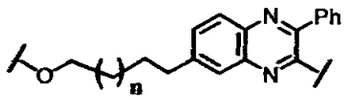
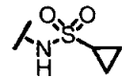
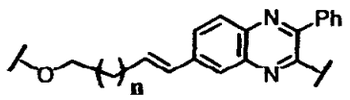
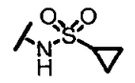
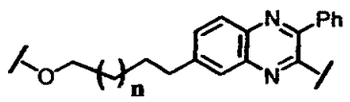
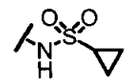
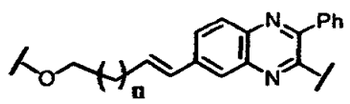
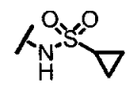
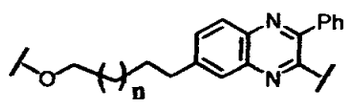
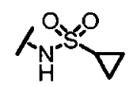
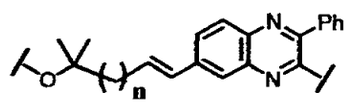
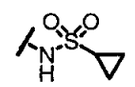
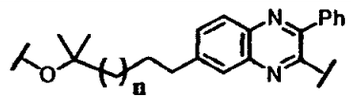
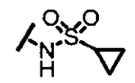
(XVII)

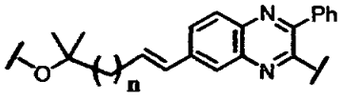
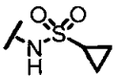
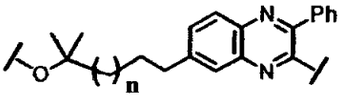
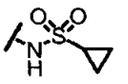
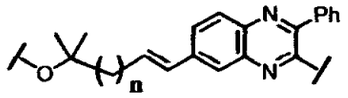
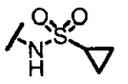
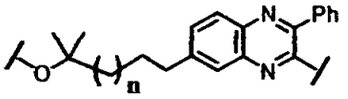
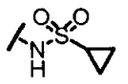
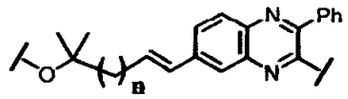
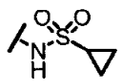
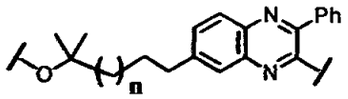
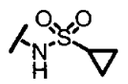
TABLA 3

Ejemplo#	R	L-Ar	n	G
1555.			4	
1556.			4	

1557.			3	
1558.			3	
1559.			2	
1560.			2	
1561.			1	
1562.			1	
1563.			4	
1564.			4	
1565.			3	
1566.			3	
1567.			2	
1568.			2	

000518

1569.			1	
1570.			1	
1571.			4	
1572.			4	
1573.			3	
1574.			3	
1575.			2	
1576.			2	
1577.			1	
1578.			1	
1579.			4	
1580.			4	

1581.			3	
1582.			3	
1583.			2	
1584.			2	
1585.			1	
1586.			1	

16. Una composición farmacéutica que comprende una cantidad inhibitoria de un compuesto de acuerdo a la reivindicación 1 o una sal, éster o prodroga del mismo farmacéuticamente aceptable, en combinación con un vehículo o excipiente farmacéuticamente aceptable.

17. Un método para tratar una infección viral en un sujeto, que comprende administrar al sujeto una cantidad inhibitoria de una composición farmacéutica de acuerdo a la reivindicación 17.

18. El método de acuerdo a la reivindicación 18, donde la infección viral es por virus de la hepatitis C.

19. Un método para inhibir la replicación de virus de la hepatitis C, que comprende proveer una cantidad inhibitoria de proteasa NS3 de virus de la hepatitis C de la composición farmacéutica de la reivindicación 17.

20. El método de la reivindicación 18 que además comprende administrar en forma concurrente un agente adicional anti-virus de la hepatitis C.

21. El método de la reivindicación 19 donde dicho agente adicional anti-virus de la hepatitis C se selecciona del grupo formado por α-interferón, β-interferón, ribavarina y adamantina.

22. El método de la reivindicación 20, donde dicho agente adicional anti-virus de la hepatitis C es un inhibidor de helicasa, polimerasa, metaloproteasa, o IRES del virus de la hepatitis C.

23. La composición farmacéutica de la reivindicación 17, que además comprende otro agente anti-VHC.

24. La composición farmacéutica de la reivindicación 17, que además comprende un agente que se selecciona entre interferón, ribavirina, amantadina, otro inhibidor de proteasa de VHC, un inhibidor de polimerasa de VHC, un inhibidor de helicasa de VHC, o un inhibidor de sitio interno de entrada a ribosoma.

25. La composición farmacéutica de la reivindicación 17, que además comprende interferón tratado con PEG.

26. La composición farmacéutica de la reivindicación 17, que además comprende otros agentes anti-viral, anti-bacteriano, anti-fúngico o anti-cancerígeno, o un modulador de la inmunidad.

27. La composición de la reivindicación 17, que además comprende un inhibidor de citocromo P450 monooxigenasa o una sal del mismo farmacéuticamente aceptable.

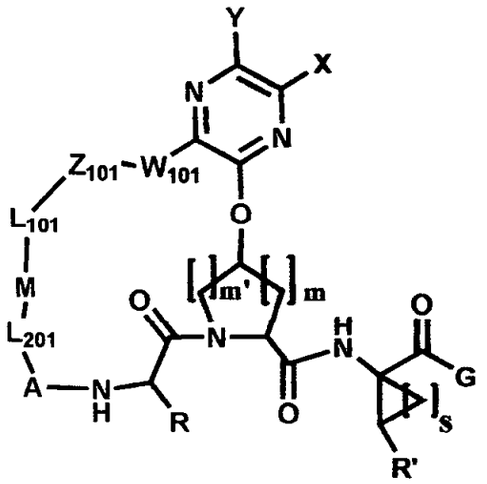
28. La composición de la reivindicación 28, donde el inhibidor de citocromo P450 monoxigenasa es ritonavir.

29. Un método para coadministrar a un paciente con necesidad por un tratamiento anti-virus de la hepatitis C, que comprende un inhibidor de citocromo P450 monooxigenasa o una sal del mismo farmacéuticamente aceptable y un compuesto como se establece en la reivindicación 1 o una sal del mismo farmacéuticamente aceptable.

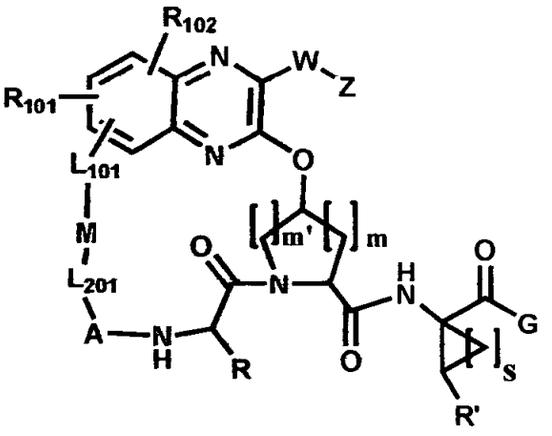
COMPUESTOS QUE CONTIENEN QUINOXALINA COMO INHIBIDORES DEL VIRUS DE LA HEPATITIS C

Resumen

Compuestos de fórmula I y II o sales, ésteres, o prodrogas farmacéuticamente aceptables de los mismos



(I)



(II)

que inhiben la actividad serina proteasa, en particular la actividad proteasa NS3-NS4A del virus de la hepatitis C (VHC). En consecuencia, los compuestos de la presente invención interfieren con el ciclo de vida del virus de la hepatitis C y también son útiles como agentes antivirales. La presente invención se relaciona además con composiciones farmacéuticas que comprenden los compuestos antes mencionados para administrar a un sujeto que sufre de infección por VHC. La invención también se relaciona con métodos para tratar una infección por VHC en un sujeto mediante la administración de una composición farmacéutica que comprende los compuestos de la presente invención.

LISTADO DE SECUENCIAS

<110> ENANTA PHARMACEUTICALS, INC.
YONGHUA, Gia
OR, Yat Sun
WANG, Zhe

<120> COMPUESTOS QUE CONTIENEN QUINOXALINA COMO INHIBIDORES DEL VIRUS DE LA HEPATITIS C

<130> 4056.4146 WO

<140> PCT/US2008/083541
<141> 2008-11-14

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<151> 2008-02-01

<150> US 60/987,958
<151> 2007-11-14

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1 5

Industria y Comercio
SUPERINTENDENCIA

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

000526

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

(21) Nº de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s) **ENANTA PHARMACEUTICALS, INC.**

(72) Inventor(es) **YONGHUA GAI, YAT SUN OR, ZHE WANG**

(74) Apoderado: **DRA. MARGARITA CASTELLANOS ABONDANO**

(30) Prioridad	(31) No. Prioridad	32) Fecha	(33) País
	60/987.958	**14/11/2007**	**US**
	61/025.458	**01/02/2008**	**US**

(85) Fecha inicio fase nacional:
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: **14/11/2008**
No. de solicitud **PCT/US2008/083541**

(87) Publicación internacional
Fecha: **22/05/2009**
Nº publicación: **WO 2009/064975 A1**

(54) Titulo: **COMPUESTOS QUE CONTIENEN QUINOXALINA COMO INHIBIDORES DEL VIRUS DE LA HEPATITIS C**

Industria y Comercio
SUPERINTENDENCIA

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

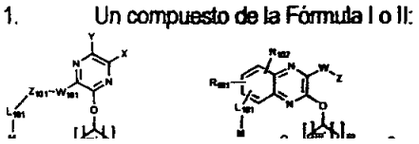
000527

(21) N° de solicitud:	(51) Int. Cl.:
22) Fecha de solicitud:	(71)Solicitante(s) **ENANTA PHARMACEUTICALS, INC.**
(30) Prioridad (31) N° Prioridad 32) Fecha (33) País **60/987.958 14/11/2007 US** **61/025.458 01/02/2008 US**	(72) Inventor(es) **YONGHUA GAI** **YAT SUN OR** **ZHE WANG**
	(74) Apoderado: **MARGARITA CASTELLANOS ABONDANO**
(85) Fecha limite inicio fase nacional: (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: **14/11/2008** N° de solicitud **PCT/US2008/083541**	(87) Publicación internacional Fecha: **22/05/2009** N° publicación: **WO 2009/064975 A1**

(54) Titulo: **COMPUESTOS QUE CONTIENEN QUINOXALINA COMO INHIBIDORES DEL VIRUS DE LA HEPATITIS C**

Reivindicación(es):

1. Un compuesto de la Fórmula I o II:



A está ausente o se selecciona entre –(C=O)–, –$S(O)_2$, -C=N-OR_1 o –C(=N-CN);
L_{201} está ausente o se selecciona entre -C_1-C_8 alquileno, –C_2-C_8 alquenileno, o –C_2-C_8 alquinileno cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C_1-C_8 alquileno sustituido, –C_2-C_8 alquenileno sustituido, o –C_2-C_8 alquinileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquileno, o–C_3-C_{12} cicloalquileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquenileno, o–C_3-C_{12} cicloalquenileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N;
M está ausente o se selecciona entre O, S, SO, SO_2 o NR_1; en donde R_1 se selecciona en cada oportunidad entre el grupo formado por:
(i) hidrógeno;
(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;
(iii) heterocicloalquilo o heterocicloalquilo sustituido;
(iv) –C_1-C_8 alquilo, –C_2-C_8 alquenilo, o –C_2-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C_1-C_8 alquilo sustituido, –C_2-C_8 alquenilo sustituido, o –C_2-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquilo, o –C_3-C_{12} cicloalquilo sustituido; –C_3-C_{12} cicloalquenilo, o –C_3-C_{12} cicloalquenilo sustituido;
L_{101} está ausente o se selecciona entre -C_1-C_8 alquileno, –C_2-C_8 alquenileno, o –C_2-C_8 alquinileno cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C_1-C_8 alquileno sustituido, –C_2-C_8 alquenileno sustituido, o –C_2-C_8 alquinileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquileno, o–C_3-C_{12} cicloalquileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquenileno, o–C_3-C_{12} cicloalquenileno sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N;
Z_{101} está ausente o se selecciona entre arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;
W_{101} está ausente o se selecciona entre –O– –S– –NR_1– –

heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, heterocíclico, o heterocíclico sustituido;
o X y Y juntos forman un grupo C_2- C_8-alquileno o un grupo C_2-C_8-heteroalquileno;
R_{101} y R_{102}se seleccionan en forma independiente entre el grupo formado por:
(i) hidrógeno, halógeno, CN, CF_3, N_3, NO_2, OR_1, SR_1, SO_2R_2, –NHS(O)$_2$–R_2, -NH(SO_2)NR_3R_4, NR_3R_4, CO_2R_1, COR_1, $CONR_1R_2$, $N(R_1)COR_2$;
(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;
(iii) heterocicloalquilo o heterocicloalquilo sustituido;
(iv) –C_1-C_8 alquilo, –C_2-C_8 alquenilo, o –C_2-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C_1-C_8 alquilo sustituido, –C_2-C_8 alquenilo sustituido, o –C_2-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquilo, o –C_3-C_{12} cicloalquilo sustituido; –C_3-C_{12} cicloalquenilo, o –C_3-C_{12} cicloalquenilo sustituido;
R_y R' se seleccionan en forma independiente entre sí entre el grupo formado por:
(i) –C_1-C_8 alquilo, –C_2-C_8 alquenilo, o –C_2-C_8 alquinilo cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S, o N; –C_1-C_8 alquilo sustituido, –C_2-C_8 alquenilo sustituido, o –C_2-C_8 alquinilo sustituido cada uno con 0, 1, 2, o 3 heteroátomos seleccionados entre O, S o N; –C_3-C_{12} cicloalquilo, o –C_3-C_{12} cicloalquilo sustituido; –C_4-C_{12} alquilcicloalquilo, o –C_4-C_{12} alquilcicloalquilo sustituido; –C_3-C_{12} cicloalquenilo, o –C_3-C_{12} cicloalquenilo sustituido; –C_4-C_{12} alquilcicloalquenilo, o –C_4-C_{12} alquilcicloalquenilo sustituido;
(ii) arilo; arilo sustituido; heteroarilo; heteroarilo sustituido;
(iii) heterocicloalquilo o heterocicloalquilo sustituido;
....

879000

CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Ref.: **PODER** conferido por **ENANTA PHARMACEUTICALS, INC.**

Yo, **XIMENA CASTELLANOS ABONDANO,** mayor de edad, identificada y domiciliada como aparece al pié de mi firma, atentamente manifiesto a Uds. que sustituyo en la Dra.

02472, ESTADOS UNIDOS DE AMERICA, debidamente legalizado por Apostilla el día **24 de agosto de 2007,** bajo el número **1251520**, con las mismas facultades que me fueron conferidas, para tramitar la solicitud de Patente PCT Entrada en Fase Nacional en Colombia, para: **COMPUESTOS QUE CONTIENEN QUINOXALINA COMO INHIBIDORES DEL VIRUS DE LA HEPATITIS C.-**

De la Señora Jefe,

Acepto

Ximena Castellanos Abondano
C.C. No. **39.773.330** de Usaquén
T.P.A. No. **58.236** del C.S.J.
Calle 94 A No. 7 A-09 – Bogotá
PBX: 7560770

Margarita Castellanos Abondano
C.C. No. **39.779.654** de Usaquén
T.P.A. No. **70.819** del C.S.J.
Calle 94 A No. 7 A-09 – Bogotá
PBX: 7560770

Bogotá, D.C.
XCA/MCA/gcb/ P1976

MEMORIAL SUSTITUCION PODER

NOTARIA 41 DEL CÍRCULO DE BOGOTÁ D.C.
DEPARTAMENTO DE CUNDINAMARCA
REPÚBLICA DE COLOMBIA

El Notario 41 del Círculo de Bogotá, da fe de que compareció personalmente: [illegible]
identificada (o) con: [illegible] y tarjeta profesional de abogado No. [illegible] del Consejo Superior de la Judicatura, quien autentica la firma puesta por ella (el) mismo en este escrito.
(Art. 84 C. P. C. Decreto. 2282/89 mod. 36)

9 JUN. 2010

[illegible]

NOTARIA 41 DEL CÍRCULO DE BOGOTÁ D.C.
REPÚBLICA DE COLOMBIA

personalmente: [illegible]
identificada (o) con: [illegible] y tarjeta profesional de abogado No. [illegible] del Consejo Superior de la Judicatura, quien autentica la firma puesta por ella (el) mismo en este escrito.
(Art. 84 C. P. C. Decreto. 2282/89 mod. 36)

9 JUN. 2010

[illegible]

COLOMBIA

PODER

El (los) **ENANTA PHARMACEUTICALS, INC.**

Domiciliados en
500 Arsenal Street, Watertown, MA 02472, Estados Unidos de Amèrica

Nombran por el presente a **XIMENA CASTELLANOS A. y/o MARGARITA CASTELLANOS A.** abogadas con oficinas en la Calle 94A No. 7A-09, Bogotá-Colombia para

y para obtener la protección de mi (nuestra) propiedad Industrial y con este fin autorizamos a dichos apoderados para que nos representen ante cualesquiera autoridades o personas de los órdenes administrativo, contencioso –administrativo y judicial en todo lo relacionado con los siguientes actos y gestiones:

a) Obtención de patentes de invención, modelos y dibujos industriales; registro de marcas de fabrica, de servicio, colectivas o defensivas y de denominaciones de origen, depósito de nombres y enseñas comerciales; su renovación, prórroga, inscripción de traspaso y cambio de nombre o domicilio, cancelación voluntaria y el registro de licencias de uso de esos derechos;
b) Para la obtención de registros sanitarios;
c) Acciones de oposición, observación, cancelación, nulidad, medidas cautelares y en general los juicios civiles, penales, administrativos o contencioso - administrativos que promovamos o se nos promuevan.

Pudiendo en todos los actos y gestiones arriba mencionados sustituir éste mandato, transigir, desistir, recibir, cancelar, renunciar, aceptar notificaciones y nombrar apoderados judiciales y extrajudiciales.

Finalmente, este poder ratifica la validez de todos los actos y solicitudes que, a nombre de la poderdante hubieren realizado

POWER OF ATTORNEY

000529

I (we) the undersigned **ENANTA PHARMACEUTICALS, INC.**

Of
500 Arsenal Street, Watertown, MA 02472, United States of America

hereby grant(s) Power of Attorney to **XIMENA CASTELLANOS A. and /or MARGARITA CASTELLANOS** a. attorneys residing at Calle 94A No. 7A-09, Bogotá- Colombia, to

and to obtain the protection of my (our Industrial Property, for which purpose we authorize the said attorneys to represent us before any authorities, or persons, specially those, administrative, contentious and judicial, in all matters concerning the following:

a) Obtainment of patents, models and designs, registration of trademarks, service, collective and defensive marks, and of designations of origin; the deposit of trade names and ensigns; its renewal, extension, recordal of assignments, change of name or domicile, voluntary cancellation, and the registration of licenses of use of the above rights;
b) For the obtainment of Sanitary registrations;
c) Actions of opposition, cancellation, nullity, infringement, granting of licenses; and in general the civil, criminal and administrative suits related to those rights; actions and suits instituted by us or against us;

In all the above matters they may substitute this power of attorney, compromise, desist, cancel, receive, renounce, accept notifications and appoint attorneys in fact, in or out of court.

Finally, this power of attorney ratifies the validity of all acts and applications made by the representatives in the name of

Dado y firmado hoy 10 de Agosto de 2007

en Watertown, MA

por ENANTA PHARMACEUTICALS, INC.
Paul J. Mellett, Jefe de la Oficina Financiera
(El notario debe suscribir el documento en la pagina siguiente)

(Se requiere legalización consular o mediante apostilla)

Given and signed this 10 August 2007

in Watertown MA

by _____
Paul J. Mellett, Chief Financial Officer
Enanta Pharmaceuticals, Inc.

(Notary shall execute on the other side)
(Consular legalization or apostille is required)

Esta copia coincide con el original que tuve a la vista
Bogotá D.C.
9 JUN 2010
JUANITA LALINDE GARCIA
NOTARIA CUARENTA Y UNO (E.N.)

CASTELLANOS & CO
ABOGADOS COLOMBIA
Calle 94A No. 7A-09- P.O.Box 6349 - Bogotá, Colombia
Tels.: (571) 610 74 20 / - Fax (571) 610 07 06 - e-mail info@castellanosyco.com

COLOMBIA

0005..

CERTIFICADO NOTARIAL (Sociedad)

Hoy 16 de 8 del año 2007
compareció (eron) personalmente

PAUL J. MELLETT

a quienes conozco como la(s) personas que firma(n) en representación de la Sociedad (Compañía) denominada

Certifico
a) Que
ENANTA PHARMACEUTICALS, INC.

es una sociedad/Compañía legalmente constituida y existente de acuerdo con las leyes del estado de Delaware

b) Que el domicilio de dicha Sociedad/Compañía es
500 Arsenal Street, Watertown, MA 02472, Estados Unidos de América

c) Que el objeto u objetos para los cuales se otorga el presente poder están comprendidos dentro del objeto social de la mencionada Sociedad /Compañía.
d) Que el Sr.
esta autorizado para otorgar el presente poder. Lo anterior esta probado por medio de los siguientes documentos, que certifico he visto*

(Ciudad) WATERTOWN

(Estado) Massachusetts

(Notario Público)

*Los documentos debe identificarse con fecha y origen.

NOTARIAL CERTIFICATION (Corporation)

On this 16 day of August of 2007
personally appeared

PAUL J. MELLETT

whom I know to be the person(s) who signed this document as representative(s) of the Corporation /Company named

I certify:
a) That
ENANTA PHARMACEUTICALS, INC.

is a corporation (Company legally constituted and in existence in accordance with the laws of Delaware

b) That the domicile of said Corporation/Company is
500 Arsenal Street, Watertown, MA 02472, United Stated of America.

c) That the purpose or purposes for which the present Power of Attorney is granted are comprised within the object set forth in the charter of the mentioned Corporation/Company
d) That Mr.
is (are) authorized to grant the present Power of Attorney. The aforementioned was duly proven through the following documents and I duly certify having seen them*:

(City) Watertown

(State) Massachusetts

(Notary Public)

*Documents must be identified with date and origin

R... ...PASCUALE
COMM... ...TS

Rachael A. Pascuale

Esta copia es fiel y exacta con el original que tuve a la vista
Bogotá, D.C.
- 9 JUN 2010
JUANITA LALINDE GAROA
NOTARIA VEINTIUNO (ENC)

CASTELLANOS & CO
ABOGADOS COLOMBIA
Calle 94A No 7A-09- P.O.Box 6349 - Bogotá, Colombia
Tels.. (571) 610 74 20 / - Fax (571) 610 07 06 - e-mail info@castellanosyco.com

4056.1106 CO

P1520

000531

The Commonwealth of Massachusetts

William Francis Galvin
Secretary of the Commonwealth

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country:* United States of America

This public document

2. *has been signed by:* Rachael DePasquale

3. *acting in the capacity of:* Notary Public

4. *bears the seal/stamp of:* the State of Massachusetts

whose commission expires on: November 15, 2013

7. *by:* the Secretary of the Commonwealth

8. *No.:* 1251520

9. *Seal/stamp:* *Great Seal of the Commonwealth*

10. *Signature:*

William Francis Galvin

William Francis Galvin
Secretary of the Commonwealth

la copia ... con el ... que tuve a la vista

9 JUN 2010

JUAN ... LALINDE GARCIA
NOTARIA CUARENTA Y UNO (ENC)

prepared by TCoughlin

TRADUCCIÓN OFICIAL No. 201-07, DE UN DOCUMENTO ESCRITO EN INGLES, SELLADO CON EL SELLO DEL SUSCRITO TRADUCTOR OFICIAL, HOY SEPTIEMBRE 19 DEL 2007, EN LA CIUDAD DE BOGOTA D.C., REPUBLICA DE COLOMBIA

(PODER... SELLO NOTARIAL .../...)
Firma y sello de
RACHAEL A. DePASQUALE
Notario público Mancomunidad de Massachussets
Comisión vence: Noviembre 15, 2013.

ADJUNTO AL DOCUMENTO SE ENCUENTRA LO SIGUIENTE:
LA MANCOMUNIDAD DE MASSACHUSSETS
William Francis Galvin
Secretario de la Mancomunidad

APOSTILLE
(CONVENCION DE LA HAYE DE 5 OCTOBRE 1961)

1. PAIS: ESTADOS UNIDOS DE AMERICA
   ESTE DOCUMENTO PUBLICO
2. HA SIDO FIRMADO POR: RACHAEL DEPASQUALE
3. ACTUANDO EN CAPACIDAD DE: NOTARIO PUBLICO
4. LLEVA EL SELLO DEL ESTADO DE MASSACHUSSETS
   Cuya comisión vence en: NOVIEMBRE 15, 2013.

6. EL DIA: 24 DE AGOSTO DEL 2007
7. POR: EL SECRETARIO DE LA MANCOMUNIDAD
8. No.1251520
9. SELLO/ESTAMPILLA GRAN SELLO DE LA MANCOMUNIDAD
10. FIRMA

FIRMADO POR: WILLIAM FRANCIS GALVIN
SECRETARIO DE LA MANCOMUNIDAD

Esta copia es fiel y concuerda con el original que tuve a la vista
Bogotá, D.C.
- 9 JUN 2010
JUANITA LALINDE GAROZA
NOTARIA

Sergio Eleuterio Latorre Mendoza
Traductor e Interprete Oficial
Resol No. 2089 Minjusticia 1991

MINISTERIO DE
RELACIONES EXTERIORES

2007 SET 20 A 11:07

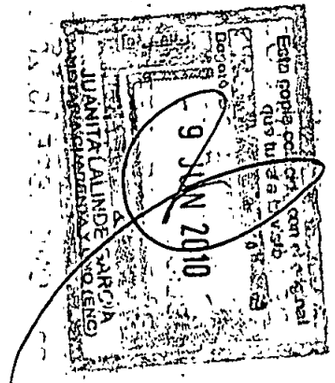
JEFE DE LEGALIZACIONES
BOGOTA D.C.

NO SE ASUME
RESPONSABILIDAD
DEL TEXTO

899816

Sergio Latorre

ESTA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS



Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
MARGARITA CASTELLANOS ABONDANO
Apoderado(a) y/o Representante de
ENANTA PHARMACEUTICALS INC

REFERENCIA		
	Radicación No.	10 069276
	Solicitud internacional	PCT/US2008/083541
	Fecha inicio fase nacional	14/06/2010
	Trámite	11
	Evento	378
	Actuación	480
	Oficio No.	007892

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. El solicitante deberá aclarar y corregir la numeración del capitulo reivindicatorio (folios 502 y 503) concerniente a la reivindicación numero 2.

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Continua en la página siguiente...

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 18 JUN. 2010
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