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(72) Inventeurs/Inventors:
CRESCENZI, BENEDETTA, IT;
DONGHI, MONICA, IT;
FERRARA, MARCO, IT;
GARDELLI, CRISTINA, IT;
HARPER, STEVEN, IT;
KOCH, UWE, IT;
ROWLEY, MICHAEL, IT;
SUMMA, VINCENZO, IT

(73) Propriétaire/Owner:
MSD ITALIA S.R.L., IT

(74) Agent: NORTON ROSE FULBRIGHT CANADA

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(54) Title: MACROCYCLIC COMPOUNDS AS ANTIVIRAL AGENTS

(57) **Abrégé/Abstract:**

The present invention relates to macrocyclic compounds of formula (I): wherein W, n, m, R¹, R², R³, R⁴, R⁵, R^a, M, Z and ring B are defined herein, and pharmaceutically acceptable salts thereof, pharmaceutical compositions comprising them, and their use for the treatment or prevention of infection by hepatitis C virus.



(74) **Agent(suite/continued):** LLP/S.E.N.C.R.L., S.R.L.

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[GB/IT]; Irbm, Via Pontina KM 30.600, I-00040 Pomezia (rome) (IT). **SUMMA, Vincenzo** [IT/IT]; Irbm, Via Pontina KM 30.600, I-00040 Pomezia (rome) (IT).

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(74) **Agent: MAN, Jocelyn**; European Patent Department, Hoddesdon Hertfordshire EN11 9BU (GB).

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(71) **Applicant (for all designated States except US): ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA** [IT/IT]; Via Pontina KM 30.600, I-00040 Pomezia (rome) (IT).

(72) Inventors; and

(75) **Inventors/Applicants (for US only): CRESCENZI, Benedetta** [IT/IT]; Irbm, Via Pontina KM 30.600, I-00040 Pomezia (rome) (IT). **DONGHI, Monica** [IT/IT]; Irbm, Via Pontina KM 30.600, I-00040 Pomezia (rome) (IT). **FERRARA, Marco** [IT/IT]; Irbm, Via Pontina KM 30.600, I-00040 Pomezia (rome) (IT). **GARDELLI, Cristina** [IT/IT]; Irbm, Via Pontina KM 30.600, I-00040 Pomezia (rome) (IT). **HARPER, Steven** [GB/IT]; Irbm, Via Pontina KM 30.600, I-00040 Pomezia (rome) (IT). **KOCH, Uwe** [DE/IT]; Irbm, Via Pontina KM 30.600, I-00040 Pomezia (rome) (IT). **ROWLEY, Michael**

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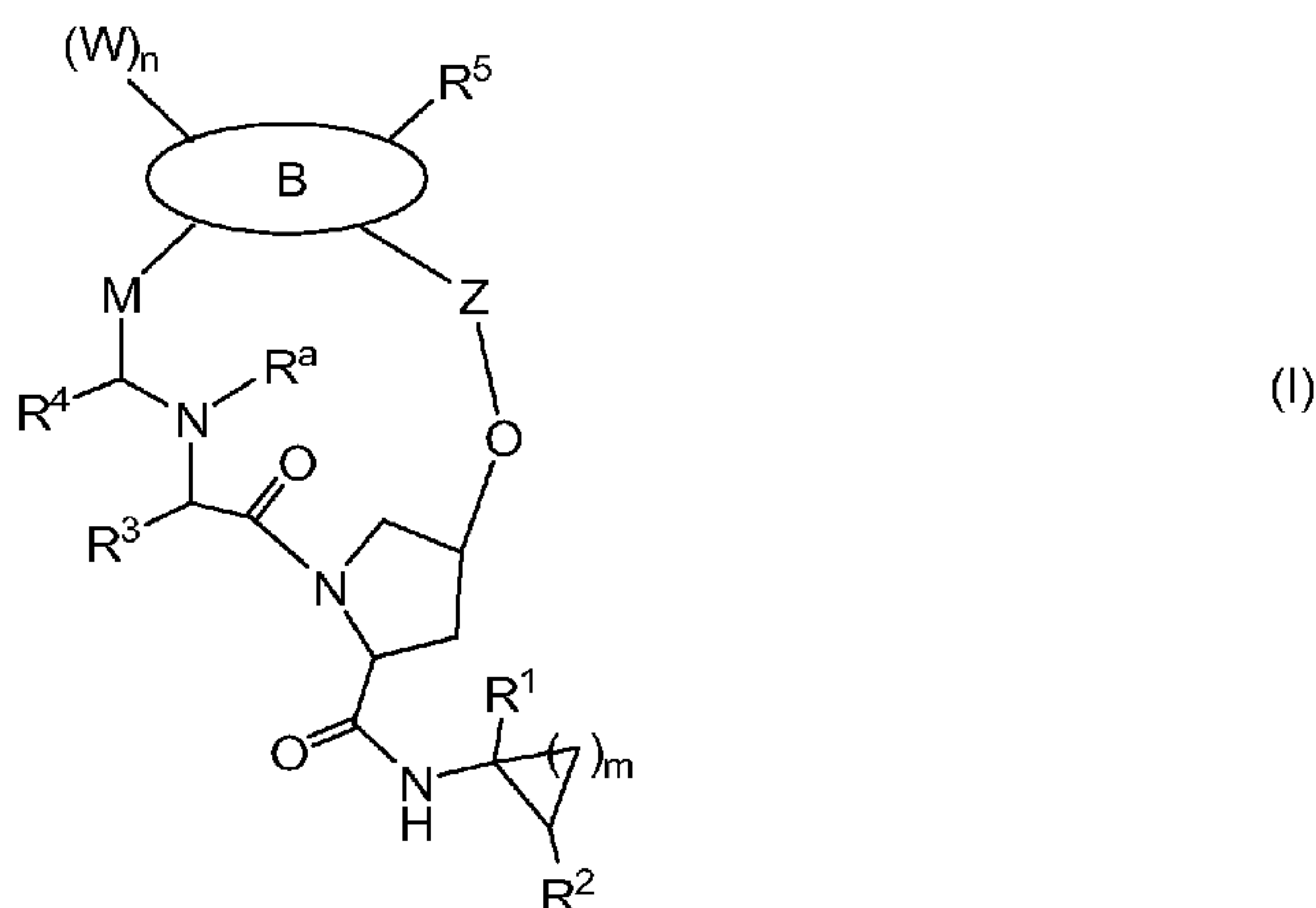
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(54) Title: MACROCYCLIC COMPOUNDS AS ANTIVIRAL AGENTS



(57) **Abstract:** The present invention relates to macrocyclic compounds of formula (I): wherein W, n, m, R¹, R², R³, R⁴, R⁵, R^a, M, Z and ring B are defined herein, and pharmaceutically acceptable salts thereof, pharmaceutical compositions comprising them, and their use for the treatment or prevention of infection by hepatitis C virus.

WO 2007/148135 A1

Macrocyclic compounds as antiviral agents

The present invention relates to macrocyclic compounds that are useful as inhibitors of the hepatitis C virus (HCV) NS3 protease, their synthesis, and their use for treating or preventing HCV infection.

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be 2-15% of the world's population. According to the World Health Organization, there are more than 170 million infected individuals worldwide, with at least 3 to 4 million people being infected each year. Once infected, about 20% of people clear the virus, but the rest harbor HCV the rest of their lives. Ten to twenty percent of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. The viral disease is transmitted parenterally by contaminated blood and blood products, contaminated needles, or sexually and vertically from infected mothers or carrier mothers to their offspring.

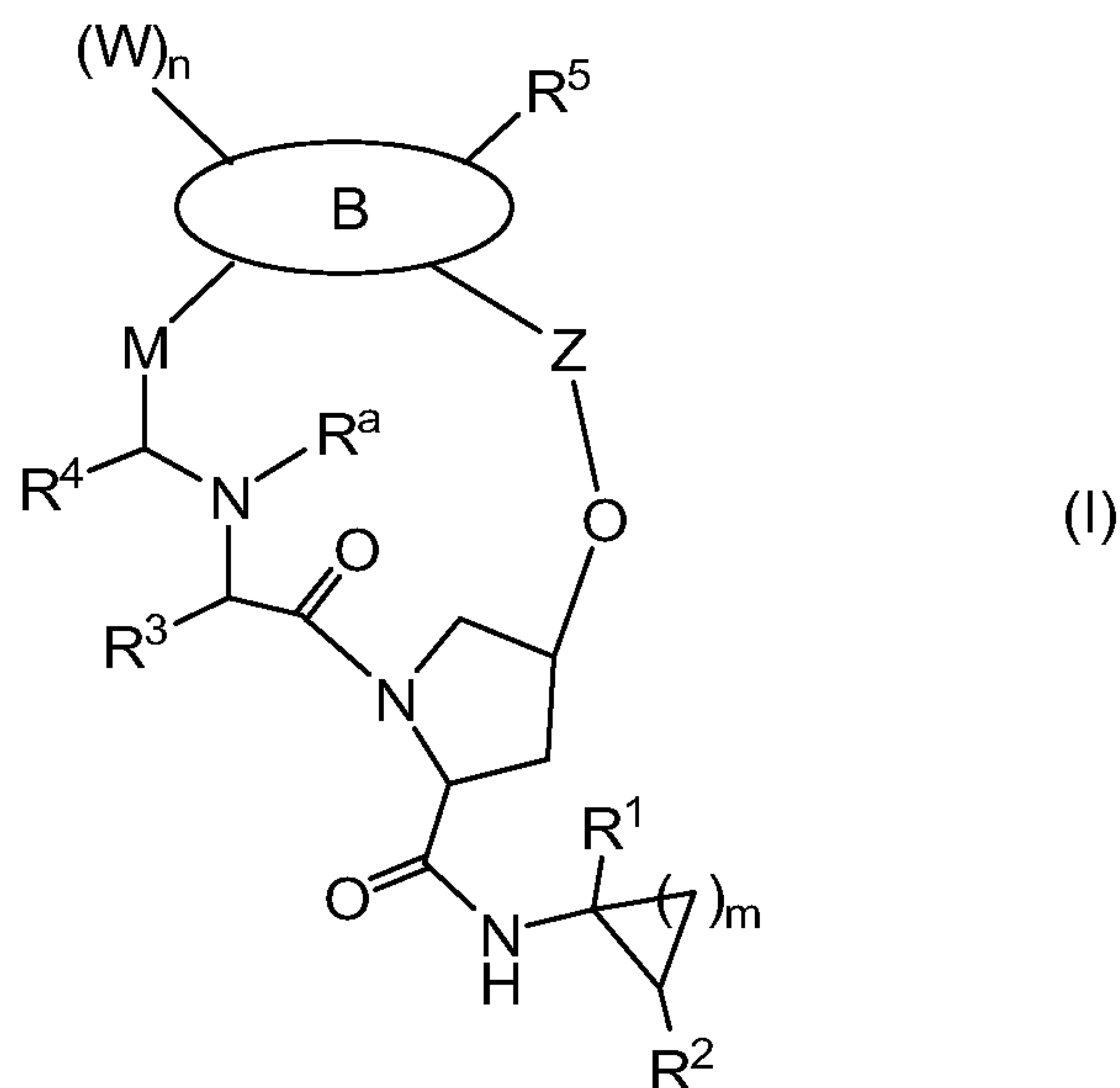
Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon- α alone or in combination with the nucleoside analog ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine for HCV. Consequently, there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection.

Several virally-encoded enzymes are putative targets for therapeutic intervention, including a metalloprotease (NS2-3), a serine protease (NS3), a helicase (NS3), and an RNA-dependent RNA polymerase (NS5B). The NS3 protease is located in the N-terminal domain of the NS3 protein, and is considered a prime drug target since it is responsible for an intramolecular cleavage at the NS3/4A site and for downstream intermolecular processing at the NS4A/4B, NS4B/5A and NS5A/5B junctions. Previous research has identified classes of peptides, such as hexapeptides as well as tripeptides discussed in U.S. patent applications US2005/0020503, US2004/0229818, and US2004/00229776, showing degrees of activity in inhibiting the NS3 protease. The aim of the present invention is to provide further compounds which exhibit activity against the HCV NS3 protease.

Macrocyclic compounds that exhibit activity against the HCV NS3 protease have already been disclosed in published International patent application nos. WO2006/119061, WO2007/015855 and WO2007/016441 (all Merck & Co., Inc.)

Thus, in one aspect, there is provided the compound of formula (I):

- 2 -



or a pharmaceutically acceptable salt thereof,
wherein:

m is 1, 2, 3 or 4;

5 n is 0, 1 or 2;

R^1 is CO_2R^6 , $\text{CONR}^6\text{SO}_2R^6$ or $\text{CONR}^6\text{SO}_2\text{N}(R^6)_2$;

R^2 is H, C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-8} cycloalkyl, wherein said alkyl, alkenyl or cycloalkyl is optionally substituted with 1 to 3 halo;

10 R^3 is C_{1-6} alkyl, $(\text{CH}_2)_{0-3}\text{C}_{3-8}$ cycloalkyl, $(\text{CH}_2)_{0-3}$ aryl or $(\text{CH}_2)_{0-3}\text{Het}$, optionally substituted by halo, OR^6 , SR^6 , $\text{N}(R^6)_2$, C_{1-6} alkyl, NO_2 , CN , CF_3 , $\text{NR}^6\text{SO}_2R^6$, $\text{SO}_2\text{N}(R^6)_2$, NHCO_2R^6 , NHCOR^6 , NHCONHR^6 , CO_2R^6 , $\text{C(O)}R^6$ or $\text{CON}(R^6)_2$;

R^4 is hydrogen, halo, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(\text{CH}_2)_{0-3}\text{C}_{3-8}$ cycloalkyl, $(\text{CH}_2)_{0-3}$ aryl or C_{1-6} alkoxy, optionally substituted by halo, OR^6 , SR^6 , $\text{N}(R^6)_2$, C_{1-6} alkyl, NO_2 , CN , CF_3 , $\text{NR}^6\text{SO}_2R^6$, $\text{SO}_2\text{N}(R^6)_2$, NHCO_2R^6 , NHCOR^6 , NHCONHR^6 , CO_2R^6 , $\text{C(O)}R^6$ or $\text{CON}(R^6)_2$;

15 R^5 is hydrogen, halo, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, CN , NO_2 , C_{3-8} cycloalkyl, $\text{N}(R^6)_2$, aryl or heteroaryl, optionally substituted by 1 to 8 halo, C_{1-4} alkyl or $\text{N}(R^6)_2$;

each R^6 is independently hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;

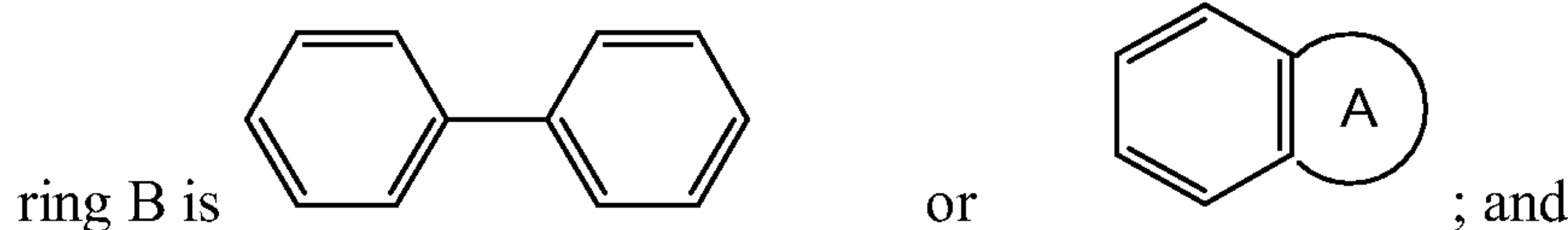
R^a is hydrogen or C_{1-4} alkyl;

20 or R^a and R^3 are joined to form a 5- to 7-membered heterocycle containing 1, 2 or 3 N atoms, which heterocycle is optionally substituted by C_{1-4} alkyl;

each W is independently halo, OR^6 , C_{1-6} alkyl, CN , NO_2 , CF_3 , OCF_3 , OCHF_2 , CO_2R^6 , $\text{CON}(R^6)_2$, COR^6 , $\text{NR}^6\text{C(O)}R^6$, aryl or heteroaryl;

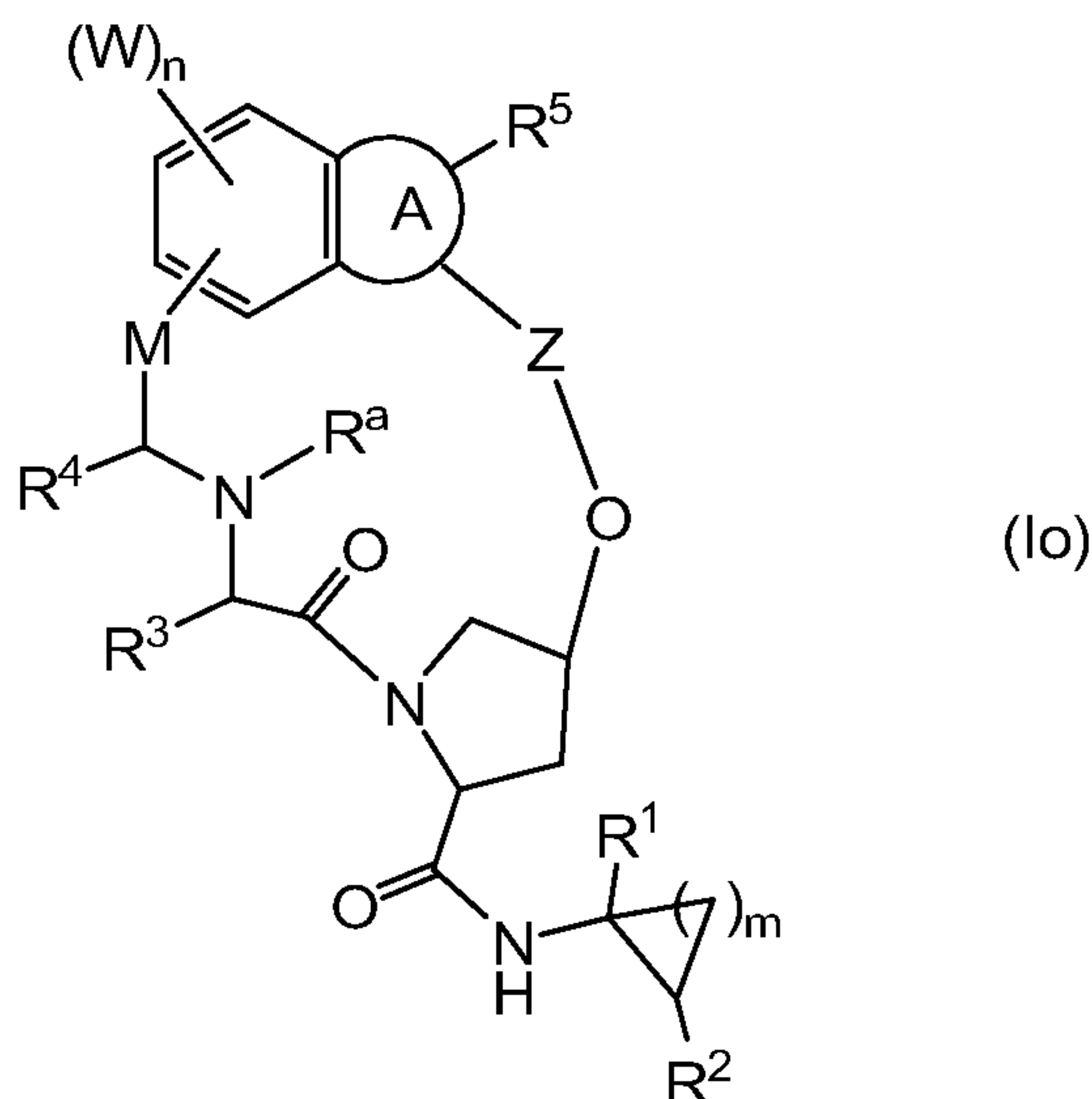
Z is a bond, $-\text{CH}_2-$ or C=O ;

25 M is C_{2-12} alkylene or C_{2-12} alkenylene, optionally substituted by halo, C_{1-6} alkyl, $(\text{CH}_2)_{0-3}\text{C}_{3-8}$ cycloalkyl or $(\text{CH}_2)_{0-3}$ aryl, and optionally containing O, NR^6 , S, SO or SO_2 ; and



ring A is pyridinyl, pyrrolidinyl or pyrimidinyl.

In one embodiment of the present invention, there is provided the compound of formula (Io):



5 or a pharmaceutically acceptable salt thereof,
wherein:

m is 1, 2, 3 or 4;

n is 0, 1 or 2;

R^1 is CO_2R^6 , $\text{CONR}^6\text{SO}_2R^6$ or $\text{CONR}^6\text{SO}_2\text{N}(\text{R}^6)_2$;

10 R^2 is H, C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-8} cycloalkyl, wherein said alkyl, alkenyl or cycloalkyl is optionally substituted with 1 to 3 halo;

R^3 is C_{1-6} alkyl, $(\text{CH}_2)_{0-3}\text{C}_{3-8}$ cycloalkyl, $(\text{CH}_2)_{0-3}$ aryl or $(\text{CH}_2)_{0-3}$ Het, optionally substituted by halo, OR^6 , SR^6 , $\text{N}(\text{R}^6)_2$, C_{1-6} alkyl, NO_2 , CN, CF_3 , $\text{NR}^6\text{SO}_2R^6$, $\text{SO}_2\text{N}(\text{R}^6)_2$, NHCO_2R^6 , NHCOR^6 , NHCONHR^6 , CO_2R^6 , $\text{C}(\text{O})R^6$ or $\text{CON}(\text{R}^6)_2$;

15 R^4 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(\text{CH}_2)_{0-3}\text{C}_{3-8}$ cycloalkyl, $(\text{CH}_2)_{0-3}$ aryl or C_{1-6} alkoxy, optionally substituted by halo, OR^6 , SR^6 , $\text{N}(\text{R}^6)_2$, C_{1-6} alkyl, NO_2 , CN, CF_3 , $\text{NR}^6\text{SO}_2R^6$, $\text{SO}_2\text{N}(\text{R}^6)_2$, NHCO_2R^6 , NHCOR^6 , NHCONHR^6 , CO_2R^6 , $\text{C}(\text{O})R^6$ or $\text{CON}(\text{R}^6)_2$;

R^5 is hydrogen, halo, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, CN, NO_2 , C_{3-8} cycloalkyl, $\text{N}(\text{R}^6)_2$, aryl or heteroaryl, optionally substituted by 1 to 8 halo, C_{1-4} alkyl or $\text{N}(\text{R}^6)_2$;

20 each R^6 is independently hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;

R^a is hydrogen or C_{1-4} alkyl;

or R^a and R^3 are joined to form a 5- to 7-membered heterocycle containing 1, 2 or 3 N atoms, which heterocycle is optionally substituted by C_{1-4} alkyl;

25 each W is independently halo, OR^6 , C_{1-6} alkyl, CN, NO_2 , CF_3 , OCF_3 , OCHF_2 , CO_2R^6 , $\text{CON}(\text{R}^6)_2$, COR^6 , $\text{NR}^6\text{C}(\text{O})R^6$, aryl or heteroaryl;

Z is a bond or $\text{C}=\text{O}$;

M is C_{2-12} alkylene or C_{2-12} alkenylene, optionally substituted by halo, C_{1-6} alkyl, $(\text{CH}_2)_{0-3}\text{C}_{3-8}$ cycloalkyl or $(\text{CH}_2)_{0-3}$ aryl, and optionally containing O, NR^6 , S, SO or SO_2 ; and

ring A is pyridinyl, pyrrolidinyl or pyrimidinyl.

In another embodiment of the present invention, m is 1 or 2. Preferably, m is 1.

In another embodiment of the present invention, n is 0 or 1. Preferably, n is 0.

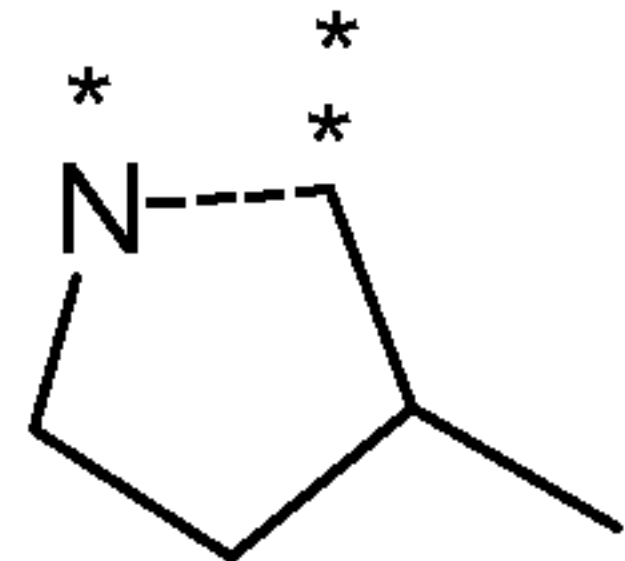
In another embodiment, R^1 is CO_2R^6 , $CONR^6SO_2R^6$ or $CONR^6SO_2N(R^6)_2$ where R^6 is as
 5 hereinbefore defined. Preferably, R^1 is CO_2R^6 or $CONR^6SO_2R^6$ where R^6 is as hereinbefore
 defined. More preferably, R^1 is CO_2H or $CONHSO_2R^6$ where R^6 is as hereinbefore defined.
 Especially, R^1 is CO_2H or $CONHSO_2-C_{3-8}$ cycloalkyl. More especially, R^1 is CO_2H or
 $CONHSO_2-C_{3-6}$ cycloalkyl. Most especially, R^1 is CO_2H or $CONHSO_2$ -cyclopropyl.

In another embodiment, R^2 is C_{1-6} alkyl or C_{2-6} alkenyl. Preferably, R^2 is C_{1-4} alkyl or C_{2-}
 10 4 alkenyl. More preferably, R^2 is C_{1-2} alkyl or $-CH=CH_2$. Most preferably, R^2 is ethyl or $-$
 $CH=CH_2$.

In another embodiment, R^3 is C_{1-6} alkyl, or $(CH_2)_{0-3}C_{3-8}$ cycloalkyl, optionally substituted by
 halo, OR^6 or C_{1-6} alkyl, where R^6 is as hereinbefore defined. Preferably, R^3 is C_{1-6} alkyl or
 $(CH_2)_{0-3}C_{3-8}$ cycloalkyl, optionally substituted by halo. More preferably, R^3 is C_{1-4} alkyl or C_{3-}
 15 6 cycloalkyl, optionally substituted by fluoro or chloro. Most preferably, R^3 is methyl, propyl,
 butyl, cyclopentyl or cyclohexyl, optionally substituted by fluoro. Especially, R^3 is methyl,
 i propyl, i butyl, CF_3 , cyclopentyl or cyclohexyl.

In another embodiment, R^a is hydrogen or C_{1-2} alkyl. Preferably, R^a is hydrogen or methyl.

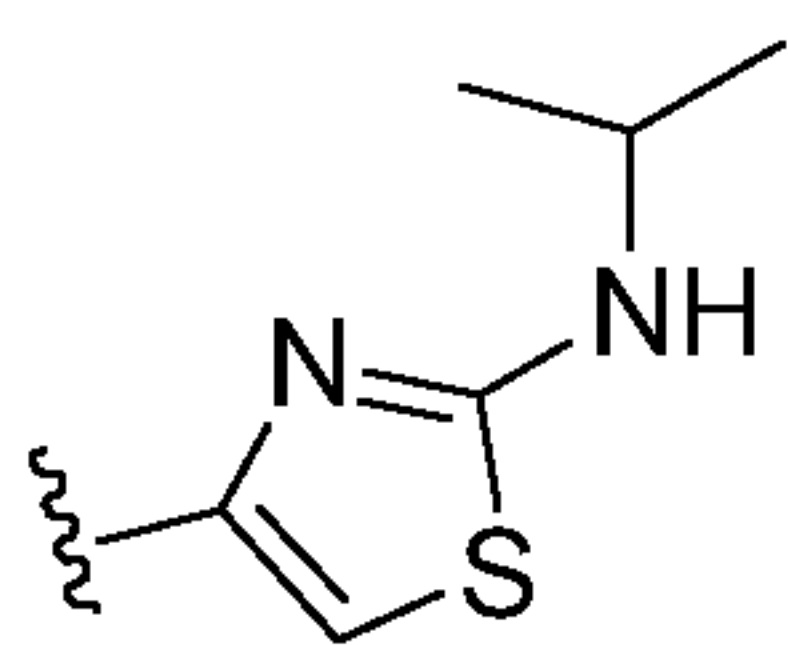
In another embodiment, R^a and R^3 are joined to form a 5- or 6- membered heterocycle
 20 containing 1 or 2 N atoms, which heterocycle is optionally substituted by C_{1-4} alkyl. Preferably, R^a
 and R^3 are joined to form a 5- or 6- membered heterocycle containing one N atom, which
 heterocycle is optionally substituted by C_{1-4} alkyl. More preferably, R^a and R^3 are joined to form a
 pyrrolidinyl or a piperidinyl ring, optionally substituted by C_{1-2} alkyl. Most preferably, R^a and R^3
 are joined to form a pyrrolidinyl ring, optionally substituted by methyl. Especially, R^a and R^3 form

 where * indicates the nitrogen atom to which R^a is attached and ** indicates the
 25 carbon atom to which R^3 is attached.

In another embodiment, R^4 is hydrogen, C_{1-6} alkyl, $(CH_2)_{0-3}C_{3-8}$ cycloalkyl, $(CH_2)_{0-3}$ phenyl
 or C_{1-6} alkoxy, optionally substituted by halo, OR^6 , SR^6 , $N(R^6)_2$, C_{1-6} alkyl, NO_2 or CN , where R^6 is
 as hereinbefore defined. Preferably, R^4 is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, optionally substituted
 30 by halo or OR^6 , where R^6 is as hereinbefore defined. More preferably, R^4 is hydrogen or C_{1-}
 6 alkyl, optionally substituted by halo. Most preferably, R^4 is hydrogen or C_{1-4} alkyl, optionally
 substituted by fluoro or chloro. Especially, R^4 is hydrogen or C_{1-2} alkyl, optionally substituted by
 fluoro. Examples of suitable R^4 groups include hydrogen, methyl, CF_3 and CF_2CF_3 .

In another embodiment, R^5 is hydrogen, halo, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy,
 35 C_{3-8} cycloalkyl, aryl or heteroaryl, optionally substituted by $N(R^6)_2$. Preferably, R^5 is hydrogen, C_{1-}
 6 alkyl, C_{3-8} cycloalkyl, phenyl or thiazolyl, optionally substituted by NHR^6 . More preferably, R^5 is

hydrogen, C₁₋₄alkyl, phenyl or thiazolyl, where thiazolyl is optionally substituted by NHR⁶. Most preferably, R⁵ is hydrogen, phenyl or



When R⁵ is other than hydrogen, preferably it is attached to the carbon atom adjacent to the nitrogen atom of the pyridinyl, pyrrolidinyl or pyrimidinyl moiety.

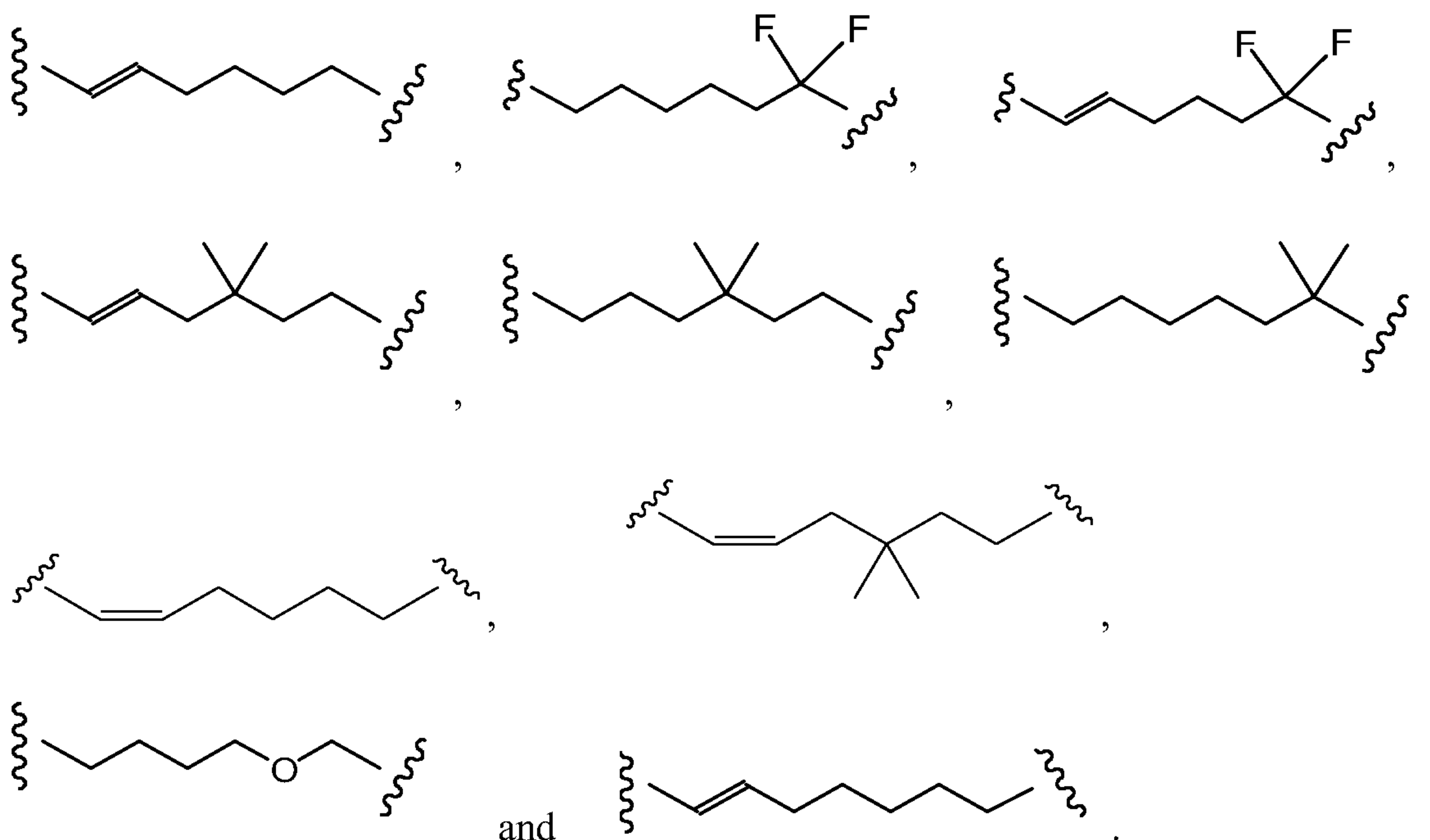
In another embodiment, each W is independently halo, OR⁶, C₁₋₆alkyl, CF₃, CO₂R⁶, CON(R⁶)₂, COR⁶ or NR⁶C(O)R⁶, where R⁶ is as hereinbefore defined. Preferably, each W is independently halo, OR⁶, CF₃, CO₂R⁶ or CONHR⁶, where R⁶ is as hereinbefore defined. More preferably, each W is independently fluoro, chloro, OC₁₋₆alkyl or CF₃. Most preferably, each W is independently OC₁₋₄alkyl or CF₃. Especially, each W is independently OC₁₋₂alkyl. Most especially, W is methoxy.

In another embodiment, Z is a bond when A is pyridinyl or pyrimidinyl.

In another embodiment, Z is C=O when A is pyrrolidinyl. Preferably, Z is attached to the nitrogen atom of the pyrrolidinyl moiety.

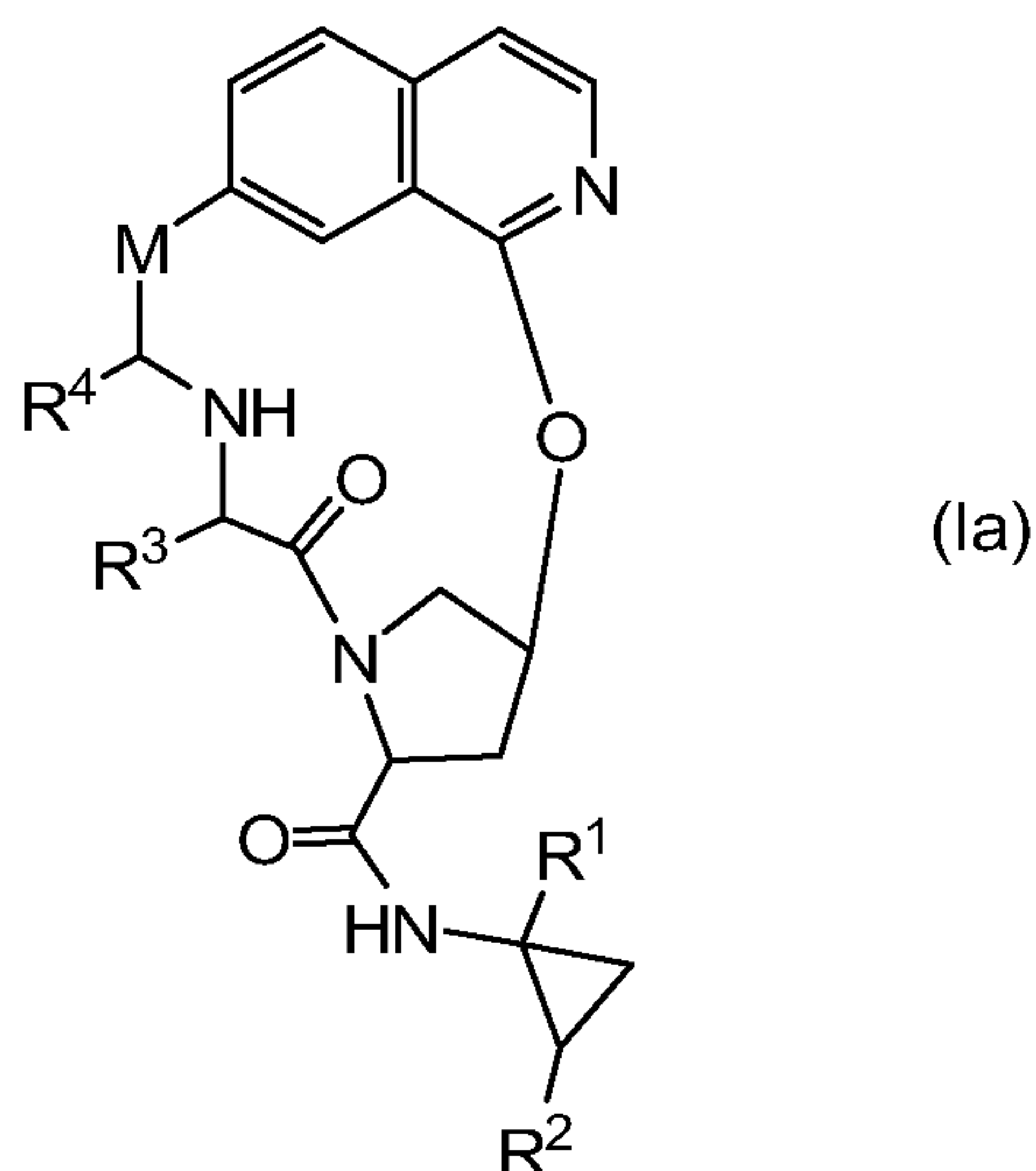
In another embodiment, Z is -CH₂- when ring B is biphenyl.

In another embodiment, M is C₂₋₈alkylene or C₂₋₈alkenylene, optionally substituted by halo, C₁₋₄alkyl or C₃₋₆cycloalkyl, and optionally containing O. Preferably, M is C₄₋₇alkylene or C₄₋₇alkenylene, optionally substituted by fluoro, chloro or C₁₋₄alkyl, and optionally containing O. More preferably, M is C₅₋₇alkylene or C₅₋₇alkenylene, optionally substituted by fluoro or methyl, and optionally containing O. Examples of suitable M groups include pentylene, hexylene, heptylene,



In another embodiment, ring A is pyridinyl or pyrrolidinyl.

In another embodiment of the present invention, there is provided the compound of formula (Ia):



or a pharmaceutically acceptable salt thereof,

wherein R^1 , R^2 , R^3 , R^4 and M are as defined in relation to formula (I).

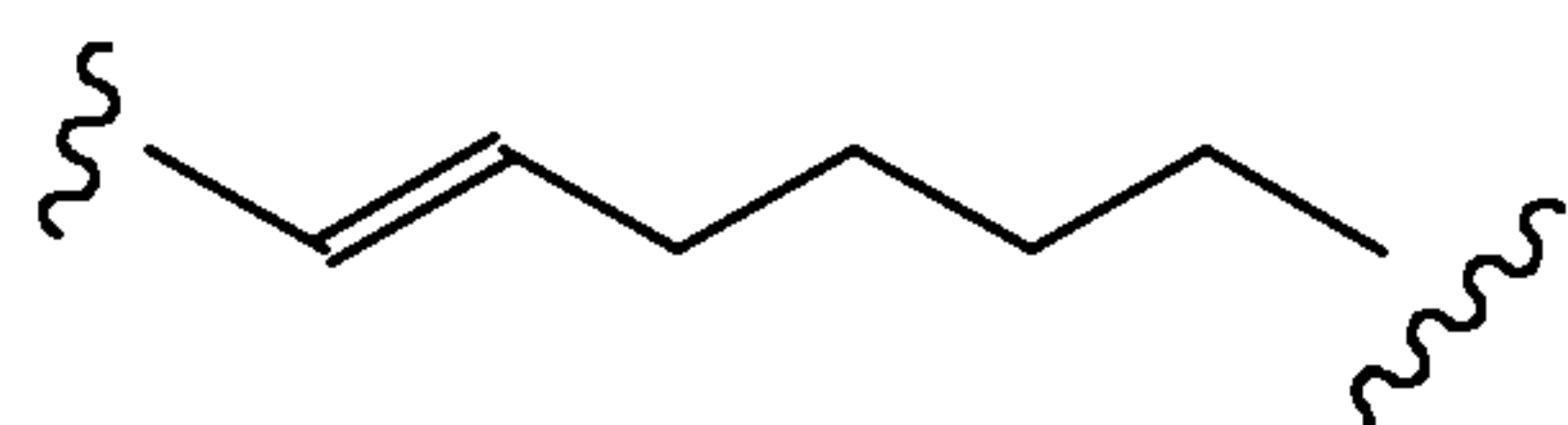
Preferably, R^1 is $C(O)NR^6SO_2R^6$ where R^6 is as defined in relation to formula (I). More preferably, R^1 is $C(O)NHSO_2R^6$ where R^6 is as defined in relation to formula (I). Most preferably, R^1 is $C(O)NHSO_2-C_{3-6}$ cycloalkyl. Especially R^1 is $C(O)NHSO_2$ -cyclopropyl.

Preferably, R^2 is C_{2-6} alkenyl. More preferably, R^2 is $-CH=CH_2$.

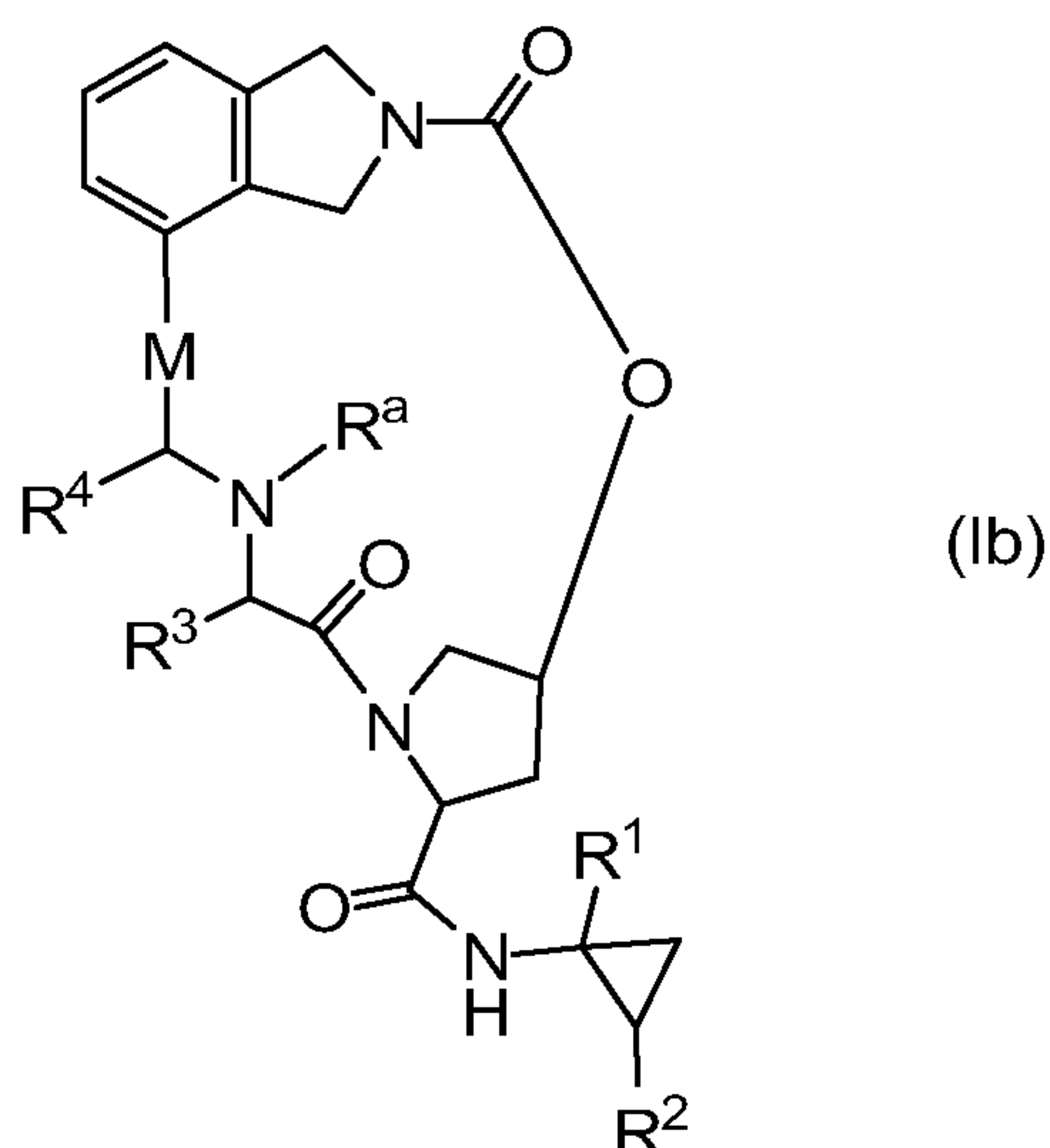
Preferably, R^3 is C_{1-6} alkyl or $(CH_2)_{0-3}C_{3-8}$ cycloalkyl, optionally substituted by halo. More preferably, R^3 is C_{1-4} alkyl or C_{3-6} cycloalkyl, optionally substituted by fluoro or chloro. Most preferably, R^3 is C_{1-4} alkyl or C_{5-6} cycloalkyl, optionally substituted by fluoro. Especially, R^3 is *i*propyl, cyclopentyl or CF_3 .

Preferably, R^4 is hydrogen, halo, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl or phenyl, optionally substituted by halo or OR^6 , where R^6 is as hereinbefore defined. More preferably, R^4 is hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl, optionally substituted by halo. Most preferably, R^4 is hydrogen or C_{1-4} alkyl, optionally substituted by fluoro or chloro. Especially, R^4 is hydrogen or C_{1-2} alkyl, optionally substituted by fluoro. More especially, R^4 is hydrogen, methyl or CF_3 .

Preferably, M is C_{3-12} alkylene or C_{3-12} alkenylene, optionally substituted by halo or C_{1-6} alkyl. More preferably, M is C_{4-8} alkylene or C_{4-8} alkenylene, optionally substituted by fluoro or C_{1-4} alkyl. Most preferably, M is C_{6-7} alkylene or C_{6-7} alkenylene, optionally substituted by C_{1-2} alkyl. Especially, M is hexylene or



In another embodiment of the present invention, there is provided the compound of formula (Ib):



or a pharmaceutically acceptable salt thereof,

5 wherein R^1 , R^2 , R^3 , R^4 and M are as defined in relation to formula (I).

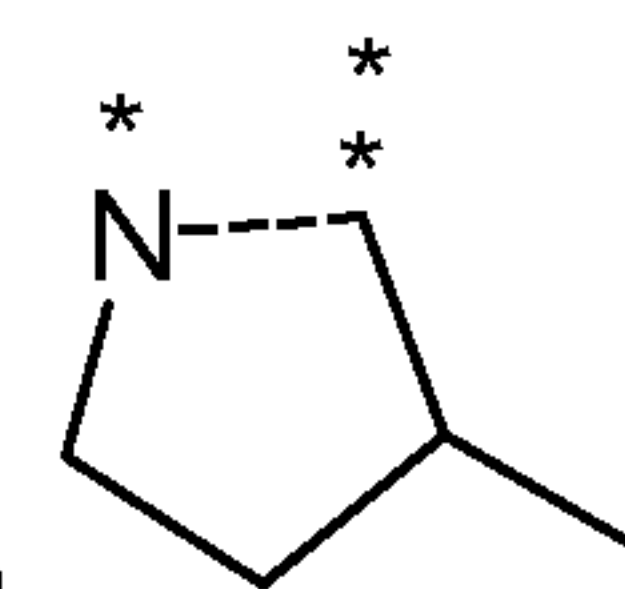
Preferably, R^1 is CO_2R^6 or $\text{C(O)NR}^6\text{SO}_2R^6$ where R^6 is as defined in relation to formula (I). More preferably, R^1 is CO_2R^6 or C(O)NHSO_2R^6 where R^6 is as defined in relation to formula (I). Most preferably, R^1 is CO_2H or $\text{C(O)NHSO}_2\text{-C}_{3-6}\text{cycloalkyl}$. Especially R^1 is CO_2H or $\text{C(O)NHSO}_2\text{-cyclopropyl}$.

10 Preferably, R^2 is $\text{C}_{1-4}\text{alkyl}$ or $\text{C}_{2-4}\text{alkenyl}$. More preferably, R^2 is $\text{C}_{1-2}\text{alkyl}$ or $-\text{CH}=\text{CH}_2$. Most preferably, R^2 is ethyl or $-\text{CH}=\text{CH}_2$.

Preferably, R^3 is $\text{C}_{1-6}\text{alkyl}$ or $(\text{CH}_2)_{0-3}\text{C}_{3-8}\text{cycloalkyl}$, optionally substituted by halo. More preferably, R^3 is $\text{C}_{1-4}\text{alkyl}$ or $\text{C}_{3-6}\text{cycloalkyl}$, optionally substituted by fluoro or chloro. Most preferably, R^3 is $\text{C}_{1-4}\text{alkyl}$ or $\text{C}_{5-6}\text{cycloalkyl}$, optionally substituted by fluoro. Especially, R^3 is methyl, i propyl, i butyl, CF_3 , cyclopentyl or cyclohexyl.

Preferably, R^a is hydrogen or $\text{C}_{1-2}\text{alkyl}$. More preferably, R^a is hydrogen or methyl.

Preferably, R^a and R^3 are joined to form a 5- or 6-membered heterocycle containing 1 or 2 N atoms, which heterocycle is optionally substituted by $\text{C}_{1-4}\text{alkyl}$. More preferably, R^a and R^3 are joined to form a 5- or 6- membered heterocycle containing one N atom, which heterocycle is optionally substituted by $\text{C}_{1-4}\text{alkyl}$. Most preferably, R^a and R^3 are joined to form a pyrrolidinyl or a piperidinyl ring, optionally substituted by $\text{C}_{1-2}\text{alkyl}$. Especially, R^a and R^3 are joined to form a

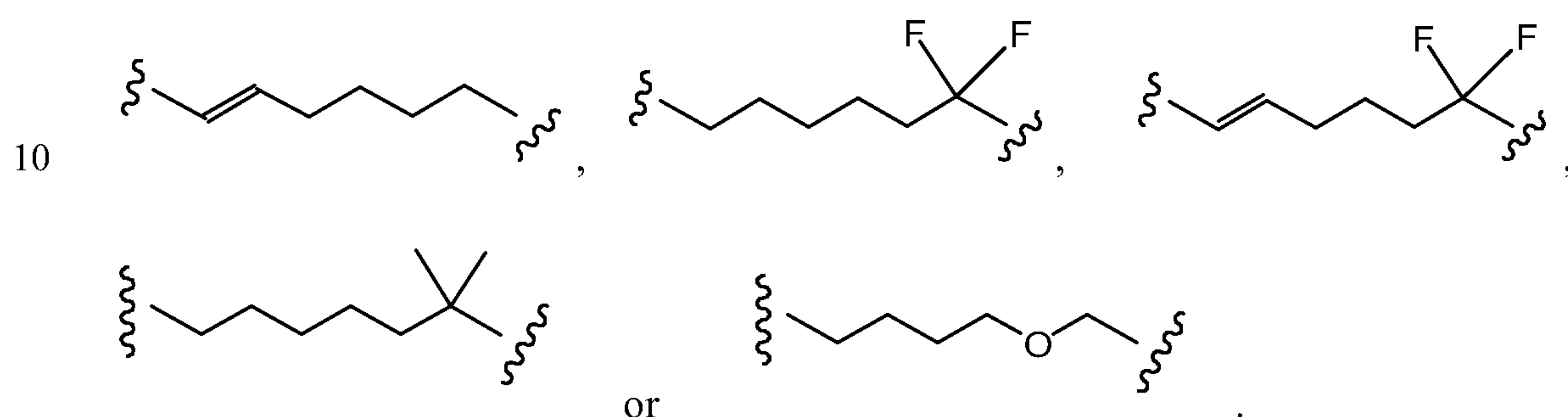


pyrrolidinyl ring, optionally substituted by methyl. More especially, R^a and R^3 form where * indicates the nitrogen atom to which R^a is attached and ** indicates the carbon atom to which R^3 is attached.

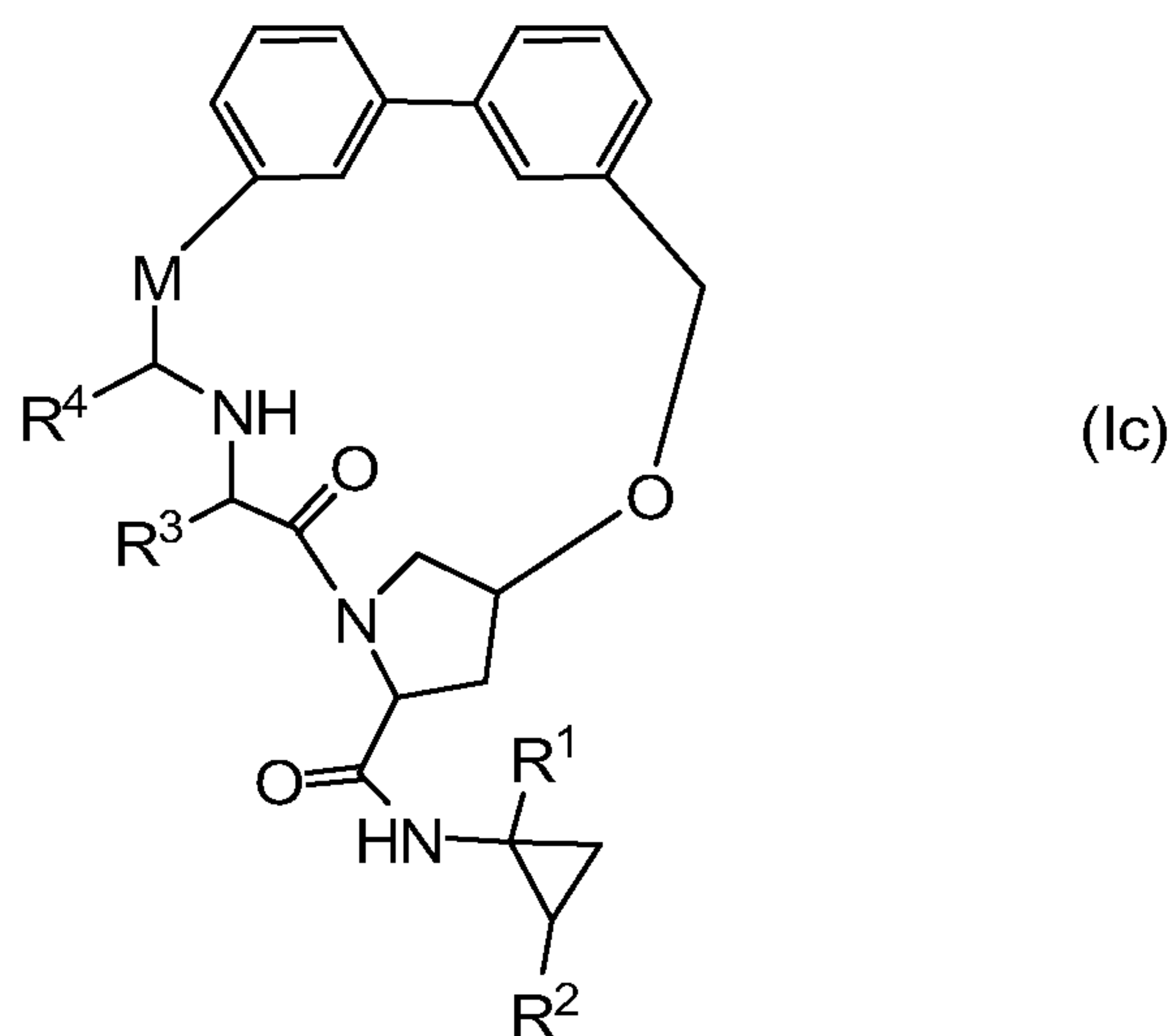
25 Preferably, R^4 is hydrogen, halo, hydroxy, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkoxy}$, $\text{C}_{3-8}\text{cycloalkyl}$ or phenyl, optionally substituted by halo or OR^6 , where R^6 is as hereinbefore defined. More preferably, R^4 is

hydrogen, C₁₋₆alkyl or C₃₋₈cycloalkyl, optionally substituted by halo. Most preferably, R⁴ is hydrogen or C₁₋₄alkyl, optionally substituted by fluoro or chloro. Especially, R⁴ is hydrogen or C₁₋₂alkyl, optionally substituted by fluoro. More especially, R⁴ is hydrogen, methyl, CF₃ or CF₂CF₃.

5 Preferably, M is C₂₋₈alkylene or C₂₋₈alkenylene, optionally substituted by halo or C₁₋₆alkyl. More preferably, M is C₄₋₇alkylene or C₄₋₇alkenylene, optionally substituted by fluoro, chloro or C₁₋₄alkyl. Most preferably, M is C₅₋₇alkylene or C₅₋₇alkenylene, optionally substituted by fluoro or C₁₋₂alkyl. Especially, M is pentylene, hexylene,



15 In another embodiment of the present invention, there is provided the compound of formula (Ic):



or a pharmaceutically acceptable salt thereof,

wherein R¹, R², R³, R⁴ and M are defined in relation to formula (I).

20 Preferably, R¹ is C(O)NR⁶SO₂R⁶ where R⁶ is as defined in relation to formula (I). More preferably, R¹ is C(O)NHSO₂R⁶ where R⁶ is as defined in relation to formula (I). Most preferably, R¹ is C(O)NHSO₂-C₃₋₆cycloalkyl. Especially, R¹ is C(O)NHSO₂-cyclopropyl.

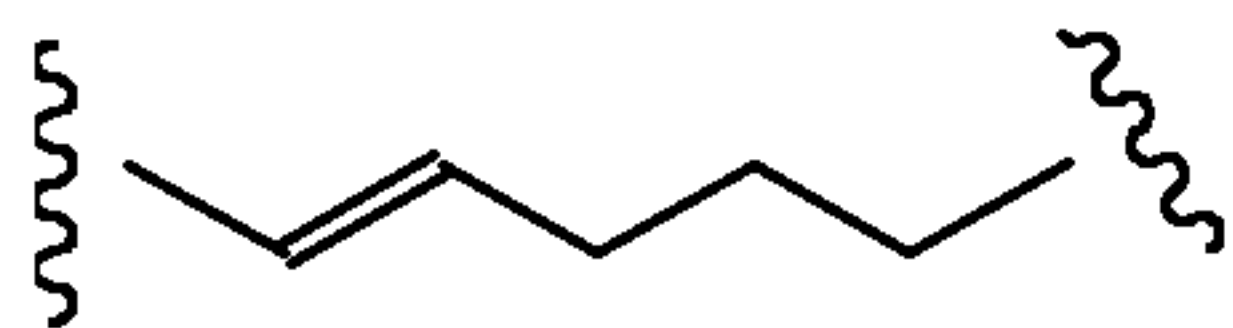
Preferably, R² is C₂₋₆alkenyl. More preferably, R² is -CH=CH₂.

Preferably, R³ is C₁₋₆alkyl or (CH₂)₀₋₃C₃₋₈cycloalkyl, optionally substituted by halo. More preferably, R³ is C₁₋₄alkyl or C₃₋₆cycloalkyl. Most preferably, R³ is C₃₋₄alkyl or C₅₋₆cycloalkyl.

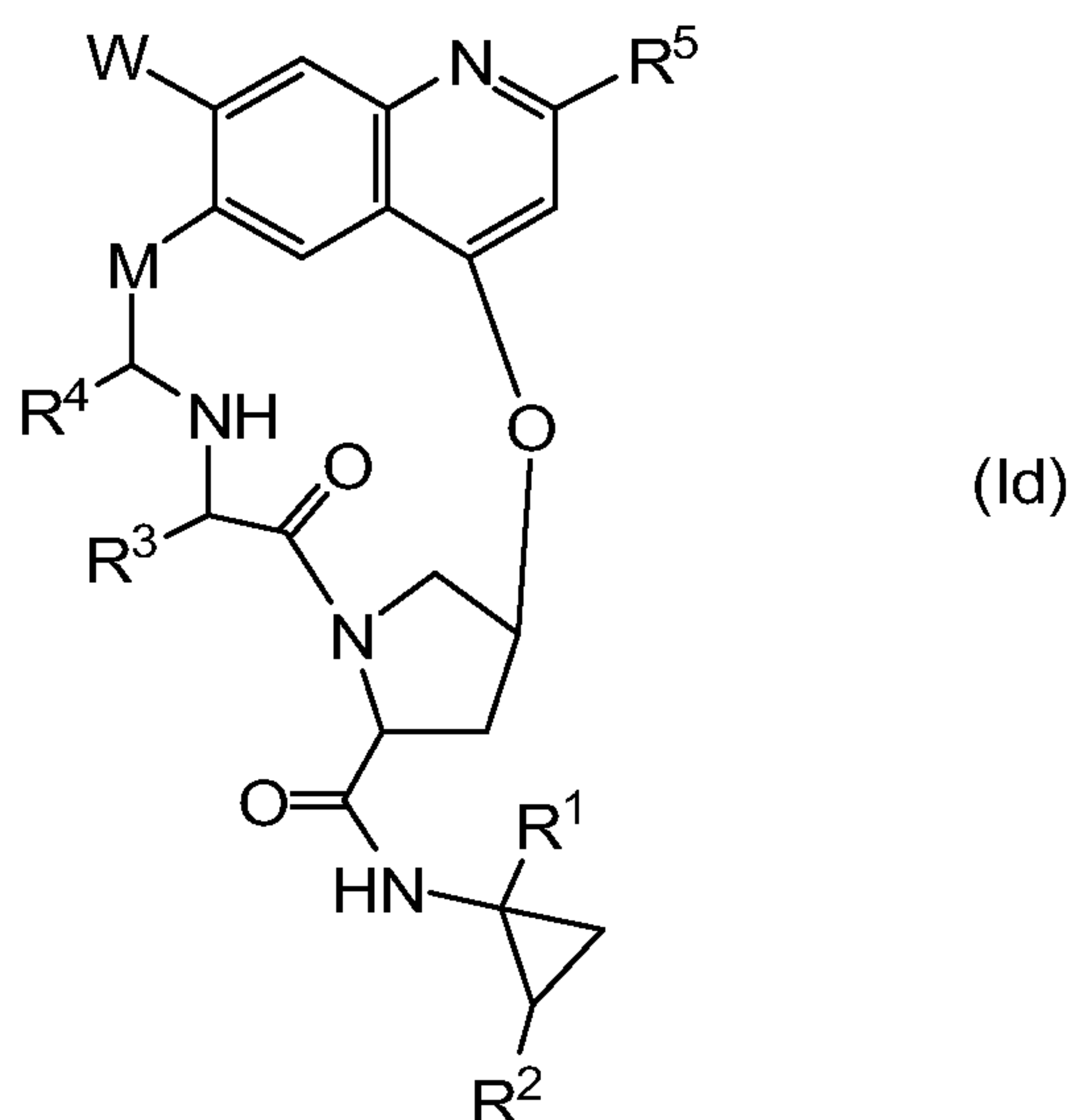
25 Especially, R³ is ^tbutyl or cyclohexyl.

Preferably, R^4 is hydrogen or C_{1-6} alkyl. More preferably, R^4 is hydrogen or C_{1-4} alkyl. Most preferably, R^4 is hydrogen or C_{1-2} alkyl. Especially, R^4 is hydrogen.

Preferably, M is C_{2-8} alkylene or C_{2-8} alkenylene, optionally substituted by halo or C_{1-6} alkyl. More preferably, M is C_{3-7} alkylene or C_{3-7} alkenylene, optionally substituted by C_{1-4} alkyl. Most preferably, M is C_{4-6} alkenylene or C_{4-6} alkenylene, optionally substituted by C_{1-2} alkyl. Especially, M is pentylene or



10 In another embodiment of the present invention, there is provided the compound of formula (Id):



or a pharmaceutically acceptable salt thereof,

wherein R^1 , R^2 , R^3 , R^4 , R^5 , M and W are defined in relation to formula (I).

15 Preferably, R^1 is $C(O)NR^6SO_2R^6$ where R^6 is as defined in relation to formula (I). More preferably, R^1 is $C(O)NHSO_2R^6$ where R^6 is as defined in relation to formula (I). Most preferably, R^1 is $C(O)NHSO_2-C_{3-6}$ cycloalkyl. Especially, R^1 is $C(O)NHSO_2$ -cycopropyl.

Preferably, R^2 is C_{2-6} alkenyl. More preferably, R^2 is $-CH=CH_2$.

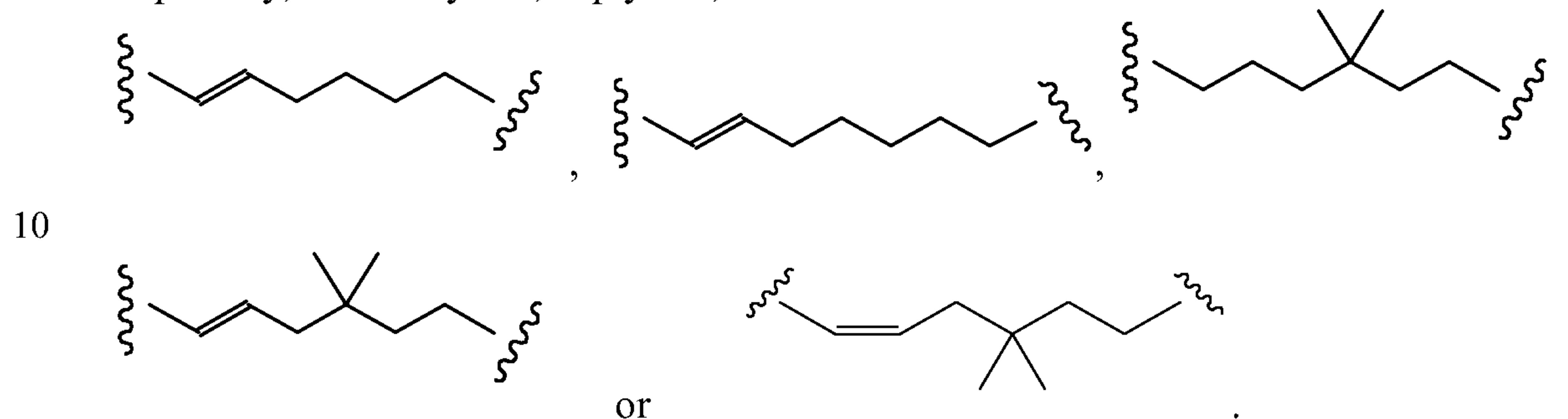
Preferably, R^3 is C_{1-6} alkyl or $(CH_2)_{0-3}C_{3-8}$ cycloalkyl, optionally substituted by halo. More preferably, R^3 is C_{1-4} alkyl or C_{3-6} cycloalkyl. Most preferably, R^3 is C_{3-4} alkyl or C_{5-6} cycloalkyl. Especially, R^3 is cyclohexyl.

Preferably, R^4 is hydrogen or C_{1-6} alkyl. More preferably, R^4 is hydrogen or C_{1-4} alkyl. Most preferably, R^4 is hydrogen or C_{1-2} alkyl. Especially, R^4 is hydrogen.

25 Preferably, R^5 is hydrogen, halo, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, aryl or heteroaryl. More preferably, R^5 is hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl or aryl. Most preferably, R^5 is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl or phenyl. Especially, R^5 is hydrogen, C_{1-2} alkyl, C_{5-6} cycloalkyl or phenyl. More especially, R^5 is phenyl.

Preferably, W is halo, OR⁶, C₁₋₆alkyl, CF₃, CO₂R⁶, CON(R⁶)₂, COR⁶ or NR⁶C(O)R⁶, where R⁶ is as hereinbefore defined. More preferably, W is fluoro, chloro, OC₁₋₆alkyl, CF₃, CO₂C₁₋₆alkyl, or CONHC₁₋₆alkyl. Most preferably, W is fluoro, chloro, OC₁₋₄alkyl or CF₃. Especially, W is OC₁₋₂alkyl. More especially, W is methoxy.

5 Preferably, M is C₃₋₁₂alkylene or C₃₋₁₂alkenylene, optionally substituted by halo or C₁₋₆alkyl. More preferably, M is C₄₋₈alkylene or C₄₋₈alkenylene, optionally substituted by fluoro or C₁₋₄alkyl. Most preferably, M is C₆₋₇alkylene or C₆₋₇alkenylene, optionally substituted by C₁₋₂alkyl. Especially, M is hexylene, heptylene,



When any variable occurs more than one time in formula (I) or in any substituent, its definition on each occurrence is independent of its definition at every other occurrence.

15 As used herein, the term "alkyl" as a group or part of a group refers to any linear or branched chain alkyl group having a number of carbon atoms in the specified range. Thus, for example, "C₁₋₆alkyl" refers to all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and iso-propyl, ethyl and methyl. As another example, "C₁₋₄alkyl" refers to n-, iso-, sec- and t-butyl, n- and iso-propyl, ethyl and methyl.

20 The term "alkoxy" represents any linear or branched chain alkyl group having a number of carbon atoms in the specified range and attached through an oxygen bridge. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, i-butoxy and t-butoxy.

25 The term "alkenyl" as a group or part of a group refers to any linear or branched chain alkyl group containing at least one double bond, which may occur at any point along the chain, and having a number of carbon atoms in the specified range. E- and Z- forms are both included, where applicable. Examples of suitable alkenyl groups include vinyl, allyl, butenyl and pentenyl.

30 The term "cycloalkyl" refers to any cyclic alkyl ring having a number of carbon atoms in the specified range. Examples of suitable cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The terms "alkylene" and "alkenylene" as a group or part of a group refer to the groups "alkyl" and "alkenyl" respectively, when they are divalent, i.e. attached at two atoms.

The term "halogen" or "halo" means fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo and iodo, respectively).

The term "aryl" as a group or part of a group means a carbocyclic aromatic ring. Examples of suitable aryl groups include phenyl and naphthyl.

The term "Het" as a group or part of a group means a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1 to 4 heteroatoms selected from N, O and S.

5 The term "heteroaryl" as a group or part of a group means a 5- to 10-membered heteroaromatic ring system containing 1 to 4 heteroatoms selected from N, O and S. Examples of such groups include pyrrolyl, furanyl, thienyl, pyridyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, oxadiazolyl, thiadiazolyl, triazinyl, tetrazolyl, indolyl, benzothienyl, benzimidazolyl, benzofuryl, quinolyl and isoquinolyl.

10 Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heteroaryl ring described as containing from "1 to 3 heteroatoms" means the ring can contain 1, 2, or 3 heteroatoms.

Where a compound or group is described as "optionally substituted" one or more substituents may be present. Furthermore, optional substituents may be attached to the
15 compounds or groups which they substitute in a variety of ways, either directly or through a connecting group of which the following are examples: amine, amide, ester, ether, thioether, sulfonamide, sulfamide, sulfoxide, urea, thiourea and urethane. As appropriate an optional substituent may itself be substituted by another substituent, the latter being connected directly to the former or through a connecting group such as those exemplified above.

20 Specific compounds within the scope of this invention include those named in the Examples and Table hereinbelow and their pharmaceutically acceptable salts.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts.
25 Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulfonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulfuric acid. Salts of amine groups may also comprise
30 quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

35 The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

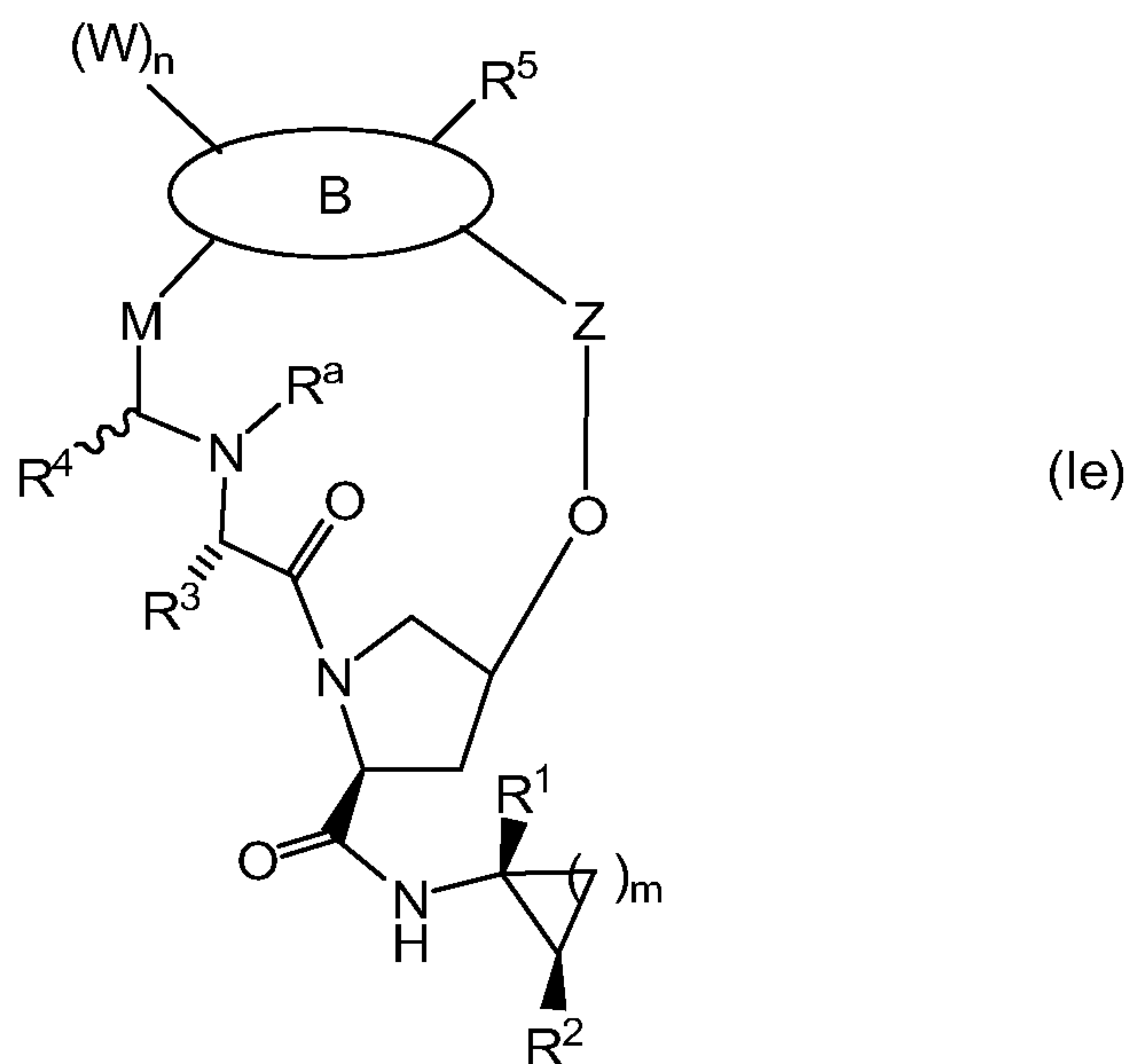
The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulfate ester, or reduction or oxidation of a susceptible functionality.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The present invention also includes within its scope any enantiomers, diastereomers, geometric isomers and tautomers of the compounds of formula (I). It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the invention.

The preferred compounds of the present invention will have the stereochemistry as shown in formula (Ie):



The present invention further provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treatment or prevention of infection by hepatitis C virus in a human or animal.

A further aspect of the invention provides a pharmaceutical composition comprising a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier. The composition may be in any suitable

form, depending on the intended method of administration. It may for example be in the form of a tablet, capsule or liquid for oral administration, or of a solution or suspension for administration parenterally.

The pharmaceutical compositions optionally also include one or more other agents for the treatment of viral infections such as an antiviral agent, or an immunomodulatory agent such as α -, β - or γ -interferon.

In a further aspect, the invention provides a method of inhibiting hepatitis C virus protease and/or of treating or preventing an illness due to hepatitis C virus, the method involving administering to a human or animal (preferably mammalian) subject suffering from the condition a therapeutically or prophylactically effective amount of the pharmaceutical composition described above or of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof. "Effective amount" means an amount sufficient to cause a benefit to the subject or at least to cause a change in the subject's condition.

The term "subject" (alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The dosage rate at which the compound is administered will depend on a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age of the patient, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition and the host undergoing therapy. Suitable dosage levels may be of the order of 0.02 to 5 or 10 g per day, with oral dosages two to five times higher. For instance, administration of from 10 to 50 mg of the compound per kg of body weight from one to three times per day may be in order. Appropriate values are selectable by routine testing. The compound may be administered alone or in combination with other treatments, either simultaneously or sequentially. For instance, it may be administered in combination with effective amounts of antiviral agents, immunomodulators, anti-infectives or vaccines known to those of ordinary skill in the art. It may be administered by any suitable route, including orally, intravenously, cutaneously and subcutaneously. It may be administered directly to a suitable site or in a manner in which it targets a particular site, such as a certain type of cell. Suitable targeting methods are already known.

An additional aspect of the invention provides a method of preparation of a pharmaceutical composition, involving admixing at least one compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable adjuvants, diluents or carriers and/or with one or more other therapeutically or prophylactically active agents.

As noted above, the present invention also relates to a method of inhibiting HCV NS3 protease, inhibiting HCV replication, or preventing or treating HCV infection with a compound of the present invention in combination with one or more therapeutic agents and a pharmaceutical composition comprising a compound of the present invention and one or more therapeutic agents

selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent. Such therapeutic agents active against HCV include ribavirin, levovirin, viramidine, thymosin alpha-1, interferon- β , interferon- α , pegylated interferon- α (peginterferon- α), a combination of interferon- α and ribavirin, a combination of peginterferon- α and ribavirin, a
5 combination of interferon- α and levovirin, and a combination of peginterferon- α and levovirin. Interferon- α includes recombinant interferon- α 2a (such as Roferon interferon available from Hoffmann-LaRoche, Nutley, NJ), pegylated interferon- α 2a (PegasysTM), interferon- α 2b (such as Intron-A interferon available from Schering Corp., Kenilworth, NJ), pegylated interferon- α 2b (PegIntronTM), a recombinant consensus interferon (such as interferon alfacon-1), and a purified
10 interferon- α product. Amgen's recombinant consensus interferon has the brand name Infergen®. Levovirin is the L-enantiomer of ribavirin which has shown immunomodulatory activity similar to ribavirin. Viramidine represents an analog of ribavirin disclosed in WO 01/60379 (ICN Pharmaceuticals). In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course
15 of therapy or concurrently in divided or single combination forms.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS3 serine protease. HCV NS3 protease inhibitors are disclosed in WO 98/22496, WO 98/46630, WO 99/07733, WO 99/07734, WO 99/38888, WO 99/50230, WO 99/64442, WO 00/09543, WO 00/59929, GB-
20 2337262, WO 02/48116, WO 02/48172, and U.S. Patent No. 6,323,180.

Ribavirin, levovirin, and viramidine may exert their anti-HCV effects by modulating intracellular pools of guanine nucleotides via inhibition of the intracellular enzyme inosine monophosphate dehydrogenase (IMPDH). Thus, inhibition of IMPDH represents another useful target for the discovery of inhibitors of HCV replication. Therefore, the compounds of the
25 present invention may also be administered in combination with an inhibitor of IMPDH, such as VX-497, disclosed in WO 97/41211 and WO 01/00622 (Vertex); another IMPDH inhibitor, such as that disclosed in WO 00/25780 (Bristol-Myers Squibb); or mycophenolate mofetil [see A.C. Allison and E.M. Eugui, Agents Action, 44 (Suppl.): 165 (1993)].

For the treatment of HCV infection, the compounds of the present invention may also be
30 administered in combination with the antiviral agent amantadine (1-aminoadamantane) [see J. Kirschbaum, Anal. Profiles Drug Subs. 12: 1-36 (1983)].

The compounds of the present invention may also be combined for the treatment of HCV infection with antiviral 2'-C-branched ribonucleosides disclosed in R. E. Harry-O'kuru, et al., J. Org. Chem., 62: 1754-1759 (1997); M. S. Wolfe, et al., Tetrahedron Lett., 36: 7611-7614
35 (1995); U.S. Patent No. 3,480,613; WO 01/90121; WO 01/92282; WO 02/32920; WO 04/002999; WO 04/003000; and WO 04/002422. Such 2'-C-branched ribonucleosides include 2'-C-methyl-cytidine, 2'-C-methyl-uridine, 2'-C-methyl-adenosine, 2'-C-methyl-guanosine, and 9-(2-C-methyl- β -D-ribofuranosyl)-2,6-diaminopurine, and the corresponding amino acid ester of the

ribose C-2', C-3', and C-5' hydroxyls and the corresponding optionally substituted cyclic 1,3-propanediol esters of the 5'-phosphate derivatives.

The compounds of the present invention may also be combined for the treatment of HCV infection with other nucleosides having anti-HCV properties, such as those disclosed in WO 02/51425 (Mitsubishi Pharma Corp.); WO 01/79246, WO 02/32920 and WO 02/48165 (Pharmasset, Ltd.); WO 01/68663 (ICN Pharmaceuticals); WO 99/43691; WO 02/18404 (Hoffmann-LaRoche); U.S. 2002/0019363; WO 02/100415; WO 03/026589; WO 03/026675; WO 03/093290; US 2003/0236216; US 2004/0006007; WO 04/011478; WO 04/013300; US 2004/0063658; and WO 04/028481.

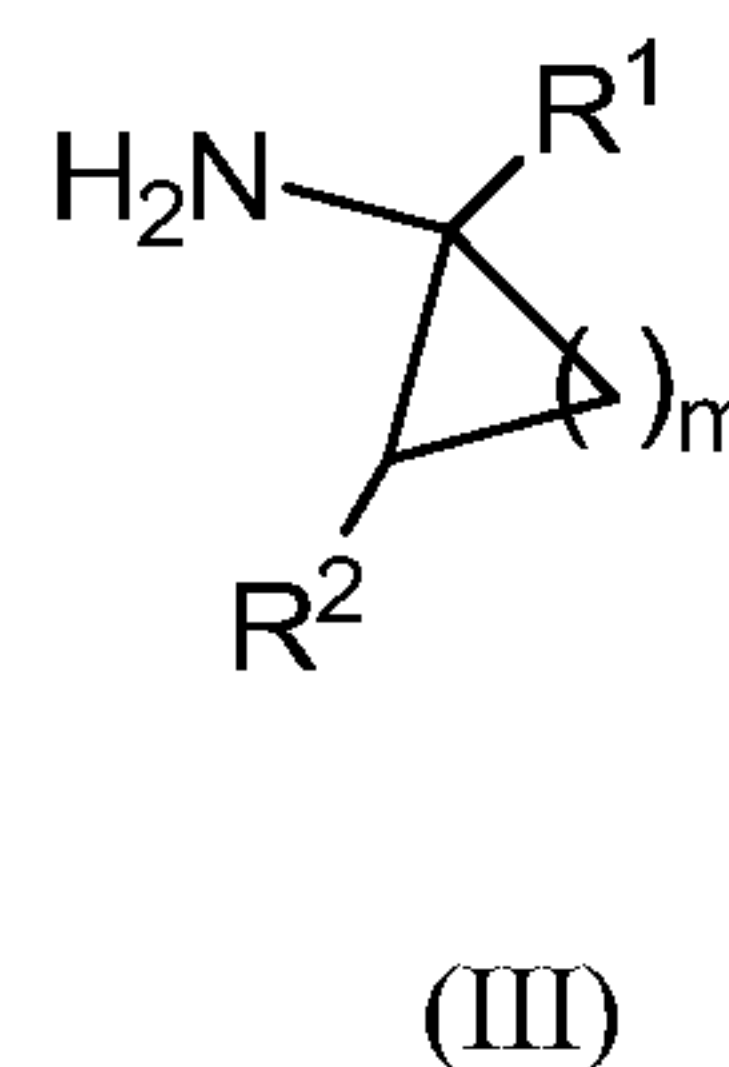
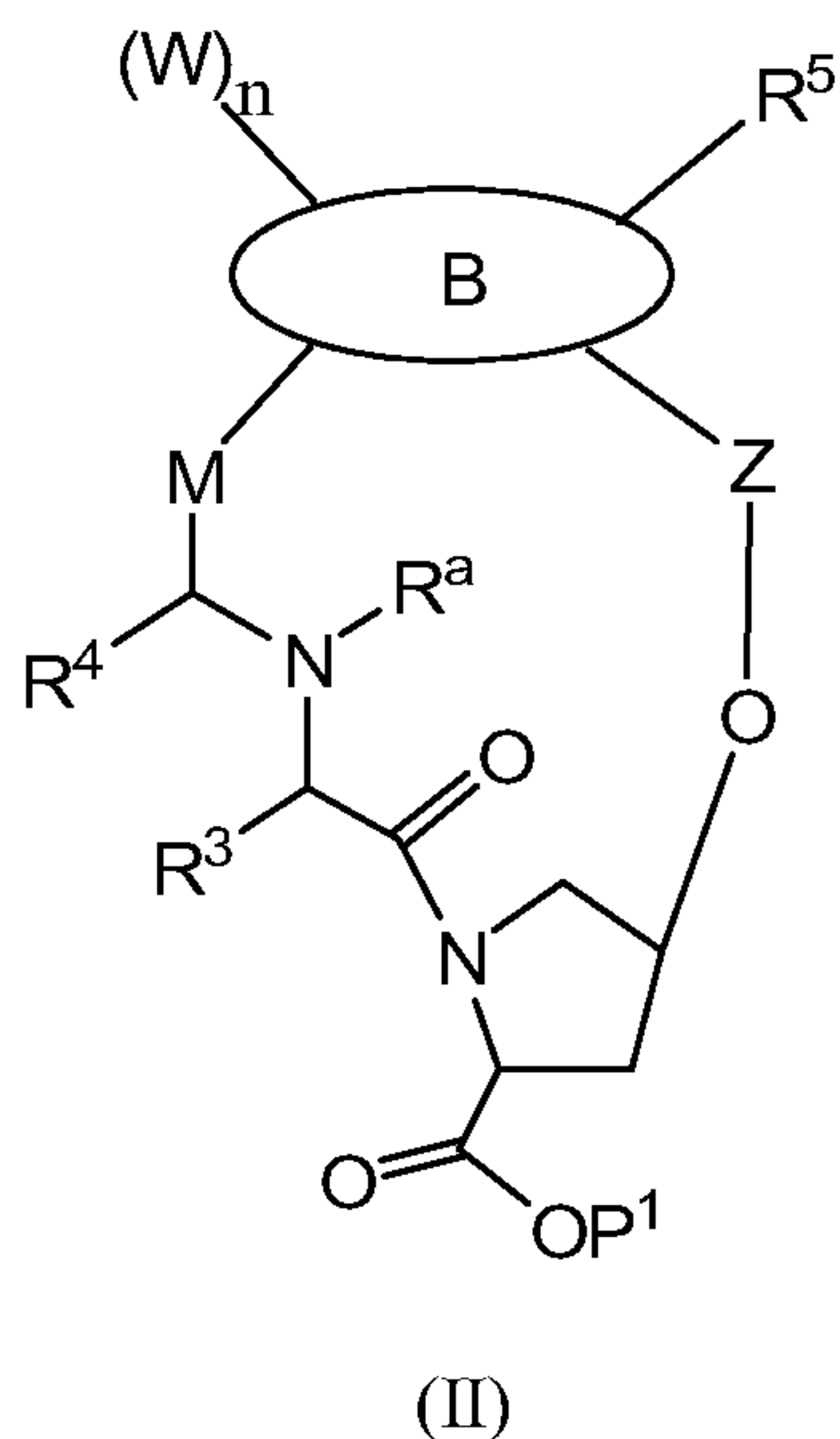
For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS5B polymerase. Such HCV NS5B polymerase inhibitors that may be used as combination therapy include those disclosed in WO 02/057287, US 6,777,395, WO 02/057425, US 2004/0067901, WO 03/068244, WO 2004/000858, WO 04/003138 and WO 2004/007512. Other such HCV polymerase inhibitors include valopicitabine (NM-283; Idenix) and 2'-F-2'-beta-methylcytidine (see also WO 2005/003147, assigned to Pharmasset, Ltd.).

The compounds of the present invention may also be combined for the treatment of HCV infection with non-nucleoside inhibitors of HCV polymerase such as those disclosed in WO 01/77091 (Tularik, Inc.); WO 01/47883 (Japan Tobacco, Inc.); WO 02/04425 (Boehringer Ingelheim); WO 02/06246, WO 03/062211, WO 2004/087714, WO 2004/110442, WO 2005/034941, WO 2005/023819, WO2006/029912, WO 2006/008556, WO 2006/027628, GB2430621, WO2006/046030, WO2006/046039, WO2006/119975, WO2007/028789 and WO2007/029029 (all Istituto di Ricerche di Biologia Molecolare P. Angeletti S.p.A.); WO 02/20497; WO 2005/016927 (in particular JTK003), and WO 2005/080399 (Japan Tobacco, Inc.); WO 2006/020082 (Bristol-Myers Squibb Company); and HCV-796 (Viropharma Inc.).

The present invention also provides a process for the preparation of compounds of formula (I).

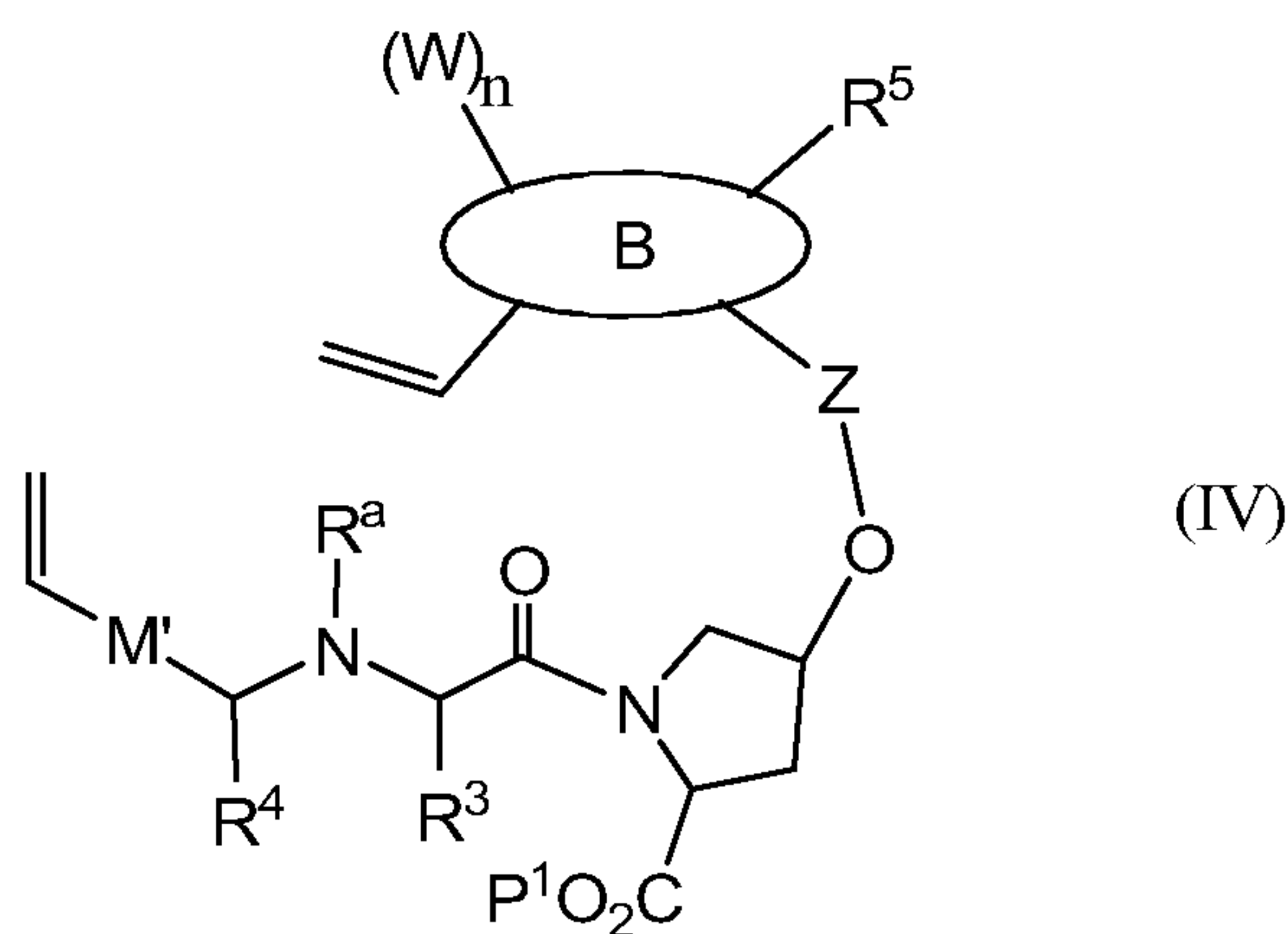
According to a general process (a), compounds of formula (I) may be prepared by the coupling of the ester of formula (II) with the amine of formula (III):

- 16 -



where m , n , R^1 , R^2 , R^3 , R^4 , R^5 , R^a , M , W , Z and ring B are as defined in relation to formula (I) and P^1 is C_{1-6} alkyl, such as methyl. The ester (II) is first hydrolysed under standard conditions (e.g. in the presence of a base, such as lithium hydroxide, in a solvent, such as THF/water, MeOH/water or dioxane/water) to give the free acid. The coupling reaction is then conveniently carried out in the presence of a coupling reagent, such as TBTU or HATU, and a base, such as diisopropylethylamine or triethylamine, in a solvent. Suitable solvents include DMF and dichloromethane. Optionally, a dehydrating agent, such as DMAP, may also be used.

The compound of formula (II) where M has 4 or more carbon atoms in the tether and one or more double bonds may be prepared by the internal ring closure of the diene of formula (IV):



where n , R^3 , R^4 , R^5 , R^a , W , Z and ring B are as defined in relation to formula (I), P^1 is as defined in relation to formula (II) and M' is a suitable precursor moiety of group M in formula (II) which can be converted into the corresponding moiety of M during the ring closure or after it using methods described in the accompanying Schemes and Examples or known to the person skilled in the art. The reaction is conveniently carried out in the presence of a metathesis catalyst, such as Zhan catalyst [dichloro(5-chloro-2-isopropoxy benzylidene)(1,3-dimethylimidazolidin-2-ylidene)ruthenium], preferably at raised temperature or under microwave irradiation, in a suitable

solvent such as dichloromethane or 1,2-dichloroethane. The resultant ring double bond may be hydrogenated to give a further compound of formula (II). The hydrogenation is preferably carried out in the presence of a suitable catalyst, such as palladium on carbon, in a suitable solvent, such as methanol or methanol/ethyl acetate mixture.

5 Compounds of formulae (II), (III) and (IV) are either well known in the art or may be prepared by conventional methodology well known to one of ordinary skill in the art using, for instance, procedures described in the accompanying Schemes and Examples, or by alternative procedures which will be readily apparent.

10 Further details of suitable procedures will be found in the accompanying Schemes and Examples. For instance compounds of formula (I) can be converted into other compounds of formula (I) using synthetic methodology well known in the art.

15 Thus, for instance, the compound of formula (I) where M is unsaturated may be converted into the compound of formula (I) where M is saturated by hydrogenation, preferably in the presence of a suitable catalyst, such as palladium on carbon, in a suitable solvent, such as methanol/ethyl acetate mixture.

20 Furthermore, the compound of formula (I) where R^a is C₁₋₄alkyl may be prepared from the compound of formula (I) where R^a is hydrogen by alkylation. The reaction may be carried out in the presence of a mild base, such as sodium cyanoborohydride, and a catalyst, such as zinc (II) chloride, in a suitable solvent, such as methanol. The alkyl source is formaldehyde or CH₃(CH₂)₀₋₂CHO.

25 During any of the described synthetic sequences, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd ed., 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

30 The compounds of the present inventions are useful in the inhibition of HCV protease (e.g., HCV NS3 protease) and the prevention or treatment of infection by HCV. For example, the compounds of this invention are useful in treating infection by HCV after suspected past exposure to HCV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

35 The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HCV protease, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

The HCV NS3 protease inhibitory activity of the present compounds may be tested using assays known in the art. One such assay is HCV NS3 protease time-resolved fluorescence (TRF) assay as described as follows:

5 HCV NS3 protease time-resolved fluorescence (TRF) assay

The NS3 protease TRF assay was performed in a final volume of 100 μ l in assay buffer containing 50 mM HEPES, pH 7.5, 150 mM NaCl, 15 % glycerol, 0.15 % TritonTM X-100, 10 mM DTT, and 0.1 % PEG 8000. The NS3 protease was pre-incubated with various concentrations of inhibitors for 10-30 minutes. The peptide substrate for the assay is Ac-C(Eu)-DDMEE-Abu-[COO]-XSAK(QSY7)-NH₂, where Eu is an europium-labeled group, Abu is 1-aminobutanoic acid which connects an ester linkage with 2-hydroxy propanoic acid (X). Hydrolysis of the peptide by NS3 protease activity causes in separation of the fluorophore from the quencher, resulting in an increase in fluorescence. Activity of the protease was initiated by adding the TRF peptide substrate (final concentration 50-100 nM). The reaction was quenched after 1 hour at room temperature with 100 μ l of 500 mM MES, pH 5.5. Product fluorescence was detected using either a Victor V2 or Fusion fluorimeter (Perkin Elmer Life and Analytical Sciences) with excitation at 340 nm and emission at 615 nm with 50-400 μ s delay. Testing concentrations of different enzyme forms was selected with a signal to background ratio of 10-30. The inhibition constants were derived using a four-parameter fit.

20 Other examples of such assays are described in e.g., International patent publication WO2005/046712. Compounds useful as HCV NS3 protease inhibitors would have a K_i less than 50 μ M, more preferably less than 10 μ M, most preferably less than 1 μ M, especially less than 100 nM, and more especially less than 50 nM.

25 The following schemes and examples serve to illustrate the invention and its practice.

¹H NMR spectra were recorded on Bruker AM series spectrometers operating at (reported) frequencies between 300 and 600 MHz. Chemical shifts (δ) for signals corresponding to non-exchangeable protons (and exchangeable protons where visible) are recorded in parts per million (ppm) relative to tetramethylsilane and are measured using the residual solvent peak as reference. Signals are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad, and combinations thereof); coupling constant(s) in Hertz (Hz); number of protons. Mass spectral (MS) data were obtained on a Perkin Elmer API 100, or Waters MicroMassTM ZQ, operating in negative (ES⁻) or positive (ES⁺) ionization mode and results are reported as the ratio of mass over charge (m/z). Preparative scale HPLC separations were carried out on a Waters MicromassTM System incorporating a 2525 pump module, a MicromassTM ZMD detector and a 2767 collection module, under Fraction Linx software or on a Shimadzu preparative system.

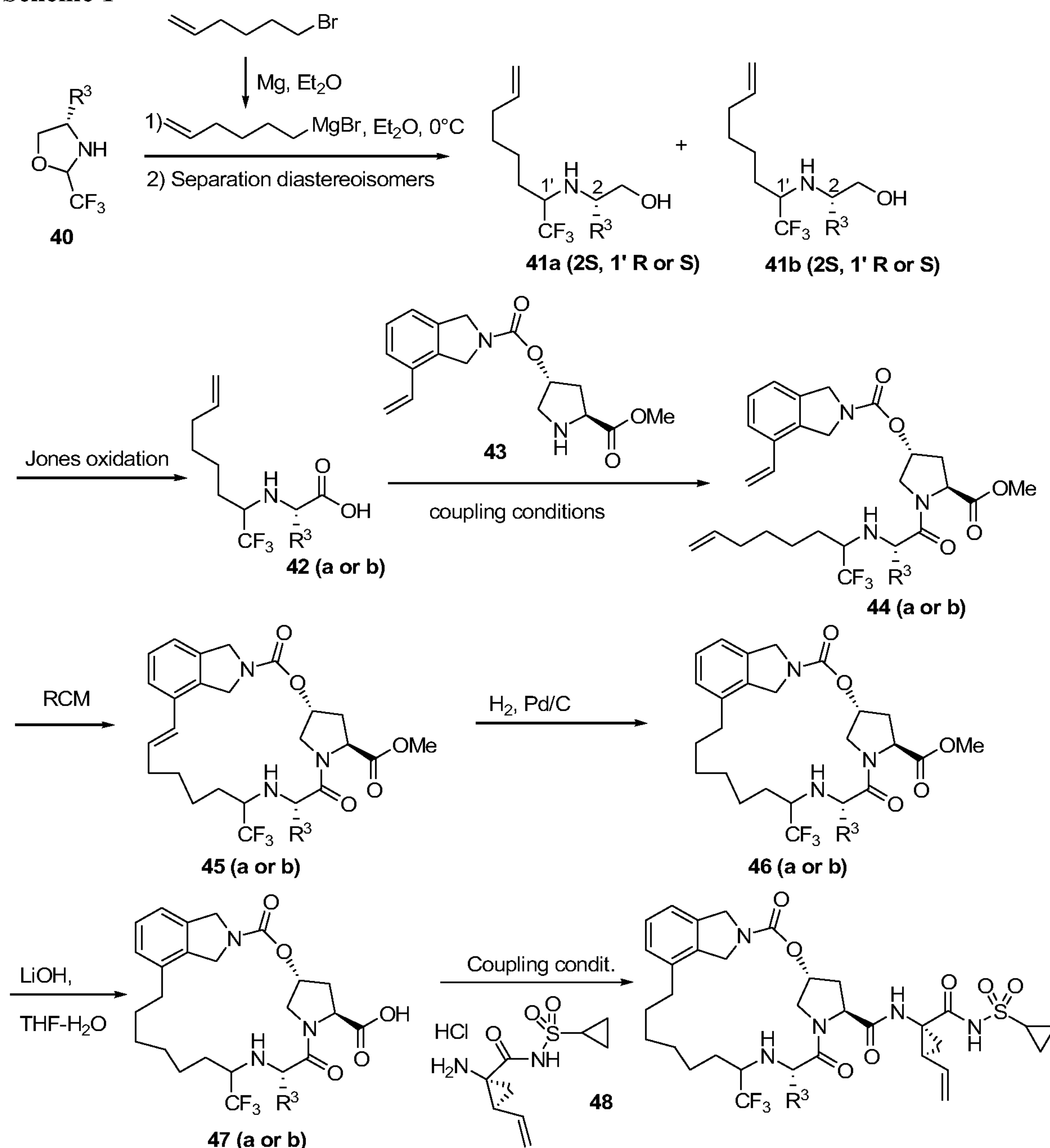
The following abbreviations are used in the examples, the schemes and the tables:

AcOH: acetic acid; dioxan(e): 1,4-dioxane; DIPEA or ⁱPr₂NEt: diisopropylethylamine; DCE: 1,2-dichloroethane; DCM: dichloromethane; DMAP: 4-dimethylaminopyridine; DMF: *N,N*-dimethylformamide; DMSO: dimethylsulfoxide; EDC: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; Et₂O: diethyl ether; EtOAc: ethyl acetate; eq.: equivalent(s); h: hour(s);

5 HATU: O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; MeCN: acetonitrile; MeOH: methanol; min: minute(s); MS: mass spectrum; MTBE: *tert* Butyl methyl ether; PCC: pyridinium chlorochromate; PE: petroleum ether 30/60; quant.: quantitative; RP-HPLC: reversed phase high-performance liquid chromatography; RP-MS-HPLC: mass-guided reversed phase high-pressure liquid chromatography; RT: room temperature; sat. aq.: saturated

10 aqueous; TBTU: O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate; TEA: triethylamine; THF: tetrahydrofuran.

Scheme 1



Compound 1: (5R,7S,10S,12R or S)-N-((1R,2S)-1-[(cyclopropylsulfonyl)amino]carbonyl}-
2-vinylcyclopropyl)-10-isopropyl-3,9-dioxo-12-(trifluoromethyl)-
6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1H,5H-2,22:5,8-dimethano-4,2,8,11-
benzoxatriazacycloicosine-7-carboxamide

Step 1: (4S)-4-isopropyl-2-(trifluoromethyl)-1,3-oxazolidine **40** (R^3 = isopropyl)

The oxazolidine **40** was obtained as a 7:3 mixture of diastereoisomers prepared as described in Organic Letters 2004, 641.

Step 2: (2S)-3-methyl-2-{[(1R or S)-1-(trifluoromethyl)hept-6-en-1-yl]amino}butan-1-ol **41a** ($R^3 = \text{isopropyl}$)

A small amount of a solution (3M) of 6-bromohex-1-ene in dry Et₂O was added dropwise to magnesium turnings (1 eq.). A small crystal of iodine was added followed by the remainder of the
 5 bromide solution. The reaction mixture was cooled to -78°C and (4S)-4-isopropyl-2-(trifluoromethyl)-1,3-oxazolidine **40** (1 eq.) dissolved in Et₂O (3M) was added dropwise. The reaction mixture was stirred at 0°C for 1h and then quenched with aqueous HCl (1N). Aqueous NaOH (1N) was added until pH = 7. The two layers were separated and the aqueous phase was diluted with brine and extracted with CH₂Cl₂. The organic layers were joined, washed with brine,
 10 dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (EtOAc/PE gradient from 5:95 to 20:80) to afford the title compound as a mixture of two diastereoisomers (50%) that were separated by RP-HPLC (stationary phase: column Waters Symmetry prep. C18, 7 µm, 19 x 300 mm, mobile phase: MeCN/H₂O containing 0.1 % TFA). Fractions containing the desired compounds as pure
 15 diastereoisomers were combined and freeze dried to afford **41a** (second eluting) and **41b** (first eluting) (67%, **41a** : **41b** = 1 : 0.14).

41a) ¹H NMR (300 MHz, CDCl₃, 300 K) δ 5.75 (ddt, J 17.0, 10.2, 6.7, 1H), 5.47-5.17 (bs, 1H), 5.06-4.90 (m, 2H), 3.96-3.70 (m, 3H), 3.24-3.09 (m, 1H) 2.13-1.74 (m, 5H), 1.60-1.34 (m, 4H), 1.07 (d, J 6.9, 3H), 1.01 (d, J 6.9, 3H). MS (ES⁺) *m/z* 268 (M+H)⁺.

20
Step 3: (2S)-3-methyl-2-{[(1R or S)-1-(trifluoromethyl)hept-6-en-1-yl]amino}butanoic acid **42a** ($R^3 = \text{isopropyl}$)
 To a solution (0.13 M) of (2S)-3-methyl-2-{[1-(trifluoromethyl)hept-6-en-1-yl]amino}butan-1-ol **41a** in acetone cooled to 0°C, Jones reagent (8N) (5 eq.) was added. The reaction mixture was
 25 stirred at 0°C for 15 min at RT overnight then was diluted with water and stirred at RT for 20 min. Aqueous NaOH (1N) was added to reach pH=5 and the mixture was extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the crude product, which was used in the following step without further purification. MS (ES⁺) *m/z* 282 (M+H)⁺.

30
Step 4: methyl N-[(1R or S)-1-(trifluoromethyl)hept-6-en-1-yl]-L-valyl-(4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}-L-prolinate **44a** ($R^3 = \text{isopropyl}$)

To a stirred mixture of (2S)-3-methyl-2-{[(1R or S)-1-(trifluoromethyl)hept-6-en-1-yl]amino}butanoic acid **42a** in CH₂Cl₂ (0.09M) were added *i*Pr₂EtN (2.4 eq.), TBTU (1.2 eq.)
 35 and after 5 min (2S,4R)-2-(methoxycarbonyl)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}pyrrolidinium chloride **43** (1 eq.). The mixture was stirred at RT overnight. Aqueous HCl (1N) was added, the organic layer was separated and washed with sat. aq. NaHCO₃ and brine, dried over Na₂SO₄ and filtered. Evaporation under reduced pressure afforded a residue, which was purified by flash chromatography on silica gel (EtOAc/PE gradient from 5:95

to 15:85) to afford compound **44a** as a white foam (24% after two steps). MS (ES⁺) *m/z* 580 (M+H)⁺.

Step 5: methyl (5*R*,7*S*,10*S*,12*R* or *S*,17*E*)-10-isopropyl-3,9-dioxo-12-(trifluoromethyl)-
 5 6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-
benzoxatriazacycloicosine-7-carboxylate **45a** (R³ = isopropyl)

Zhan catalyst I (0.15 eq.) was added to methyl N-[1-(trifluoromethyl)hept-6-en-1-yl]-L-valyl-
 (4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate **44a** in DCE (0.016 M)
 and the mixture was refluxed for 45 min. Volatiles were evaporated under reduced pressure
 10 affording a residue, which was used in the following step without further purification. MS (ES⁺)
m/z 552 (M+H)⁺.

Step 6: methyl (5*R*,7*S*,10*S*,12*R* or *S*)-10-isopropyl-3,9-dioxo-12-(trifluoromethyl)-
 15 6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-
benzoxatriazacycloicosine-7-carboxylate **46a** (R³ = isopropyl)

Palladium 10% on carbon (20% w/w) and methyl (5*R*,7*S*,10*S*,12*R* or *S*,17*E*)-10-isopropyl-3,9-
 dioxo-12-(trifluoromethyl)-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-
 4,2,8,11-benzoxatriazacycloicosine-7-carboxylate **45a** in methanol (0.035M) were stirred under a
 hydrogen atmosphere overnight. Solids were filtered over celite and the resulting solution was
 20 evaporated under reduced pressure. The residue was purified by flash chromatography on silica
 gel (EtOAc/PE gradient from 1:9 to 3:7) to afford compound **46a** as a white foam (70% over two
 steps). MS (ES⁺) *m/z* 554 (M+H)⁺.

Step 7: (5*R*,7*S*,10*S*,12*R* or *S*)-10-isopropyl-3,9-dioxo-12-(trifluoromethyl)-
 25 6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-
benzoxatriazacycloicosine-7-carboxylic acid **47a** (R³ = isopropyl)

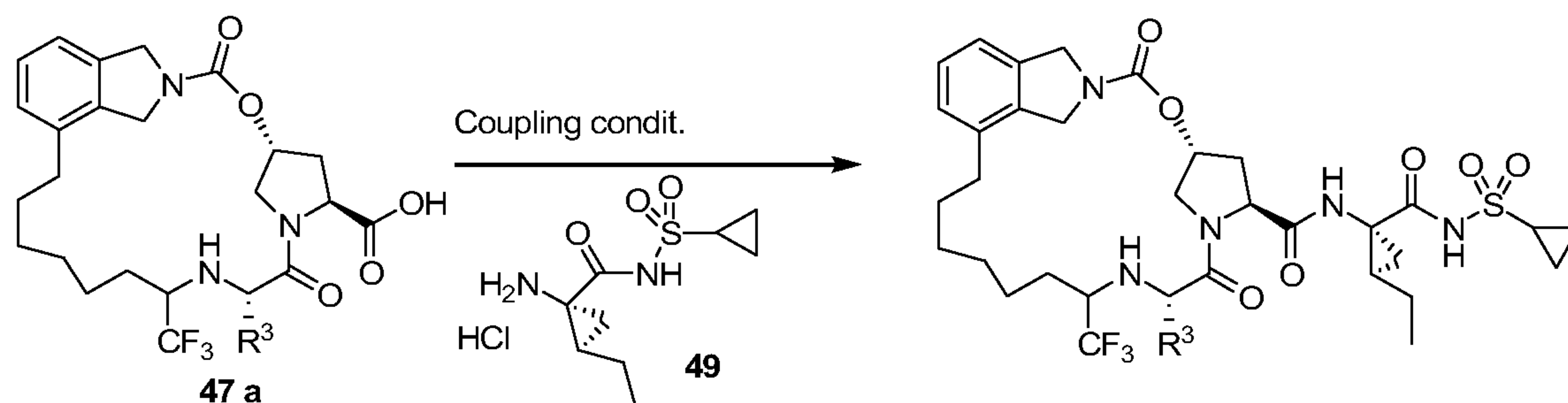
Lithium hydroxide (3 eq.) was added to a stirred mixture of methyl (5*R*,7*S*,10*S*, 12*R* or *S*)-10-
 isopropyl-3,9-dioxo-12-(trifluoromethyl)-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-
 2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxylate **46a** in THF and water (2/1
 30 v/v, 0.01 M) and the mixture was stirred at RT overnight. Aqueous HCl (1N) was added to reach
 pH = 6 and the mixture extracted with EtOAc. The organic layer was separated, dried over Na₂SO₄,
 filtered and concentrated to obtain the crude product **47a** which was used in the following step
 without further purification. MS (ES⁺) *m/z* 540 (M+H)⁺.

Step 8: (5*R*,7*S*,10*S*,12*R* or *S*)-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-
 35 vinylcyclopropyl)-10-isopropyl-3,9-dioxo-12-(trifluoromethyl)-6,7,9,10,11,12,13,14,15,16,17,18-
dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide **1**

To a stirred mixture of (5*R*,7*S*,10*S*)-10-isopropyl-3,9-dioxo-12-(trifluoromethyl)-
 6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-

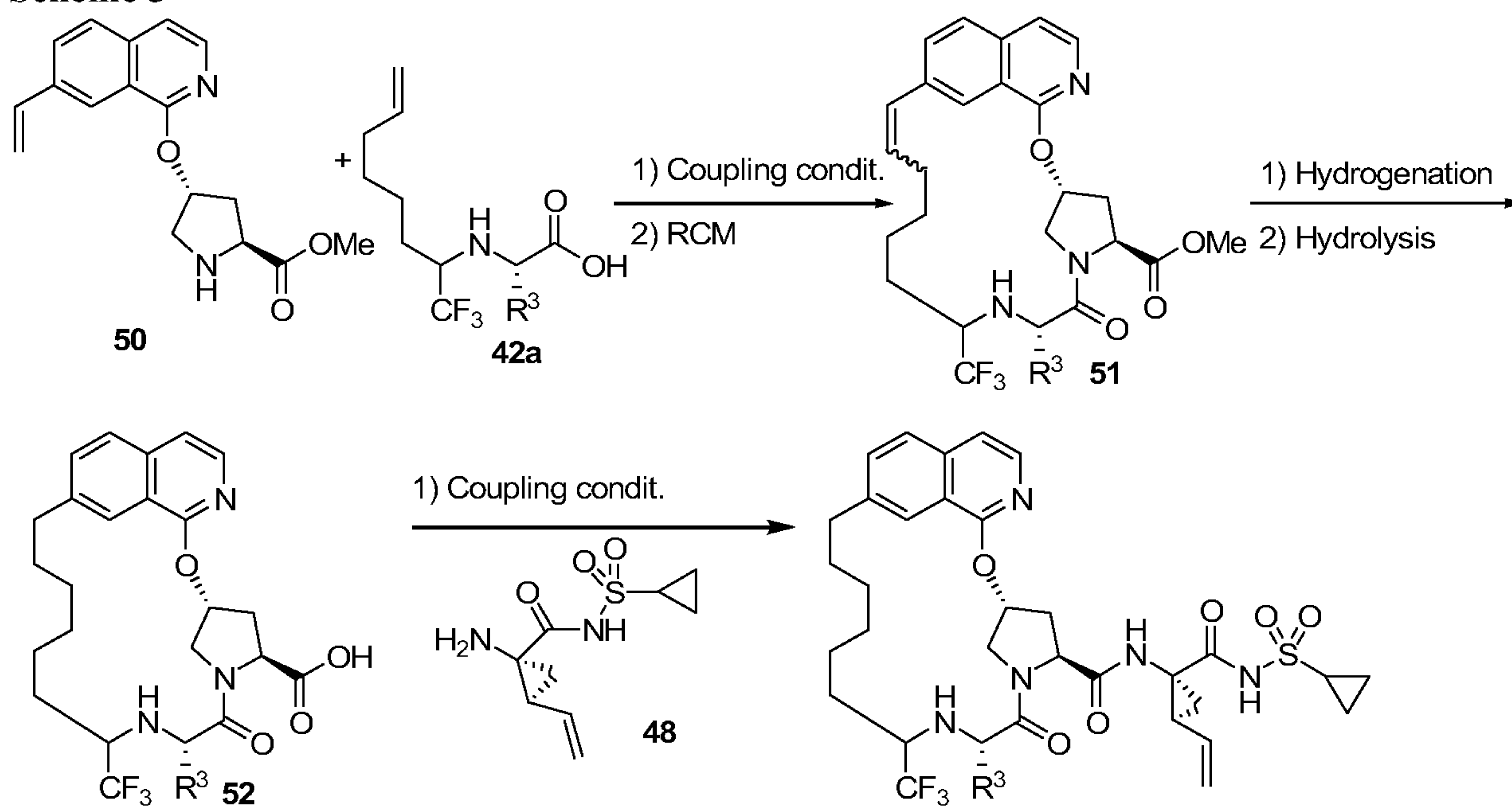
benzoxatriazacycloicosine-7-carboxylic acid **47a** in CH₂Cl₂ (5mM) were added *i*-Pr₂EtN (2.4 eq), TBTU (1.2 eq.) and after 5 min (1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropanaminium chloride **48** (prepared as described in WO 03/099274) (1.2 eq.). The mixture was stirred at RT overnight. The reaction mixture was extracted with aqueous HCl (1N), sat. aq. NaHCO₃ and brine, dried over Na₂SO₄ and filtered. Evaporation under reduced pressure afforded a residue, which was dissolved in DMSO and purified by RP-HPLC (stationary phase: column Symmetry C18, 7 μ m, 19 x 300 mm. Mobile phase: MeCN/H₂O buffered with 0.1 % TFA). Fractions containing the pure compound were combined and freeze dried to afford compound **1** as a white powder (34 %). ¹H NMR (600 MHz, DMSO-d₆, 300 K) δ 10.57 (s, 1H), 9.22 (s, 1H), 7.24 (t, J 7.5, 1H), 7.18 (d, J 7.5, 1H), 7.11 (d, J 7.5, 1H), 5.68 (ddd, J 17.2, 10.0, 9.6, 1H), 5.42 (bt, 1H), 5.28 (dd, J 17.2, 1.5, 1H), 5.12 (dd, J 10.4, 1.7, 1H), 4.67-4.56 (m, 4H), 4.40 (dd, J 11.0, 6.5, 1H), 3.96 (d, J 10.3, 1H), 3.76 (dd, J 11.7, 3.1, 1H), 3.31 (d, J 6.3, 1H), 2.92-2.86 (m, 1H), 2.92-2.30 (m, 1H), 2.55-2.50 (partially obscured by residual DMSO, 1H), 2.47-2.40 (m, 1H), 2.22 (dd, J 13.8, 6.4, 1H), 2.16 (q, J 8.8, 1H), 2.09-2.02 (m, 1H), 1.79-1.71 (m, 2H), 1.57-1.46 (m, 3H), 1.44-1.18 (m, 8H), 1.13-1.07 (m, 1H), 1.06-0.98 (m, 3H), 0.91 (d, J 6.6, 3H), 0.83 (d, J 6.6, 3H). ¹³C NMR (600 MHz, DMSO-d₆, 300 K) δ 174.08, 172.16, 169.17, 152.92, 137.09, 136.23, 135.00, 133.37, 127.93, 127.57, 126.04, 120.32, 117.87, 73.50, 64.83, 59.03, 58.87, 53.23, 52.12, 50.67, 40.79, 34.59, 33.81, 31.42, 31.17, 30.74, 28.90, 28.48, 26.43, 26.02, 23.47, 22.76, 19.09, 17.93, 5.73, 5.36. MS (ES⁺) *m/z* 752 (M+H)⁺.

Scheme 2

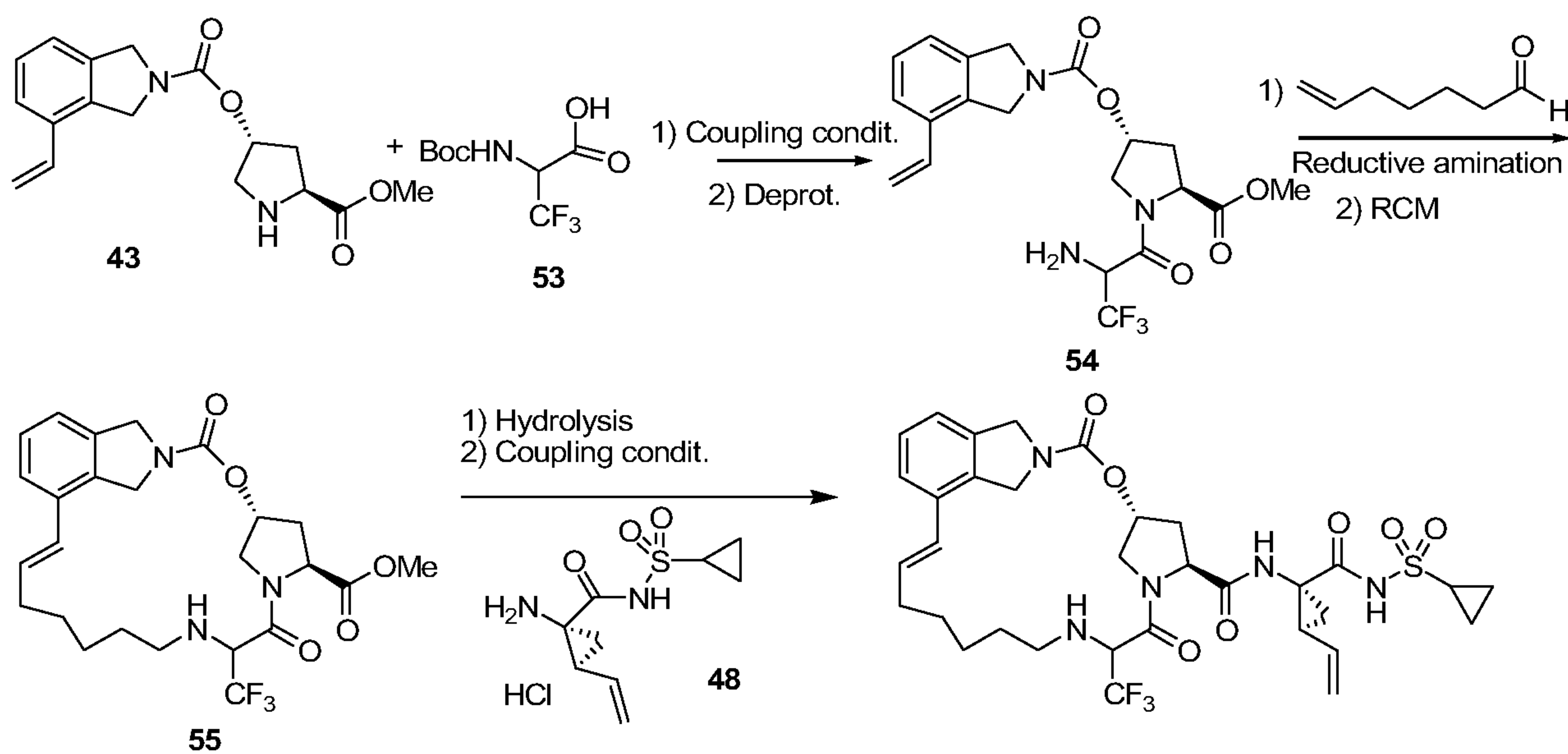


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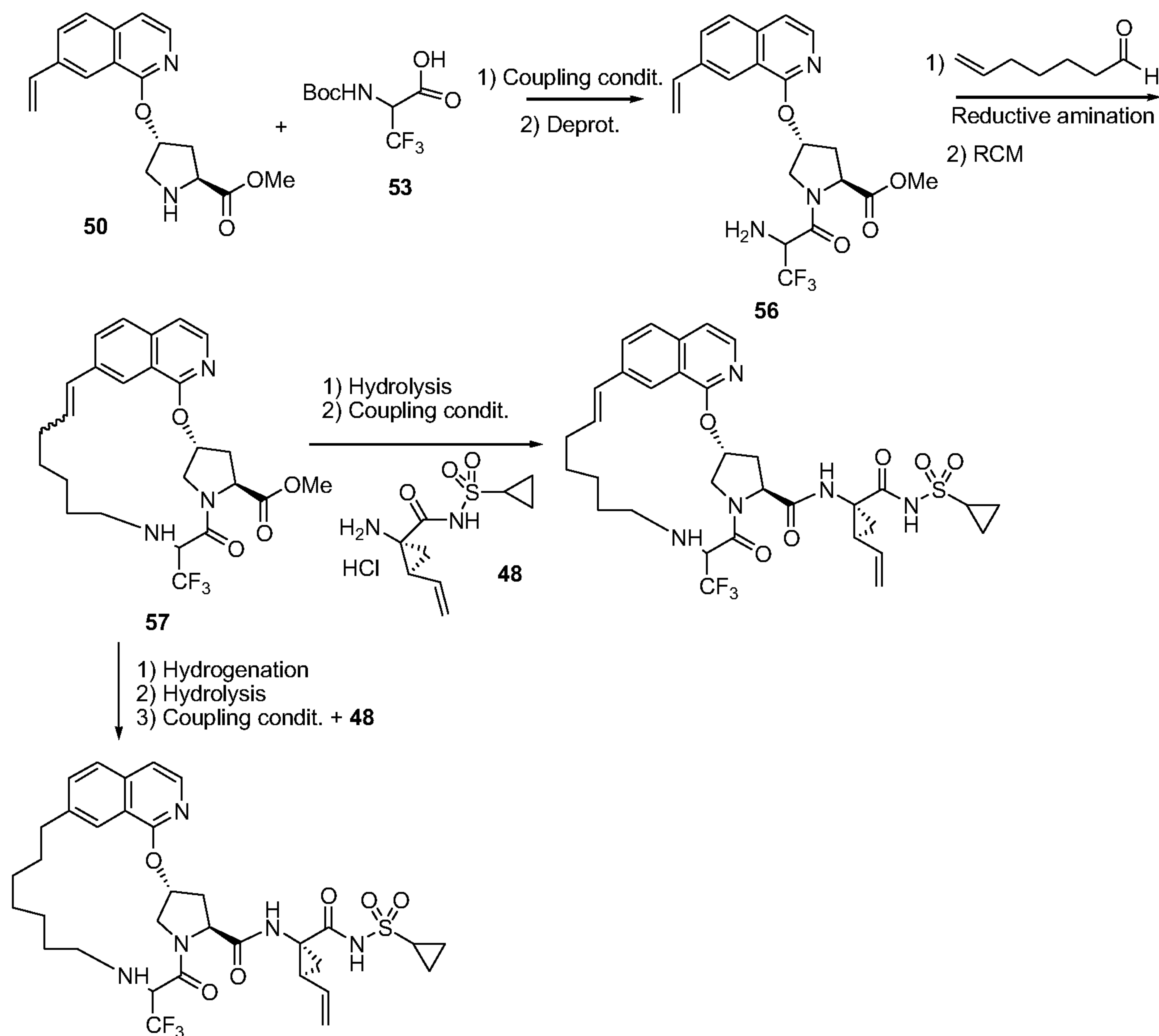
Scheme 3



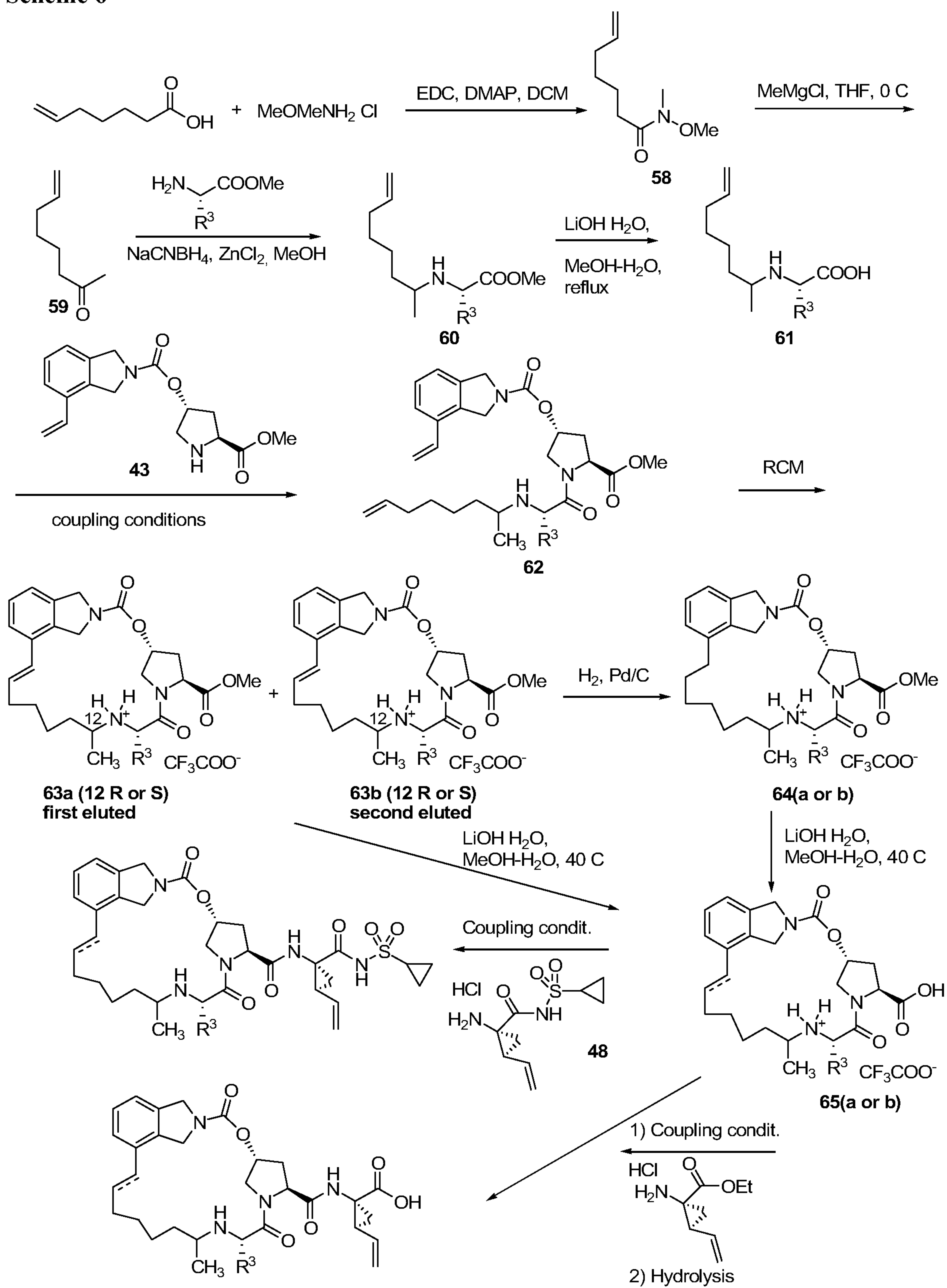
Scheme 4



Scheme 5



Scheme 6



Compounds 10 and 25:

10) (5*R*,7*S*,10*S*,12*R* or *S*)-N-((1*R*,2*S*)-1-[(cyclopropylsulfonyl)amino]carbonyl)-2-vinylcyclopropyl)-10-isopropyl-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide

5 **25) (5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclohexyl-N-((1*R*,2*S*)-1-[(cyclopropylsulfonyl)amino]carbonyl)-2-vinylcyclopropyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide**

Step 1: N-methoxy-N-methylhept-6-enamide **58**

10 EDC (1.1 eq.) was added in small portions over 1.5 h to a stirred mixture of hept-6-enoic acid, methoxy(methyl)ammonium chloride (1.1 eq.) and DMAP (1.1 eq.) in CH₂Cl₂ (0.2 M). After 14 h, the mixture was diluted with CH₂Cl₂, then washed sequentially with hydrochloric acid (1M), NaOH (1M), brine and dried (Na₂SO₄). Evaporation of the solvent afforded the title compound (97%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃, 300 K) δ 5.87-5.75 (m, 1H), 5.01 (d, J 17.1, 1H), 4.95 (d, 15 J 10.1, 1H), 3.68 (s, 3H), 3.18 (s, 3H), 2.48-2.36 (m, 2H), 2.13-2.04 (m, 2H), 1.71-1.60 (m, 2H), 1.50-1.40 (m, 2H).

Step 2: oct-7-en-2-one **59**

Methyl magnesium bromide (3M in ether, 3 eq.) was added dropwise to a stirred mixture of *N*-methoxy-*N*-methylhept-6-enamide **58** in THF (0.1 M) cooled at 0°C. After stirring for 1 h at 0°C, 20 the mixture was poured into sat. aq. NH₄Cl and diluted with EtOAc. The aqueous layer was further extracted with EtOAc, the combined organic layers were washed with brine and dried (Na₂SO₄). Evaporation of the solvent at 30 mbar afforded the title compound (96%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃, 300 K) δ 5.81 (ddt, J 17.1, 10.3, 6.7, 1H), 5.02 (dd, J 17.1, 1.5, 1H), 4.97 (d, J 25 10.3, 1H), 2.46-2.43 (m, 2H), 2.15 (s, 3H), 2.10-2.05 (m, 2H), 1.65-1.57 (m, 2H), 1.45-1.37 (m, 2H).

Step 3: Methyl (2*S*)-3-methyl-2-[(1*S* and *R*)-1-methylhept-6-en-1-yl]amino}butanoate **60** (**R**³ = *i*Pr)

A solution of NaCNBH₃ (1.2 eq.) and ZnCl₂ (0.6 eq.) in methanol (0.3 M with respect to NaCNBH₃) 30 was added dropwise to a solution of L-valine methyl ester hydrochloride (1.1 eq.) and oct-7-en-2-one **59** in methanol (0.5 M). After stirring for 2 days, volatiles were evaporated under reduced pressure and the residue partitioned between CH₂Cl₂ and sat. aq. NaHCO₃. The organic layer was dried (Na₂SO₄) and evaporated under reduced pressure affording the title compounds (57%) as a colorless oil. MS (ES⁺) *m/z* 242 (M+H)⁺.

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Step 3: Methyl (2*S*)-cyclohexyl-[(1*R* and *S*)-1-methylhept-6-en-1-yl]amino]acetate **60** (**R**³ = *c*Hex)

A solution of NaCNBH₃ (1.2 eq.) and ZnCl₂ (0.6 eq.) in methanol (0.2 M with respect to NaCNBH₃) was added dropwise to a solution of (1*S*)-1-cyclohexyl-2-methoxy-2-oxoethanaminium chloride (1.1 eq.) and oct-7-en-2-one **59** in methanol (0.05 M). After stirring overnight, volatiles were evaporated

under reduced pressure and the residue partitioned between CH₂Cl₂ and sat. aq. NaHCO₃. The organic layer was dried (Na₂SO₄) and evaporated under reduced pressure. The title compounds (obtained as a mixture of two diastereoisomers in ratio 7:2) was used in the following step without further purification. MS (ES⁺) *m/z* 282 (M+H)⁺.

5

Step 4: (2*S*)-3-methyl-2-{[(1*S* and 1*R*)-1-methylhept-6-en-1-yl]amino}butanoic acid **61** (R³ = *i*Pr)

Lithium hydroxide monohydrate (3.3 eq.) was added to a stirred mixture of methyl (2*S*)-3-methyl-2-{[(1*S* and *R*)-1-methylhept-6-en-1-yl]amino}butanoate **60** in MeOH and water (3/1 v/v, 0.03 M) and the mixture was stirred at reflux. After 22 h it was cooled to RT and MeOH was evaporated under reduced pressure. 1N HCl was added until pH = 5, and the aq. phase was extracted with CH₂Cl₂. The organic layers were dried (Na₂SO₄) and evaporated under reduced pressure affording the title compound (65%) as a white solid. MS (ES⁺) *m/z* 228 (M+H)⁺.

15

Step 4: (2*R* and *S*)-N-[(*S*)-carboxy(cyclohexyl)methyl]oct-7-en-2-aminium chloride **61** (R³ = *c*Hex)

Lithium hydroxide monohydrate (4 eq.) was added to a stirred mixture of methyl (2*S*)-cyclohexyl-{[(1*R* and *S*)-1-methylhept-6-en-1-yl]amino}acetate **60** in THF and water (3/2 v/v, 0.1 M) and the mixture was stirred at reflux. After 30 h, the mixture was cooled to RT and THF was evaporated under reduced pressure. 1N HCl was added until pH = 5, and the aq. phase was extracted with EtOAc. HCl (4N) in dioxane (2 eq.) was added to the organic layers. Drying over Na₂SO₄, filtration and evaporation under reduced pressure afforded the title compounds as mixture of diastereomers that was used in the following step without further purification. MS (ES⁺) *m/z* 268 (M+H)⁺.

20

Step 5: (2*R* and *S*)-N-{(1*S*)-1-[(2*S*,4*R*)-2-(methoxycarbonyl)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}pyrrolidin-1-yl)carbonyl]-2-methylpropyl}oct-7-en-2-aminium trifluoroacetate **62** (R³ = *i*Pr)

25

i-Pr₂EtN (4 eq.) followed by TBTU (1.2 eq.) were added to a stirred mixture of (2*S*)-3-methyl-2-{[(1*S* and 1*R*)-1-methylhept-6-en-1-yl]amino}butanoic acid **61** and (2*S*,4*R*)-2-(methoxycarbonyl)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}pyrrolidinium chloride **43** (1 eq.) in CH₂Cl₂ (0.03 M) and the mixture was stirred at RT. After 3.5 h, sat. aq. NaHCO₃ was added, the organic layer was separated and dried (Na₂SO₄). Evaporation under reduced pressure afforded a residue, which was redissolved in DMSO and purified by RP-HPLC (stationary phase: column Symmetry C18, 7 μm, 19 x 300 mm. Mobile phase: MeCN/H₂O buffered with 0.1 % TFA). Fractions containing the pure compounds were combined and freeze dried to afford the title compounds as a white powder (76 %). MS (ES⁺) *m/z* 526 (M+H)⁺.

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Step 5: (3*R*,5*S*)-1-{(2*S*)-2-cyclohexyl-2-[(1*R* and *S*)-1-methylhept-6-en-1-yl]amino}acetyl}-5-(methoxycarbonyl)pyrrolidin-3-yl-4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate **62** (R³ = *c*Hex)

i-Pr₂EtN (5eq.) followed by TBTU (1.2 eq.) were added to a stirred mixture of (2*R* and *S*)-N-[(*S*)-carboxy(cyclohexyl)methyl]oct-7-en-2-aminium chloride **61** and (2*S*,4*R*)-2-(methoxycarbonyl)-4-

{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}pyrrolidinium chloride **43** (1 eq.) in CH₂Cl₂ (0.03 M) and the mixture was stirred at RT overnight. Saturated aq. NaHCO₃ was added, the organic layer was separated and dried (Na₂SO₄). Evaporation under reduced pressure afforded a residue that was purified by flash chromatography on silica gel (EtOAc/PE + 0.05% TEA gradient from 10\90 to 35\65) to afford the title compound as a mixture of two diastereomers (45% over three steps). MS (ES⁺) *m/z* 566 (M+H)⁺.

Step 6: (5*R*,7*S*,10*S*,12*R* or *S*,17*E*)-10-isopropyl-7-(methoxycarbonyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **63a** (R³=*i*Pr)

Zhan catalyst I (0.2 eq.) was added to (2*R* and *S*)-N-{(1*S*)-1-[(2*S*,4*R*)-2-(methoxycarbonyl)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}pyrrolidin-1-yl)carbonyl]-2-methylpropyl}oct-7-en-2-aminium trifluoroacetate **62** in CH₂Cl₂ (0.016 M) and the mixture was heated under microwave irradiation at 100 °C for 40 min. Undissolved material was filtered away and the resulting solution was evaporated under reduced pressure affording a residue, which was redissolved with DMSO and purified by RP-HPLC (stationary phase: column Symmetry C18, 7 μm, 19 x 300 mm. Mobile phase: MeCN/H₂O buffered with 0.1 % TFA; the title compound **63a** was the first diastereoisomer eluted). Fractions containing the pure compounds were combined and freeze dried to afford the title compounds as a white powder (37 %). MS (ES⁺) *m/z* 498 (M+H)⁺.

Step 6: (5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclohexyl-7-(methoxycarbonyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **63a** (R³=*c*Hex)

Zhan catalyst I (0.2 eq.) was added to (3*R*,5*S*)-1-{(2*S*)-2-cyclohexyl-2-[(1*R* and *S*)-1-methylhept-6-en-1-yl)amino]acetyl}-5-(methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate **62** in CH₂Cl₂ (0.02 M) and the mixture was heated under microwave irradiation at 100 °C for 40 min. Volatiles were evaporated under reduced pressure affording a residue, which was redissolved with DMSO and purified by RP-HPLC (stationary phase: column Symmetry C18, 7 μm, 19 x 300 mm. Mobile phase: MeCN/H₂O buffered with 0.1 % TFA). The title compound **63a** was the first diastereoisomer eluted. The fractions containing the pure compounds were combined and freeze dried to afford the title compounds as a white powder (31 %).

63a) ¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 8.60 (br s, 2H), 7.35-7.15 (m, 3H), 6.27 (d, J 16.4, 1H), 6.07 (dt, J 15.8, 5.7, 1H), 5.42 (br s, 1H), 4.89-4.54 (m, 4H), 4.46 (d, J 14.8, 1H), 4.40-4.31 (m, 1H), 4.26 (d, J 12.2, 1H), 3.76-3.60 (m, 4H), 2.95-2.77 (m, 1H), 2.47-2.40 (partially obscured by residual DMSO, 1H), 2.30-2.03 (m, 3H), 2.01-1.71 (m, 6H), 1.70-0.97 (m, 14H). MS (ES⁺) *m/z* 538 (M+H)⁺.

Step 7: (5*R*,7*S*,10*S*,12*R* or *S*)-10-isopropyl-7-(methoxycarbonyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **64a** ($R^3 = iPr$)

Palladium on carbon (10% Pd, 20% weight) and (5*R*,7*S*,10*S*,12*R* or *S*,17*E*)-10-isopropyl-7-(methoxycarbonyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **63a** in MeOH (5 mM) were stirred under a hydrogen atmosphere. After 2 h, solids were filtered away on celite and the resulting solution was evaporated under reduced pressure affording the title compound (67%) as a pale brown oil. MS (ES^+) m/z 500 ($M+H$)⁺.

Step 7: (5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclohexyl-7-(methoxycarbonyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **64a** ($R^3 = cHex$)

Palladium on carbon (10% Pd, 20% weight) and (5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclohexyl-7-(methoxycarbonyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **63a** in methanol (0.013M) were stirred under a hydrogen atmosphere. After 3 h, solids were filtered away on celite and the resulting solution was evaporated under reduced pressure affording the title compound (88%) as a pale brown oil. MS (ES^+) m/z 540 ($M+H$)⁺.

Step 8: (5*R*,7*S*,10*S*,12*R* or *S*)-7-carboxy-10-isopropyl-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **65a** ($R^3 = iPr$)

Lithium hydroxide monohydrate (12 eq.) was added to a stirred mixture of (5*R*,7*S*,10*S*,12*R* or *S*)-10-isopropyl-7-(methoxycarbonyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **64a** in MeOH and water (3/1 v/v, 0.01 M) and the mixture was stirred at 40 °C. After 6 h, the mixture was cooled, TFA was added to pH = 1 and the mixture was evaporated under reduced pressure affording a residue, which was redissolved with DMSO and purified by RP-HPLC (stationary phase: column Symmetry C18, 5 μ m, 19 x 100 mm. Mobile phase: MeCN/H₂O buffered with 0.1 % TFA). Fractions containing the pure compound were combined and freeze dried to afford the title compound **65a** as a white powder (57 %). MS (ES^+) m/z 486 ($M+H$)⁺.

Step 8: (5*R*,7*S*,10*S*,12*R* or *S*)-7-carboxy-10-cyclohexyl-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **65a** ($R^3 = cHex$)

Lithium hydroxide monohydrate (5 eq.) was added to a stirred mixture of (5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclohexyl-7-(methoxycarbonyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-

dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **64a** in THF and water (2/1 v/v, 0.01 M) and the mixture was stirred at 40 °C. After 6 h the mixture was cooled, TFA was added to pH = 1 and the mixture was evaporated under reduced pressure affording a residue, which was redissolved with DMSO and purified by RP-HPLC (stationary phase: column Symmetry C18, 5 µm, 19 x 100 mm. Mobile phase: MeCN/H₂O buffered with 0.1 % TFA).
5 Fractions containing the pure compound were combined and freeze dried to afford the title compound as a white powder (44 %). MS (ES⁺) *m/z* 526 (M+H)⁺.

Step 9: (5*R*,7*S*,10*S*,12*R* or *S*)-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-isopropyl-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-
10 dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide **10**

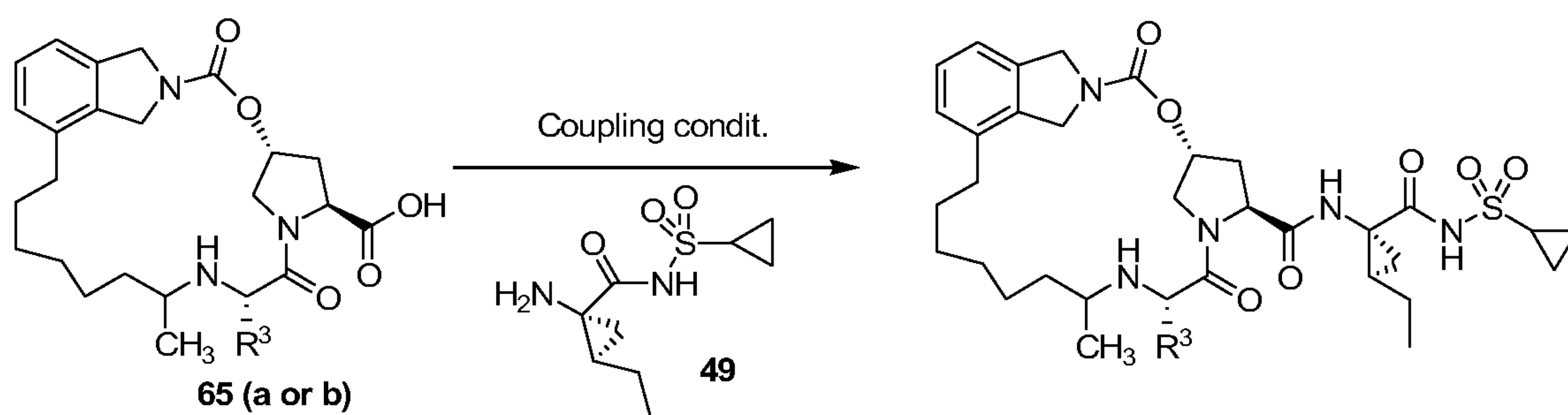
i-Pr₂EtN (7.5 eq.), DMAP (0.5 eq.) and TBTU (1.3 eq.) were added to a stirred mixture of (5*R*,7*S*,10*S*,12*R* or *S*)-10-isopropyl-7-(methoxycarbonyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **65a** and (1*R*,2*S*)-1-
15 {[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropanaminium chloride **48** (prepared as described in WO 03/099274) (1.5 eq.) in CH₂Cl₂ (0.02 M) and the mixture was stirred at RT. After 13 h, the mixture was evaporated under reduced pressure affording a residue, which was redissolved with DMSO and purified by RP-HPLC (stationary phase: column Symmetry C18, 7 µm, 19 x 300
20 mm. Mobile phase: MeCN/H₂O buffered with 0.1 % TFA). Fractions containing the pure compound were combined and freeze dried to afford the title compound **10** (TFA salt) as a white powder (57 %). ¹H NMR (600 MHz, DMSO-*d*₆, 300 K) δ 10.90 (br s, NH), 8.73 (br s, NH), 8.50-8.25 (m, NH₂), 7.26 (t, J 7.3, 1H), 7.18 (d, J 7.4, 1H), 7.14 (d, J 7.4, 1H), 5.56 (dt, J 17.5, 9.5, 1H), 5.41 (br s, 1H), 5.22 (d, J 17.5, 1H), 5.11 (d, J 11.1, 1H), 4.67 (m, 2H), 4.62-4.49 (m, 3H), 4.40-4.34 (m,
25 1H), 4.18 (d, J 12.2, 1H), 3.74 (dd, J 12.2, 2.5, 1H), 2.94-2.82 (m, 2H), 2.52-2.43 (obscured by residual DMSO, 2H), 2.42-2.34 (m, 1H), 2.23 (m, 1H), 2.15 (q, J 8.7, 1H), 2.06 (m, 1H), 1.74 (dd, J 7.6, 5.5, 1H), 1.71 (m, 1H), 1.63-1.44 (m, 3H), 1.41-0.97 (m, 20H). MS (ES⁺) *m/z* 698 (M+H)⁺.

Step 9: (5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-
30 2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide **25**

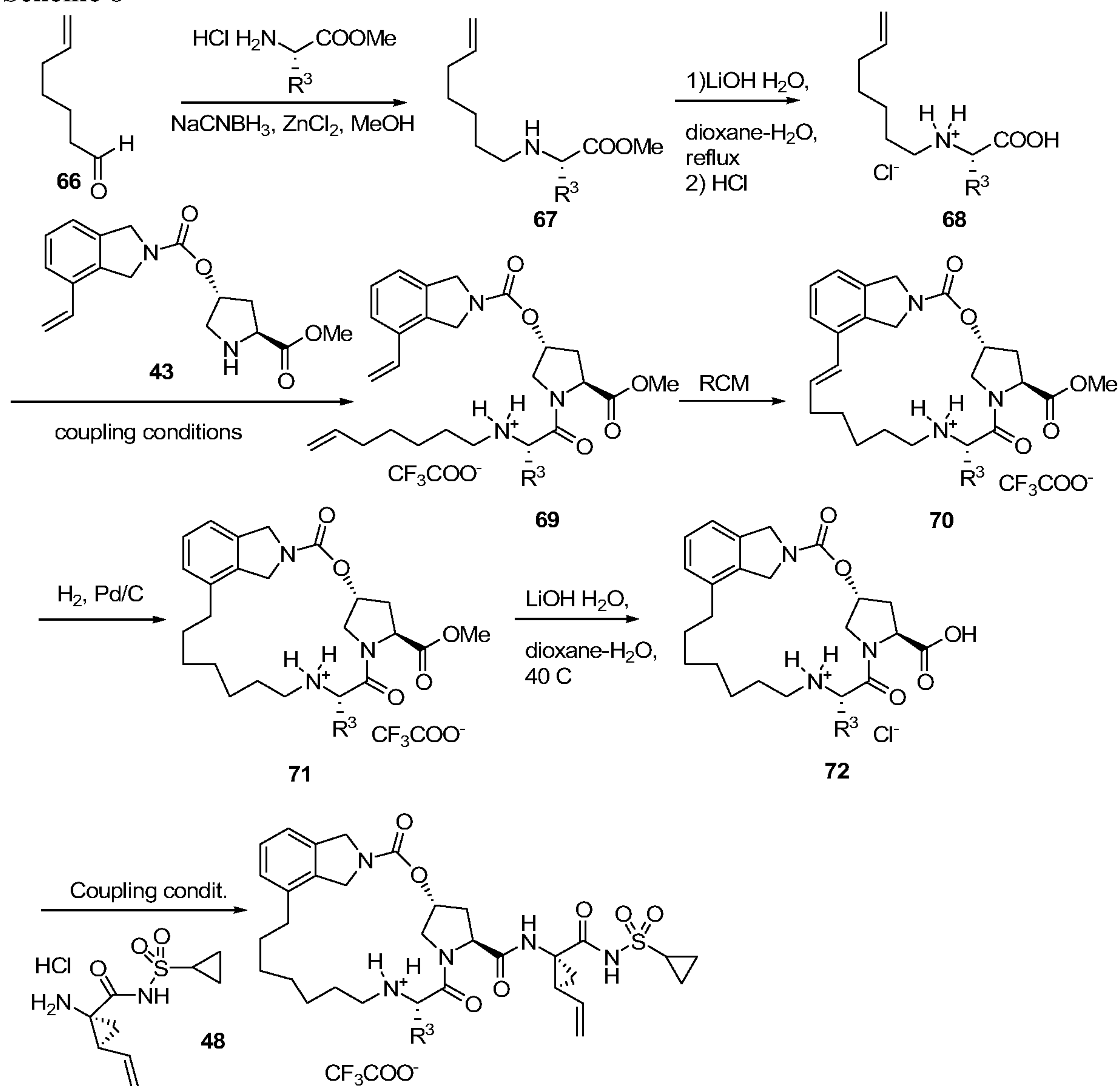
i-Pr₂EtN (6.5 eq.), DMAP (0.5 eq.) and TBTU (1.3 eq.) were added to a stirred mixture of (5*R*,7*S*,10*S*,12*R* or *S*)-7-carboxy-10-cyclohexyl-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **65a** and (1*R*,2*S*)-1-
35 {[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropanaminium chloride (prepared as described in WO 03/099274) (1.5 eq.) **48** in CH₂Cl₂ (0.02 M) and the mixture was stirred at RT overnight. Volatiles were evaporated under reduced pressure affording a residue, which was redissolved with DMSO and purified by RP-HPLC (stationary phase: column Symmetry C18, 7 µm, 19 x 300 mm. Mobile phase: MeCN/H₂O

buffered with 0.1 % TFA). Fractions containing the pure compound were combined and freeze dried to afford the title compound **25** (TFA salt) as a white powder (62 %). ¹H NMR (400 MHz, DMSO-d₆, 300 K) δ 10.85 (br s, 1H), 8.73 (br s, 1H), 8.43 (br s, 1H), 8.34-8.20 (m, 1H), 7.26 (t, J 7.5, 1H), 7.18 (d, J 7.6, 1H), 7.14 (d, J 7.4, 1H), 5.58 (dt, J 17.7, 9.1, 1H), 5.41 (br s, 1H), 5.21 (d, J 17.4, 1H), 5.11 (d, J 11.4, 1H), 4.72-4.45 (m, 5H), 4.48-4.39 (m, 1H), 4.17 (d, J 12.1, 1H), 3.76 (dd, J 12.9, 2.3, 1H), 2.97-2.78 (m, 2H), 2.47-2.34 (partially obscured by residual DMSO, 2H), 2.19-2.03 (m, 2H), 1.99-1.42 (m, 11H), 1.41-0.93 (m, 20H). MS (ES⁺) *m/z* 738 (M+H)⁺.

Scheme 7



Scheme 8



Compound 19: (5R,7S,10S)-N-((1R,2S)-1-[(cyclopropylsulfonyl)amino]carbonyl)-2-vinylcyclopropyl)-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1H,5H-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide

Step 1: Methyl (2S) -2-(hept-6-en-1-ylamino)-3-methylbutanoate **67** ($\text{R}^3 = i\text{Pr}$)

To a solution (0.3M) of L-valine, methyl ester, hydrochloride in dry MeOH was added ZnCl_2 (1.0 eq.), NaCNBH_3 (1.2 eq.), hept-6-enal **66** (1.2 eq.), and the reaction mixture was stirred at RT overnight. Then the volatiles were evaporated at reduced pressure and the residue taken-up in CH_2Cl_2 and washed with a saturated aq. solution of NaHCO_3 . The organic layer was dried over Na_2SO_4 and evaporated at reduced pressure affording the title compound (98%) as yellow pale oil. ^1H NMR (400 MHz, CDCl_3 , 300 K) δ 5.81 (ddt, J 17.0, 10.1, 6.7, 1H), 5.00 (dd, J 17.0, 1.5, 1H), 4.94 (d, J 10.1, 1H), 3.72 (s, 3H), 2.99 (d, J 5.6, 1H), 2.60-2.54 (m, 1H), 2.45-2.39 (m, 1H), 2.05 (dd, J 13.5, 6.6, 2H), 1.94-1.86 (m, 1H), 1.53-1.26 (m, 6H), 0.96 (d, J 7.1, 3H), 0.93 (d, J 6.8, 3H).

Step 2: N-[(1*S*)-1-carboxy-2-methylpropyl]hept-6-en-1-aminium chloride **68** ($R^3 = iPr$)

To a solution (0.4M) of methyl (2*S*)-2-(hept-6-en-1-ylamino)-3-methylbutanoate **67** in a 1:1 mixture of dioxane and water, LiOH (4 eq.) was added, and the reaction mixture was stirred at reflux for 24h.

- 5 The reaction mixture was then cooled and brought to pH=2 by small additions of HCl_(aq) 6N. The white precipitate was filtered and washed with H₂O and dried overnight. The title compound (71%) as a white precipitate was used in the next step without any further purification. ¹H NMR (400 MHz, DMSO-d₆, 300 K) δ 9.80 (bs, 1H), 8.95 (bs, 1H), 5.74 (ddt, J 17.0, 16.9, 6.7, 1H), 4.95 (d, J 17.0, 1H), 4.89 (d, J 10.2, 1H), 3.73-3.70 (m, 1H), 2.91-2.72 (m, 2H), 2.43-2.35 (m, 1H), 1.96 (q, J 6.7, 2H), 1.78-1.65 (m, 2H), 1.33-1.24 (m, 4H), 1.01 (d, J 7.1, 3H), 0.92 (d, J 6.8, 3H).

Step 3: N-[(1*S*)-1-[(2*S*,4*R*)-2-(methoxycarbonyl)-4-[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy]pyrrolidin-1-yl)carbonyl]-2-methylpropyl}hept-6-en-1-aminium trifluoroacetate **69** ($R^3 = iPr$)

- 15 To a solution (0.1M) of N-[(1*S*)-1-carboxy-2-methylpropyl]hept-6-en-1-aminium chloride **68** in dry CH₂Cl₂ was added (2*S*,4*R*)-2-(methoxycarbonyl)-4-[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}pyrrolidinium chloride **43** (1.2 eq.), *i*-Pr₂Et(3.2 eq.) and TBTU (1.2 eq.). The reaction mixture was stirred at RT for 4h, then taken up in DCM and washed with an aq. saturated solution of NaHCO₃. The organic phase was dried over Na₂SO₄ and the volatiles evaporated at reduced pressure. The crude was purified by flash chromatography eluting with a mixture of PE/EtOAc (7/3) in presence with 0.1% of TEA. The desired fractions were collected and the solvent evaporated. The compound was solubilized in CH₂Cl₂ and 1 eq. of TFA was added in order to obtain the complete formation of the trifluoroacetate salt. The procedure afforded the title compound (90%) as a white solid. MS (ES⁺) m/z 512 (M+H)⁺.

Step 4: N-(5*R*,7*S*,10*S*,17*E*)-10-isopropyl-7-(methoxycarbonyl)-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **70** ($R^3 = iPr$)

- 25 Zhan catalyst I (0.05 eq.) was added to N-[(1*S*)-1-[(2*S*,4*R*)-2-(methoxycarbonyl)-4-[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}pyrrolidin-1-yl)carbonyl]-2-methylpropyl}hept-6-en-1-aminium trifluoroacetate **69** in DCE (0.04 M) and the mixture was heated at 90°C for 1h. The volatiles were then evaporated at reduced pressure and the crude crystallized from a mixture of PE/EtOAc 8/2. The precipitate was collected and dried overnight. The title compound (78%) was obtained as a brownish solid. MS (ES⁺) m/z 484 (M+H)⁺.

Step 5: (5*R*,7*S*,10*S*)-10-isopropyl-7-(methoxycarbonyl)-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **71** ($R^3 = iPr$)

Palladium on carbon (10% Pd, 20% weight) and N-(5*R*,7*S*,10*S*,17*E*)-10-isopropyl-7-(methoxycarbonyl)-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **70** in MeOH (1 mM) were stirred overnight under hydrogen atmosphere. Then the catalyst was filtered-off and the volatiles
 5 evaporated. The title compound (95%) was recovered as a brown solid. MS (ES⁺) *m/z* 487 (M+H)⁺.

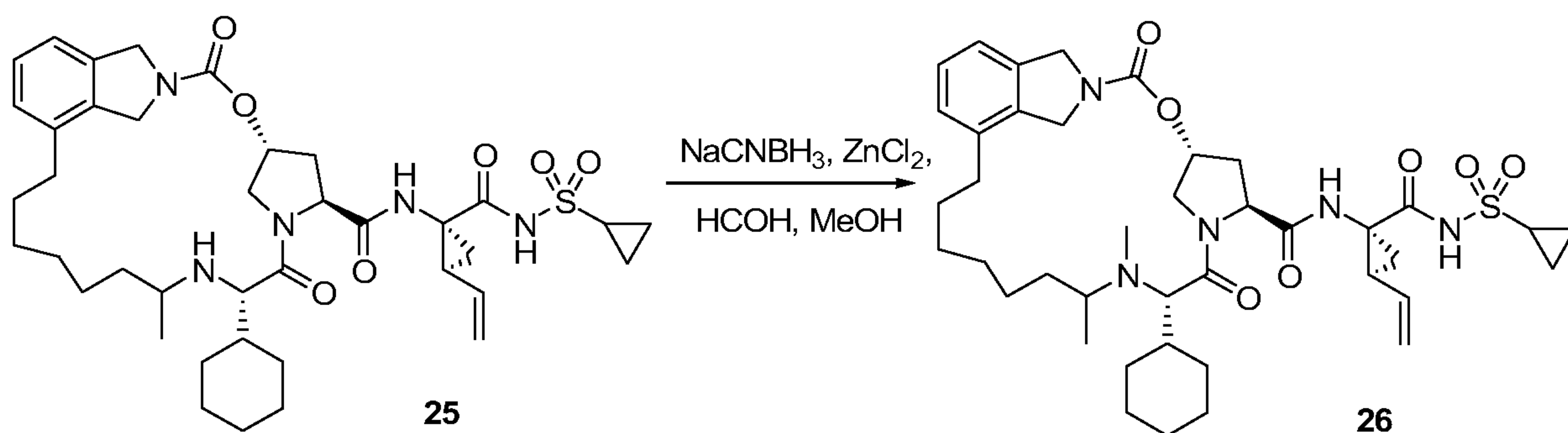
Step 6: (5*R*,7*S*,10*S*)-7-carboxy-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **72** (R³ = *i*Pr)

10 Lithium hydroxide monohydrate (5 eq.) was added to a stirred mixture of (5*R*,7*S*,10*S*)-10-isopropyl-7-(methoxycarbonyl)-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **71** in a 1:1 mixture of dioxane and H₂O (3 mM). By small aliquots of HCl_(aq) 6N the pH was brought to 6.5 and the volatiles
 15 evaporated. The crude was taken up in a mixture 95:5 H₂O:MeCN and the solid was collected by suction. The title compound (quantitative recovery) was obtained as a light grey solid. MS (ES⁺) *m/z* 472 (M+H)⁺.

Step 7: (5*R*,7*S*,10*S*)-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide **19**

20 *i*-Pr₂EtN (3.5 eq.), DMAP (0.5 eq.), TBTU (1.5 eq.) were added to a stirred mixture of (5*R*,7*S*,10*S*)-7-carboxy-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-11-ium trifluoroacetate **72** and (1*R*,2*S*)-1-
 {[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropanaminium chloride (prepared as described
 25 in WO 03/099274) (1.5 eq.) **48** (1.5 eq.) in CH₂Cl₂ (0.06 M) and the mixture was stirred at RT for 2 h. The mixture was evaporated under reduced pressure affording a residue, which was redissolved with DMSO and purified by RP-HPLC (stationary phase: column Symmetry C18, 7 μm, 19 x 300 mm. Mobile phase: MeCN/H₂O buffered with 0.1 % TFA). Fractions containing the pure compound were combined and freeze dried to afford the title compound **19** (TFA salt) as a white solid (23%).
 30 ¹H NMR (400 MHz, DMSO-d₆, 300 K) δ 10.74 (s, 1H), 8.74 (s, 1H), 8.70-8.56 (m, 2H), 7.25 (t, J 7.6, 1H), 7.17 (d, J 7.8, 1H), 7.13 (d, J 7.3, 1H), 5.56 (dt, J 17.1, 9.3, 1H), 5.39 (br s, 1H), 5.22 (d, J 17.4, 1H), 5.11 (d, J 11.3, 1H), 4.78-4.48 (m, 5H), 4.27 (br s, 1H), 3.74 (dd, J 11.6, 2.5, 1H), 2.95-2.89 (m, 2H), 2.69-2.66 (m, 1H), 2.38-2.32 (obscured by residual DMSO, 1H), 2.21-2.06(m, 3H), 1.73 (dd, J 9.7, 6.9, 2H), 1.69-1.55 (m, 4H), 1.32-1.26 (m, 1H), 4.49-4.62 (m, 7H), 1.15-1.09 (m,
 35 1H), 1.04 (dd, J 9.7, 6.9, 9H). MS (ES⁺) *m/z* 685 (M⁺H)⁺.

Scheme 9

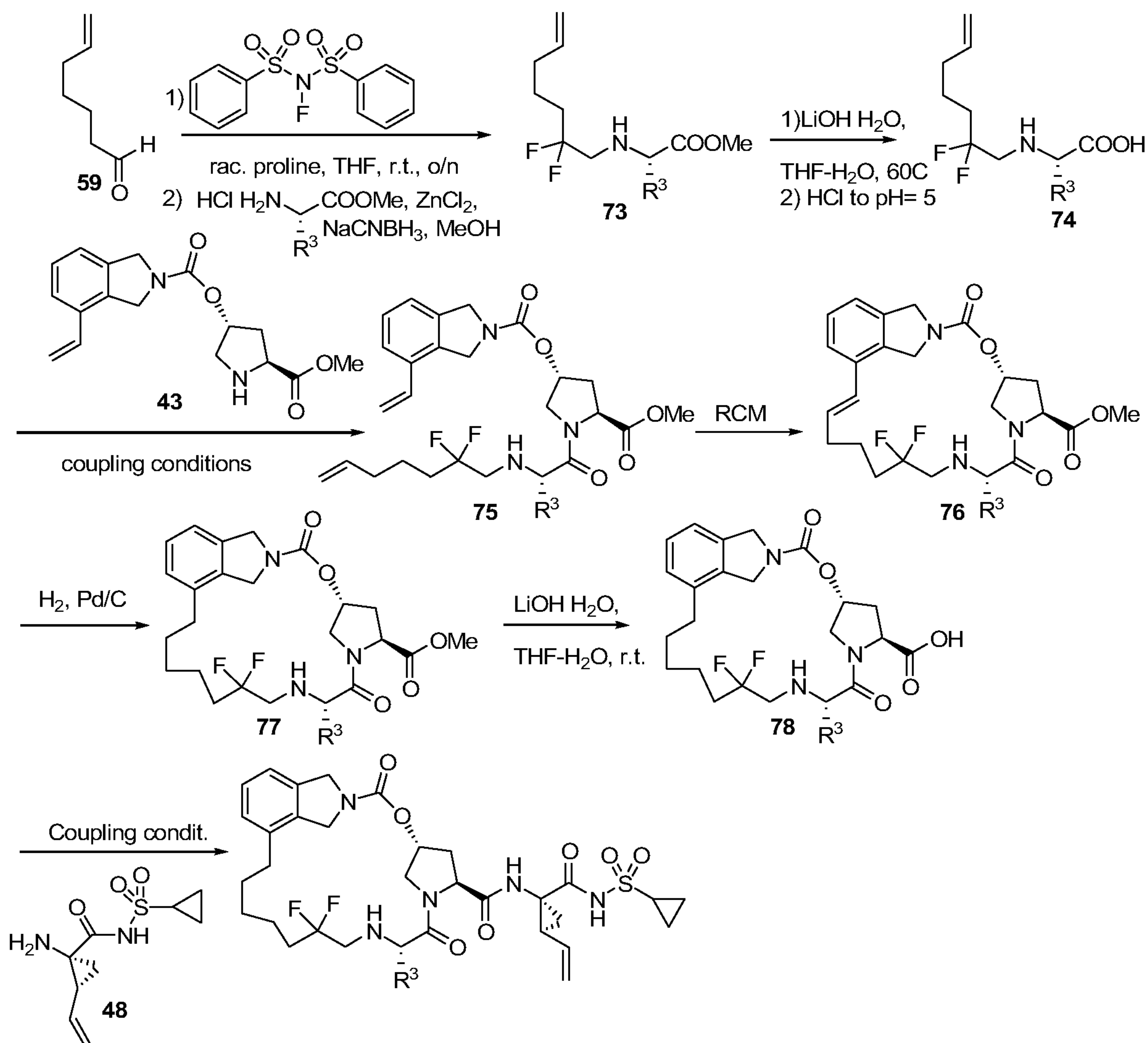


**Compound 26: (5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclohexyl-N-((1*R*,2*S*)-1-
 {[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-11,12-dimethyl-3,9-dioxo-
 6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-
 benzoxatriazacycloicosine-7-carboxamide**

A solution of NaCNBH₃ (1.2 eq.) and ZnCl₂ (0.6 eq.) in methanol (0.04 M with respect to NaCNBH₃) was added dropwise to a solution of 37% aq. formaldehyde (35 eq.) and (5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide **25** in MeOH (0.03 M).

After stirring overnight, volatiles were evaporated under reduced pressure. The residue was redissolved with DMSO and purified by RP-HPLC (stationary phase: column Symmetry C18, 7 μ m, 19 x 300 mm. Mobile phase: MeCN/H₂O buffered with 0.1 % TFA). Fractions containing the pure compound were combined and freeze dried to afford the title compound **26** (TFA salt) as a white powder (55 %). ¹H NMR (400 MHz, DMSO-d₆, 300 K) δ 10.88 (s, 1H), 8.73 (br s, 1H), 8.65 (br s, 1H), 7.26 (t, J 7.5, 1H), 7.19 (d, J 7.6, 1H), 7.13 (d, J 7.4, 1H), 5.60 (dt, J 17.3, 9.5, 1H), 5.37 (br s, 1H), 5.20 (d, J 17.0, 1H), 5.11 (d, J 11.1, 1H), 4.77-5.55 (m, 4H), 4.56-4.39 (m, 2H), 3.92 (d, J 12.1, 1H), 3.80 (dd, J 12.1, 2.5, 1H), 2.97-2.80 (m, 2H), 2.62 (d, J 4.0, 3H), 2.47-2.36 (partially obscured by residual DMSO, 3H), 2.15 (q, J 8.9, 1H), 2.10-1.93 (m, 2H), 1.92-1.41 (m, 12H), 1.40-1.81 (m, 11H), 1.17-0.94 (m, 6H). MS (ES⁺) *m/z* 752 (M+H)⁺.

Scheme 10



Compound 14: (5R,7S,10S)-N-((1R,2S)-1-[(cyclopropylsulfonyl)amino]carbonyl)-2-vinylcyclopropyl)-13,13-difluoro-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1H,5H-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide

Step 1: methyl N-(2,2-difluorohept-6-en-1-yl)-L-valinate **73**

To hept-6-enal **59** dissolved in THF (0.09M), racemic proline, followed by *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide were added. The mixture was stirred at RT overnight. The reaction mixture was diluted with Et_2O and washed with sat. aq. NaHCO_3 . The organic layer was separated, dried over Na_2SO_4 , filtered and concentrated. To the residue redissolved in MeOH (0.5 M), L-valine methyl ester hydrochloride (1.1 eq.) followed by a solution of NaCNBH_3 (1.2 eq.) and ZnCl_2 (0.6 eq.) in MeOH (0.3 M with respect to NaCNBH_3) were added dropwise. After stirring overnight, volatiles were evaporated under reduced pressure and the residue partitioned between CH_2Cl_2 and sat. aq. NaHCO_3 . The organic layer was dried (Na_2SO_4) and

evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc:PE = 5:95) to afford the title compound as a yellow oil (25%). ¹H NMR (400 MHz, DMSO-d₆, 300 K) δ 5.86 (m, 1H), 5.03 (d, J 17.2, 1H), 5.0 (d, J 10.1, 1H), 3.65 (s, 3H), 3.05-2.87 (m, 2H), 2.76-2.60 (m, 1H), 2.25-2.15 (m, 1H), 2.13-1.99 (m, 2H), 1.97-1.77 (m, 3H),
5 1.56-1.40 (m, 2H), 0.86 (d, J 6.8, 6H). MS (ES⁺) *m/z* 264 (M+H)⁺.

Step 2: N-(2,2-difluorohept-6-en-1-yl)-L-valine 74

Lithium hydroxide monohydrate (6 eq.) was added to a stirred mixture of methyl N-(2,2-difluorohept-6-en-1-yl)-L-valinate **73** in THF and water (2/1 v/v, 0.013 M) and the mixture was
10 stirred at 60°C. After 1 h, it was cooled to RT and THF was evaporated under reduced pressure. Aqueous 1N HCl was added until pH = 5, and the aq. phase was extracted with EtOAc. Drying over Na₂SO₄, filtration and evaporation under reduced pressure afforded the title compound that was used in the following step without further purification. MS (ES⁺) *m/z* 250 (M+H)⁺.

15 Step 3: methyl N-(2,2-difluorohept-6-en-1-yl)-L-valyl-(4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}-L-prolinate 75

i-Pr₂EtN (2.2 eq.) followed by TBTU (1.2 eq.) was added to a stirred mixture of N-(2,2-difluorohept-6-en-1-yl)-L-valine **74** and (2*S*,4*R*)-2-(methoxycarbonyl)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}pyrrolidinium chloride (1 eq.) in CH₂Cl₂ (0.06 M) and the mixture was
20 stirred at RT overnight. Sat. aq. NaHCO₃ was added, the organic layer was separated and dried (Na₂SO₄). Evaporation under reduced pressure afforded a residue, which was purified by flash chromatography on silica gel (EtOAc:PE = 1:9). The title compound was obtained as a yellow foam (39%). MS (ES⁺) *m/z* 548 (M+H)⁺.

25 Step 4: Methyl (5*R*,7*S*,10*S*,17*Z*)-13,13-difluoro-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxylate 76

Zhan catalyst I (0.2 eq.) was added to methyl N-(2,2-difluorohept-6-en-1-yl)-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate **75** in CH₂Cl₂ (0.02 M) and the mixture was heated under microwave irradiation at 100 °C for 15 min. Volatiles were evaporated
30 under reduced pressure affording a residue, which was purified by flash chromatography on silica gel (EtOAc:PE = 2:8). The title compound was obtained as a yellow foam (66%). MS (ES⁺) *m/z* 520 (M+H)⁺.

35 Step 5: methyl-(5*R*,7*S*,10*S*)-13,13-difluoro-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxylate 77

Palladium on carbon (10% Pd, 20% weight) and methyl (5*R*,7*S*,10*S*,17*Z*)-13,13-difluoro-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxylate **76** in MeOH (0.02M) were stirred under a hydrogen

atmosphere. After 4 h solids were filtered on celite and the resulting solution was evaporated under reduced pressure affording the title compound as a pale brown oil. MS (ES⁺) *m/z* 522 (M+H)⁺.

Step 6: (5*R*,7*S*,10*S*)-13,13-difluoro-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxylic acid **79**

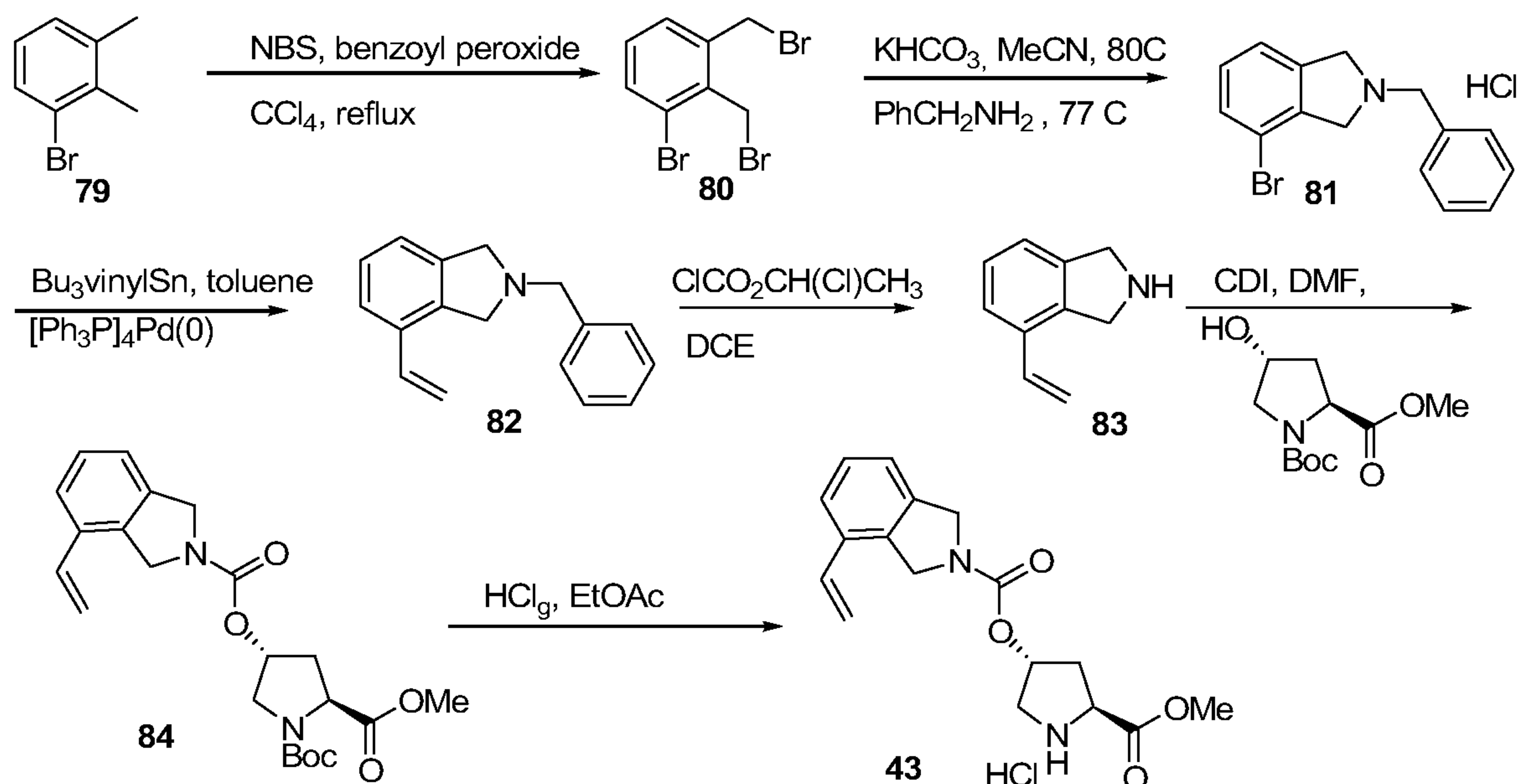
Lithium hydroxide monohydrate (3 eq.) was added to a stirred mixture of methyl (5*R*,7*S*,10*S*)-13,13-difluoro-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxylate **77** in THF and water (2/1 v/v, 0.02 M) and the mixture was stirred at RT overnight. Aqueous HCl (1N) was added to reach pH = 5 and the mixture was extracted with EtOAc. The organic layer was separated, dried over Na₂SO₄, filtered and concentrated to obtain the crude product which was used in the following step without further purification. MS (ES⁺) *m/z* 508 (M+H)⁺.

Step 7: (5*R*,7*S*,10*S*)-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-13,13-difluoro-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide **14**

i-Pr₂EtN (6.5 eq.), DMAP (0.5 eq.) and TBTU (1.3 eq.) were added to a stirred mixture of (5*R*,7*S*,10*S*)-13,13-difluoro-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxylic acid **78** and (1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropanaminium chloride (prepared as described in WO 03/099274) (1.5 eq.) **48** (1.5 eq.) in CH₂Cl₂ (0.02 M) and the mixture was stirred at RT. After 13 h, the mixture was evaporated under reduced pressure affording a residue, which was redissolved in DMSO and purified by RP-HPLC (stationary phase: column Symmetry C18, 7 μm, 19 x 300 mm. Mobile phase: MeCN/H₂O buffered with 0.1 % TFA). Fractions containing the pure compound were combined and freeze dried to afford the title compound **14** as a white powder (15 % over three steps). ¹H NMR (400 MHz, DMSO-d₆, 300 K) δ 10.66 (s, 1H), 8.97 (br s, 1H), 7.25 (t, J 7.5, 1H), 7.17 (d, J 7.3, 1H), 7.13 (d, J 7.6, 1H), 5.61 (dt, J 17.3, 9.5, 1H), 5.38 (br s, 1H), 5.25 (d, J 16.9, 1H), 5.11 (d, J 11.4, 1H), 4.73-4.54 (m, 4H), 4.45 (dd, J 10.1, 7.3, 1H), 4.04 (d, J 12.1, 1H), 3.75 (dd, J 12.0, 3.2, 1H), 3.50-3.02 (m, 3H), 2.96-2.85 (m, 1H), 2.45-2.34 (partially obscured by residual DMSO, 3H), 2.24-1.67 (m, 6H), 1.66-1.48 (m, 2H), 1.49-1.20 (m, 5H), 1.14-0.91 (m, 10H). MS (ES⁺) *m/z* 720 (M+H)⁺.

Scheme 11

- 40 -



Compound 43: (3*R*,5*S*)-5-(methoxycarbonyl)pyrrolidin-3-yl-4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate hydrochloride

5

Step 1: 1-bromo-2,3-bis(bromomethyl)benzene **80**

A suspension of 3-bromo-*o*-xylene (1.0 eq.), *N*-bromosuccinimide (2.15 eq.) and benzoyl peroxide (1.0 eq.) in CCl₄ (0.55 M) was heated to reflux under nitrogen for 15 h. The contents of the reaction flask were cooled, filtered, and the filtrate evaporated. The crude material was distilled under high vacuum. Major fractions were distilled between 88 °C and 152 °C. Pure material was recovered in 85% yield. ¹H NMR (CDCl₃) δ (ppm) 7.56 (d, J 8.0, 1H), 7.31 (d, J 8.0, 1H), 7.26 (s, 1H), 7.16 (t, J 8.0, 1H), 4.84 (s, 2H), 4.64 (s, 2H).

Step 2: 2-benzyl-4-bromoisoindoline **81**

Potassium bicarbonate (2.5 eq.) was suspended in MeCN (0.17 M) and the mixture was heated to 80 °C. Solutions of 1-bromo-2,3-bis(bromomethyl)benzene **80** (1.0 eq.) in MeCN (1.64 M) and benzylamine (1.0 eq.) in MeCN (1.64 M) were added concurrently via addition funnels over 1 h. The reaction mixture was stirred at 77 °C for 16h. The contents of the reaction flask were cooled, filtered and the solvent removed by evaporation. The reaction was partitioned between 1M K₂CO₃ and EtOAc. The organics were washed with brine, dried with anhydrous Na₂SO₄, filtered, and evaporated. Flash column chromatography (gradient elution: heptane to 10% EtOAc in heptane) gave after evaporation the title compound **81** as a pale oil. ¹H NMR (CDCl₃) δ (ppm) 7.41-7.39 (m, 2H), 7.37-7.34 (m, 2H), 7.32-7.27 (m, 2H), 7.10-7.03 (m, 2H), 4.02 (s, 2H), 3.97 (s, 2H), 3.91 (s, 2H). LRMS (ESI) *m/z* 289 (M+H)⁺.

Converted to HCl salt in HCl/MeOH by adding MTBE and filtering solid to give the corresponding HCl salt.

Step 3: 2-benzyl-4-vinylisoindoline **82**

A solution of 2-benzyl-4-bromoisoindoline **81** (1.0 eq.) and tributyl(vinyl)tin (1.2 eq.) in toluene (4 M) was degassed by bubbling nitrogen gas through the solution for 0.25h.

- 5 Tetrakis(triphenylphosphine)palladium(0) (0.02 eq.) was added and the resulting solution heated in a 100 °C oil bath under nitrogen for 24h. The contents of the reaction flask were cooled, evaporated and subjected to flash column chromatography eluting with hexane/EtOAc 95/5 to give after evaporation the title compound as a pale oil that turned pink on standing. LRMS (ESI) m/z 236 (M+H)⁺.

10

Step 4: 4-vinylisoindoline **83**

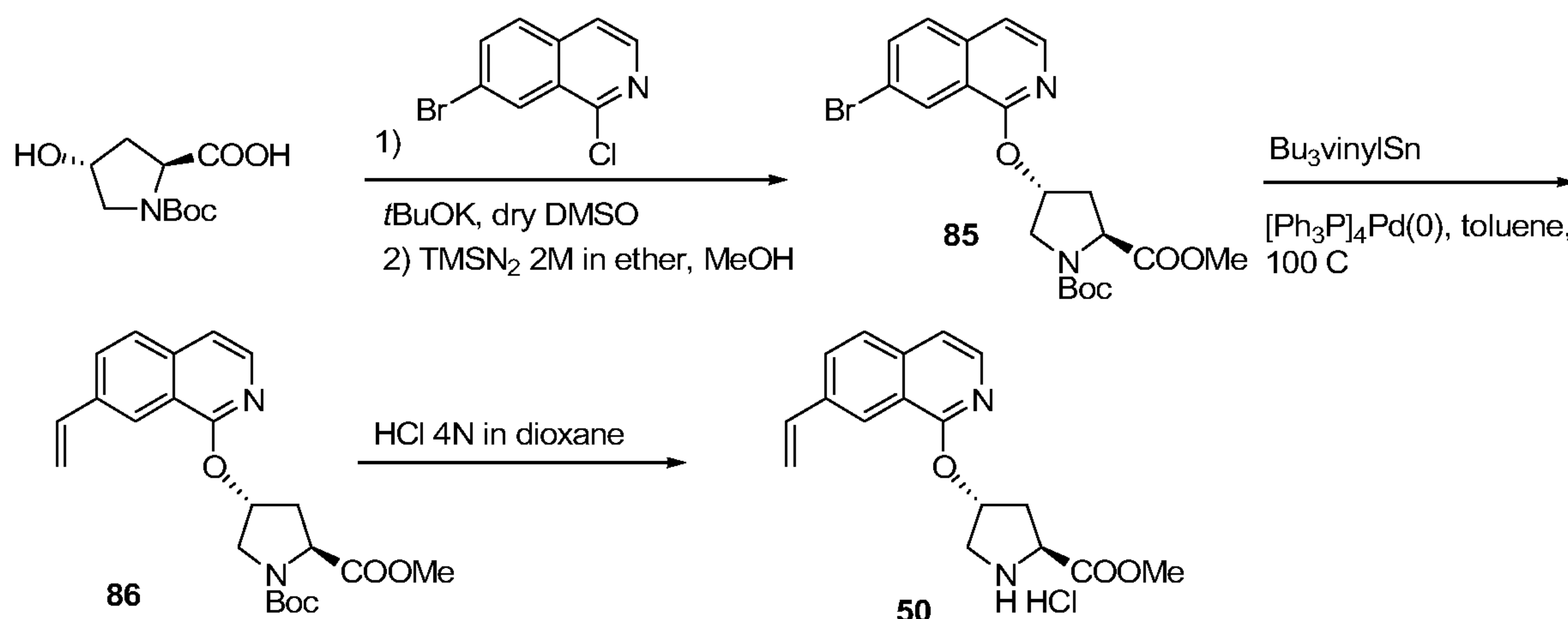
A solution of 2-benzyl-4-vinylisoindoline **82** (1.0 eq.) in DCE (0.38 M) was placed in a round bottom flask under nitrogen. To this was attached an addition funnel containing a solution of 1-chloroethyl chloroformate (1.2 eq.) in DCE. The reaction flask was cooled in an ice bath and the
15 contents of the addition funnel were added dropwise over 20 min keeping the internal reaction temperature <5 °C. After the addition was complete the reaction flask was allowed to warm to RT then heated to reflux for 45 min. The contents of the reaction flask were cooled to RT then the solvent removed by evaporation. MeOH was added and the contents of the reaction flask were heated to reflux for 30 min. The reaction flask was cooled and the solvent removed by
20 evaporation. Water was added and the resulting mixture washed with EtOAc. The aqueous layer was made basic with 2N sodium hydroxide then extracted with DCM (4×250 mL). The combined organic extracts were dried with anhydrous sodium sulfate, filtered and the filtrate evaporated. The remaining residue was subjected to flash column chromatography eluting with DCM/MeOH/ammonium hydroxide 97/3/0.3 to 95/5/0.5. Evaporation of fractions gave the title
25 compound **83** as a brown oil, (71% for two steps). LRMS (ESI) m/z 146 (M+H)⁺.

Step 5: 1-tert-butyl 2-methyl (2S,4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate **84**

A solution of 1-tert-butyl 2-methyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (1.0 eq.) in
30 DMF (0.5 M) under nitrogen was cooled to 0 °C. Solid 1,1'-carbonyldiimidazole (1.0 eq.) was added to the reaction. The contents of the reaction flask were warmed to RT and after 2 h a solution of 4-vinylisoindoline (1.0 eq.) in DMF (4 M) was added. The reaction was heated in a 60 °C oil bath for 2 h then cooled and poured into water and 5% potassium bisulfate. The resulting mixture was extracted with EtOAc. Combined organics were washed with brine, dried with
35 anhydrous sodium sulfate, filtered and evaporated. Flash column chromatography eluting with hexane/EtOAc 70/30 gave the title compound as a white foam (81%). LRMS (ESI) m/z 417 (M+H).

Scheme 12

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Compound 50: (2*S*,4*R*)-2-(methoxycarbonyl)-4-[(7-vinylisoquinolin-1-yl)oxy]pyrrolidinium chloride

5

Step 1: 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-[(7-bromoisoquinolin-1-yl)oxy]pyrrolidine-1,2-dicarboxylate **85**

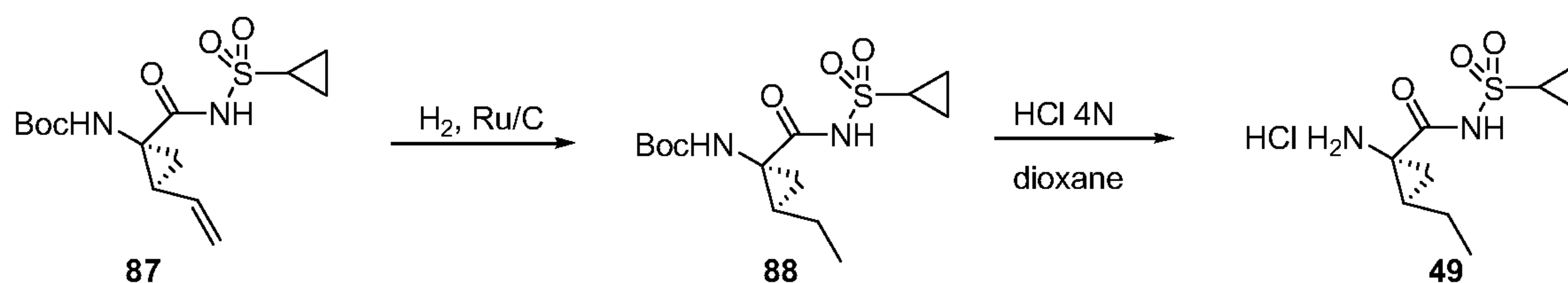
To a solution of *trans* 4-hydroxy L-BOC-proline (1 eq) in DMSO (0.2 M) at RT was added *t*BuOK (3 eq) in a single portion. The reaction mixture was stirred at RT for 30 min, cooled to 10°C and 7-bromo-1-chloroisoquinoline was added (1 eq). The resulting mixture was allowed to warm to RT and stirred overnight. The organic layer was washed with citric acid 10% solution, water and brine and the aqueous phases were back extracted with EtOAc. The combined organic phases were dried (Na₂SO₄) and the solvent evaporated under reduced pressure to give a dark solid that was dissolved in MeOH. To the stirred solution, trimethylsilyldiazomethane 2.0 M in hexanes (4.0 eq.) was added dropwise at 15 °C. The resulting mixture was stirred for 15 min after gas evolution has ceased. Volatiles were removed by rotary evaporation and the residue was purified by flash chromatography (Horizon system, column SiO₂, eluent: PE:EtOAc with EtOAc (from 60 to 80%) to give the title product **85** as a solid (71%). MS (ES⁺) *m/z* 452 (M+H⁺).

Step 2: 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-[(7-vinylisoquinolin-1-yl)oxy]pyrrolidine-1,2-dicarboxylate **86**

Aryl bromide **85** (1.0 eq.) was dissolved in toluene (0.2 M) and treated with tributylvinyltin (1.5 eq) and [Ph₃P]₄Pd(0) (0.1 eq). The reaction mixture was stirred at 80°C under N₂ atmosphere for 2 h. After cooling to RT, the reaction mixture was poured into EtOAc and washed with brine. The organic phase was separated, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (Horizon system, column SiO₂, eluent: PE:EtOAc with EtOAc from 20 to 40%) to give the title compound **86** as a viscous oil (74%). MS (ES⁺) *m/z* 399 (M+H⁺).

Step 3: (2*S*,4*R*)-2-(methoxycarbonyl)-4-[(7-vinylisoquinolin-1-yl)oxy]pyrrolidinium chloride **50**

Carbamate **86** was dissolved in a 4.0 M HCl solution in dioxane. The resulting mixture was stirred at RT for 0.5 h, during which time the product precipitated. The title compound **50** was filtered off and washed with hexane/EtOAc 1/1 v/v (96%). ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 8.30 (s, 1H), 8.01-7.98 (m, 2H), 7.89 (d, *J* 8.5, 1H), 7.43 (d, *J* 5.8, 1H), 6.93 (dd, *J* 17.6, 10.9, 1H), 6.07 (d, *J* 17.6, 1H), 5.85 (bs, 1H), 5.43 (d, *J* 11.0, 1H), 4.86 (dd, *J* 10.4, 7.7, 1H), 3.81 (s, 3H), 3.78-3.74 (m, 1H), 3.60 (d, *J* 12.8, 1H), 2.71-2.66 (m, 1H), 2.57-2.50 (m, partially obscured by residual DMSO, 1H). MS (ES⁺) *m/z* 299 (M+H⁺).

Scheme 13**Compound 49: (1*R*,2*S*)-1-amino-*N*-(cyclopropylsulfonyl)amino-2-ethylcyclopropane carboxamide hydrochloride****Step 1: *tert*-butyl ((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)carbamate **88****

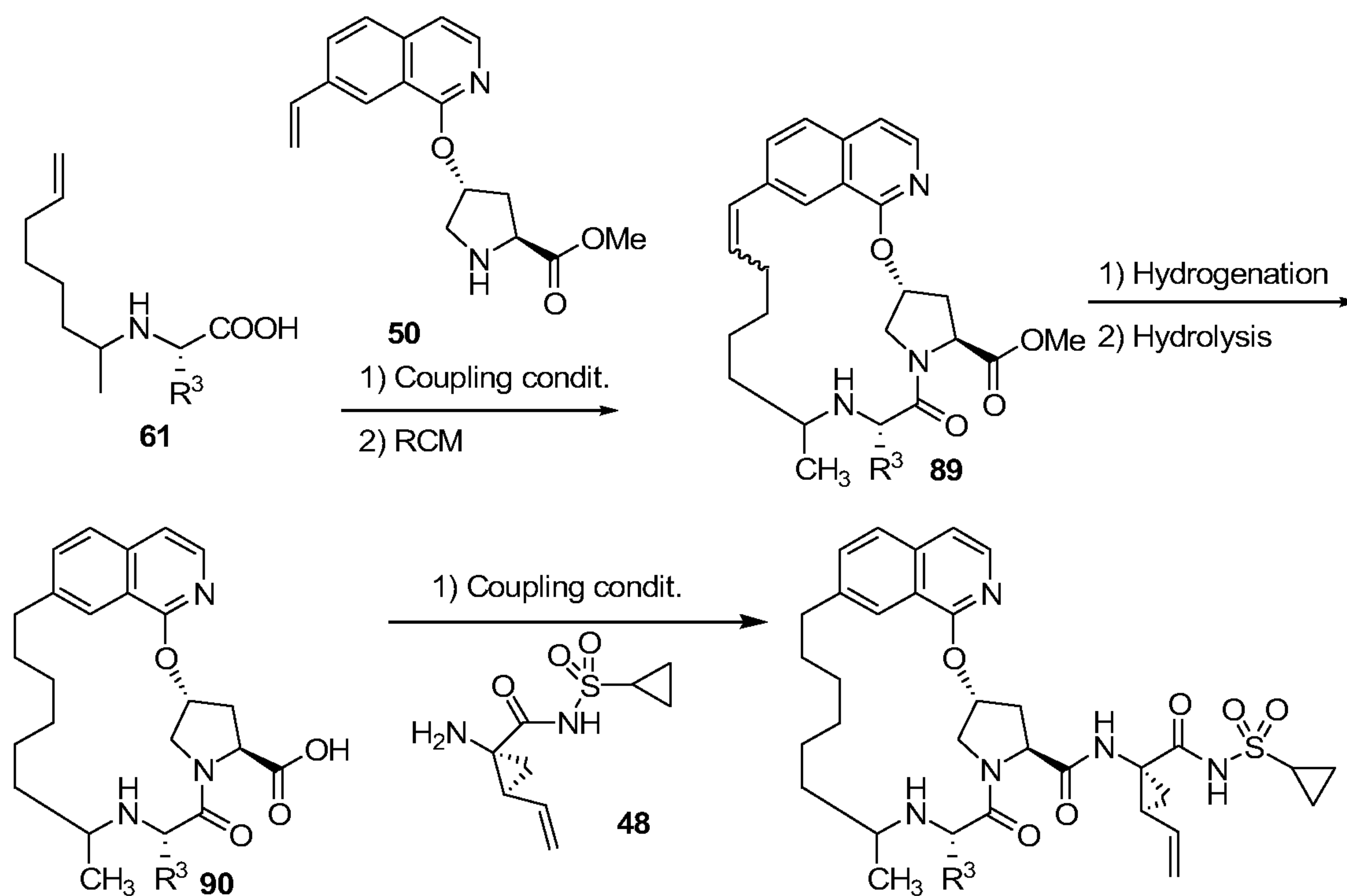
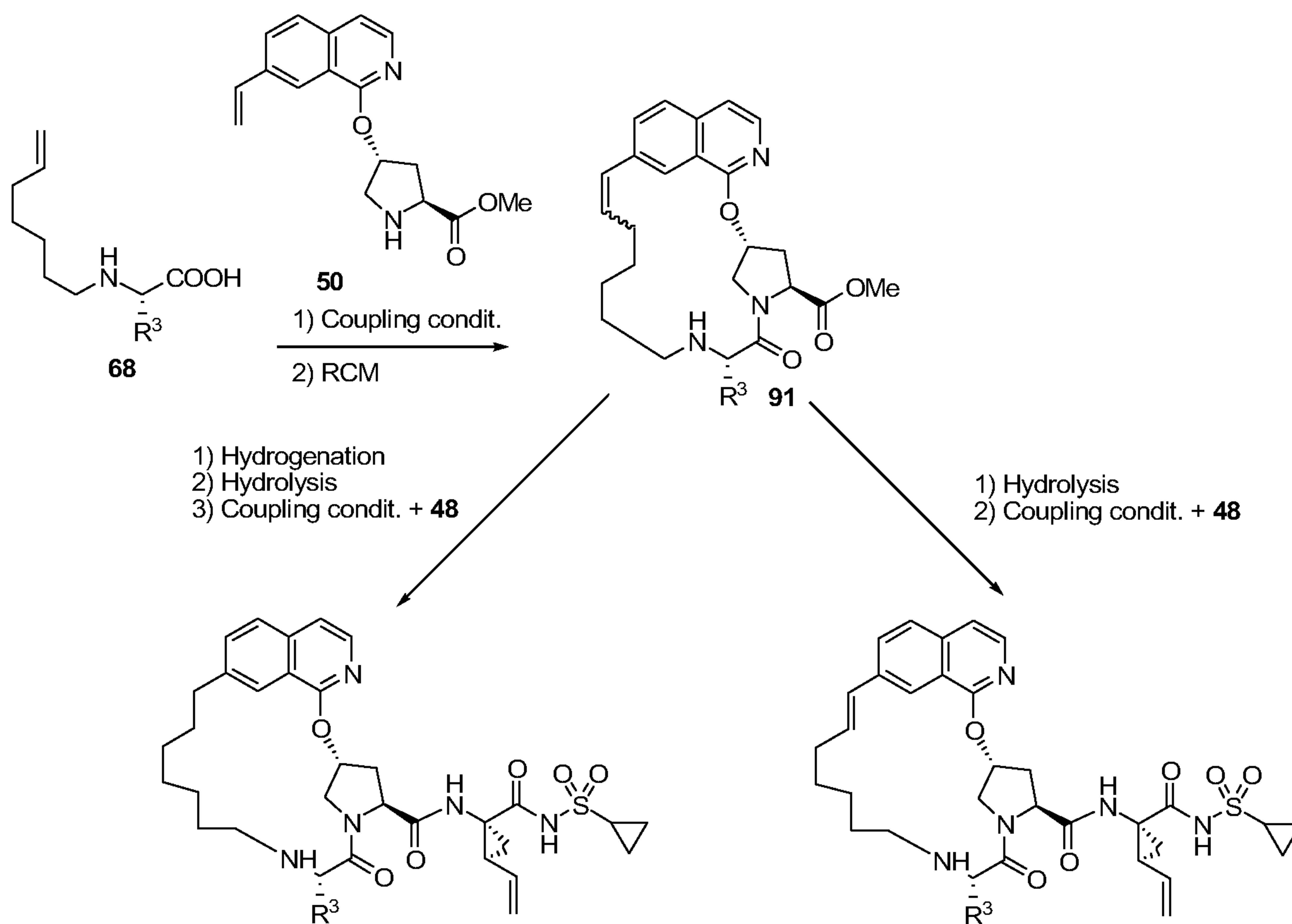
A hydrogenation vessel was charged with a solution of *tert*-butyl ((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)carbamate **87** (prepared as described in WO 03/099274) in MeOH followed by Ru/C (7.5 wt%). The vessel was placed under N₂ (20 psig) and vented to atmospheric pressure three times to remove residual oxygen. The vessel was then placed under H₂ (50 psig) and the reaction was complete in <5 h based on H₂ consumption. After 20 h, the vessel was vented to atmospheric pressure. The reaction slurry was then filtered and evaporated to a yellow oil which was brought to the following step without further purification. MS (ES⁺) *m/z* 333 (M+H⁺).

Step 2: (1*R*,2*S*)-1-amino-*N*-(cyclopropylsulfonyl)amino-2-ethylcyclopropane carboxamide hydrochloride **49**

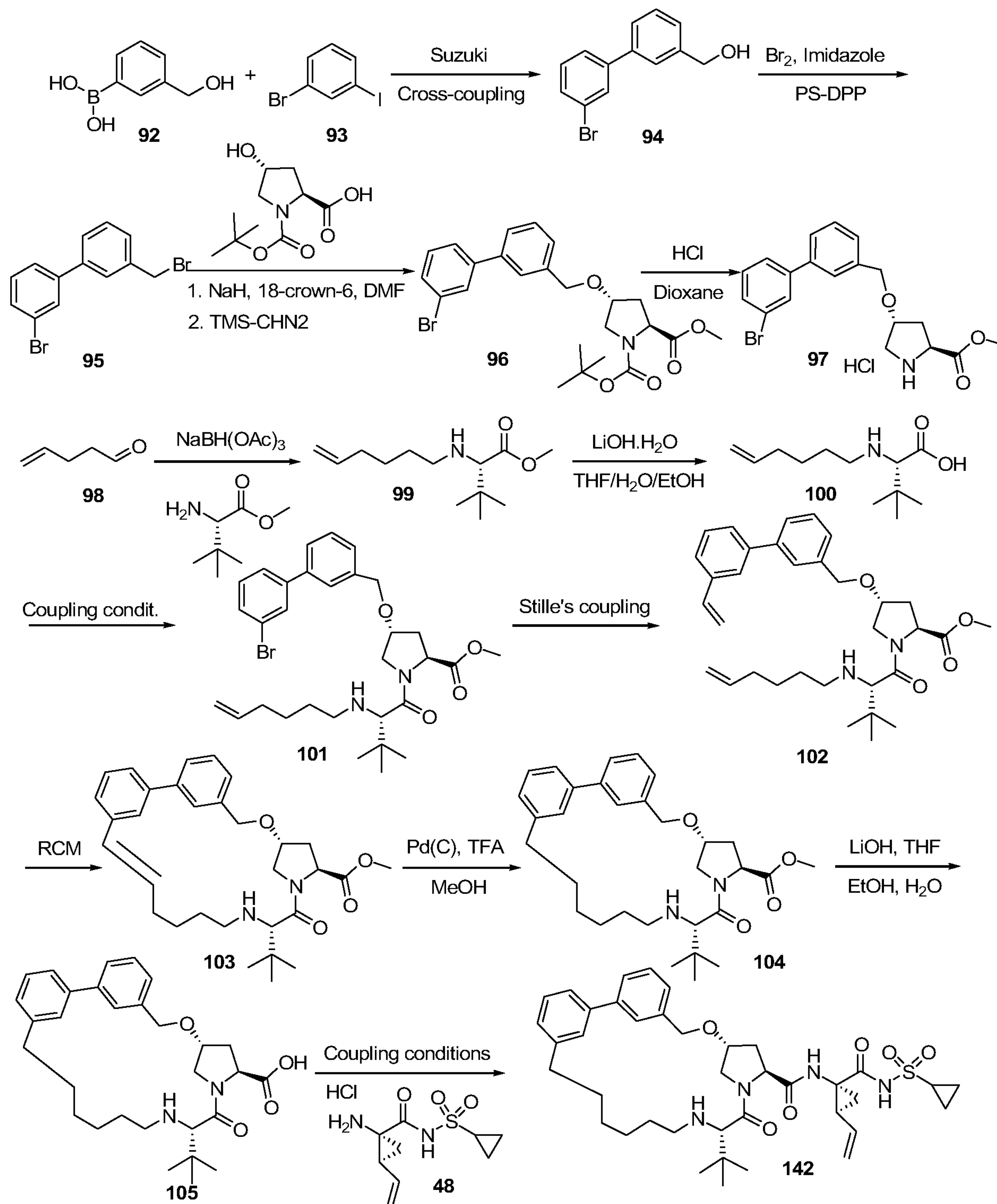
A 0.33 M solution of carbamate in 4N HCl/dioxane was stirred at RT for 12 h. The volatiles were then removed under reduced pressure to give the title compound **49** as a pale yellow solid that was used directly in the next step. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.83 (bs, 2H), 3.03 (m, 1H), 1.71-1.37 (m, 5H), 1.16-1.09 (m, 4H), 0.97 (t, *J* 7.3, 3H).

Scheme 14

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**Scheme 15**

Scheme 16



Compound 142: (9*R*,11*S*,14*S*)-14-tert-butyl-N-((1*R*,2*S*)-1-

5 **{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-13-oxo-8-oxa-12,15-**
diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-1(26),2(28),3,5,22,24-hexaene-11-carboxamide

Step 1: (3'-bromobiphenyl-3-yl)methanol **94**

To a 0.2 M solution of [3-(hydroxymethyl)phenyl]boronic acid in DME were sequentially added 1-bromo-3-iodobenzene (0.83 eq.) and a 2M solution of Na₂CO₃ (3.0 eq.). The reaction mixture was degassed, trans-bis(triphenylphosphine)palladium(II) chloride (0.01 eq.) was added and it was
5 stirred at 80°C for 6h. After cooling down to RT the reaction mixture was diluted with EtOAc and washed with saturated aq. NaHCO₃, 1N HCl and brine. The residue was dried (Na₂SO₄) and evaporated under reduced pressure to afford an oil which was purified by flash chromatography (SiO₂, PE:EtOAc=8:2) to afford the title compound **94** as an oil (80%). ¹H NMR (400 MHz, DMSO-d₆, 300 K) δ 7.87 (s, 1H), 7.71 (d, J 7.7, 1H), 7.66 (bs, 1H), 7.59 (t, J 6.8, 2H), 7.47 (t, J
10 7.7, 2H), 7.39 (d, J 7.7, 1H), 4.61 (s, 2H).

Step 2: 3-bromo-3'-(bromomethyl)biphenyl **95**

A 0.5 M solution of (3'-bromobiphenyl-3-yl)methanol **94** in DCM was added to a 10 min. prestirred suspension of triphenylphosphine resin (1.6 eq.), Br₂ (1.6 eq.) and 0.25 M solution of imidazole (1.7
15 eq.) in DCM. The reaction mixture was gently stirred at RT for 3h. The resin was then filtered off and washed with DCM, the filtrate was evaporated to dryness to afford the title compound **95** (78% crude yield) as a brown oil. The material was used in the following step without further purification. ¹H NMR (400 MHz, DMSO-d₆, 300 K) δ 7.90 (s, 1H), 7.86-7.82 (m, 1H), 7.76-7.70 (m, 1H), 7.70-7.65 (m, 1H), 7.65-7.60 (m, 1H), 7.55-7.49 (m, 2H), 7.47 (d, J 7.8, 1H), 4.81 (s,
20 2H).

Step 3: 1-tert-butyl 2-methyl (2S,4R)-4-[(3'-bromobiphenyl-3-yl)methoxy]pyrrolidine-1,2-dicarboxylate **96**

(4R)-1-(tert-butoxycarbonyl)-4-hydroxy-L-proline (1.0 eq.) in DMF was added to a 0°C cooled
25 suspension of 18-crown-6 (0.1 eq.) and NaH (3.0 eq.) in DMF (0.5 M final concentration). The reaction mixture was allowed to warm up to RT and stirred for 1 h. A 0.5M solution of 3-bromo-3'-(bromomethyl)biphenyl **95** (1.0 eq.) in DMF was added dropwise and the reaction mixture was stirred at RT overnight. The reaction mixture was quenched with aqueous HCl (1N) at 0°C and diluted with EtOAc. The organic layer was separated, washed with aqueous HCl (1N) and brine,
30 dried (Na₂SO₄) and evaporated to a solid. MS (ES⁺) m/z 498, 500 (M+Na)⁺. A 0.5 M solution of the crude material in a mixture of toluene:MeOH (2:1) was cooled to 0°C and treated dropwise with TMS-diazomethane (1.5 eq.). The reaction mixture was allowed to warm up to RT and stirred for 1 h. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography (SiO₂, PE:EtOAc=8:2) to afford the title compound **96** as a yellow oil (78%). ¹H
35 NMR (400 MHz, DMSO-d₆, 300 K) δ 7.90-7.86 (m, 1H), 7.71 (d, J 7.7, 1H), 7.69-7.58 (m, 3H), 7.54-7.44 (m, 2H), 7.40 (d, J 7.7, 1H), 4.66-4.55 (m, 2H), 4.31-4.21 (m, 2H), 3.74-3.65 (m, 3H), 3.60-3.45 (m, 2H), 2.51-2.37 (m, 1H), 2.10-2.00 (m, 1H), 1.44-1.31 (m, 9H). MS (ES⁺) m/z 512, 514 (M+Na)⁺.

Step 4: (2*S*,4*R*)-4-[(3'-bromobiphenyl-3-yl)methoxy]-2-(methoxycarbonyl)pyrrolidinium chloride **97**
1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-[(3'-bromobiphenyl-3-yl)methoxy]pyrrolidine-1,2-dicarboxylate **96**
(1.0 eq.) was dissolved at 0°C in a 4M solution of HCl in dioxane (3.0 eq.) to give a 1.0 M solution.
The reaction mixture was stirred at RT for 2h then the solvent was evaporated under reduced
5 pressure to afford the title compound **97** as a white foam (96%). ¹H NMR (400 MHz, DMSO-*d*₆,
300 K) δ 10.33-9.33 (bs, 1H), 7.89 (s, 1H), 7.77-7.71 (m, 2H), 7.67 (d, J 7.7, 1H), 7.62 (d, J 7.7,
1H), 7.54-7.43 (m, 3H), 4.63 (s, 2H), 4.55 (dd, J 10.7, 7.4 Hz, 1H), 4.41 (bs, 1H), 3.81 (s, 3H),
3.51-3.40 (m, 2H), 2.59-2.51 (m, 1H), 2.27-2.16 (m, 1H). MS (ES⁺) *m/z* 390, 392 (M+H)⁺.

10 Step 5: methyl *N*-hex-5-en-1-yl-3-methyl-L-valinate **99**

Hex-5-enal **98** (obtained from hex-5-en-1-ol via a PCC oxidation) (0.95 eq.) was added at RT to a
0.11 M solution of (2*S*)-1-methoxy-3,3-dimethyl-1-oxobutan-2-aminium chloride (1.0 eq.) and
TEA (1.0 eq.) in DCE. Sodium triacetoxyborohydride (1.0 eq.) was added in one portion and the
reaction mixture was stirred at RT overnight. The reaction mixture was diluted with
15 DCM/saturated aqueous NaHCO₃. The phases were separated; the organic layer was washed with
brine, dried (Na₂SO₄) and filtered through a short path of silica gel (PE:EtOAc=9:1) to afford the
title compound **99** as a pale yellow liquid (72 %). ¹H NMR (300 MHz, CDCl₃, 300 K) δ 5.89-5.71
(m, 1H), 5.07-4.88 (m, 2H), 3.71 (s, 3H), 2.88 (s, 1H), 2.62-2.48 (m, 1H), 2.45-2.31 (m, 1H),
2.13-1.98 (m, 2H), 1.67-1.54 (m, 1H), 1.53-1.35 (m, 4H), 0.95 (s, 9H).

20 Step 6: *N*-hex-5-en-1-yl-3-methyl-L-valine **100**

A 0.25M solution of methyl *N*-hex-5-en-1-yl-3-methyl-L-valinate **99** in a mixture of MeOH:water
(3:1) was treated with LiOH (3.0 eq.) at RT. The reaction mixture was stirred at 70°C for 3h. The
organic solvent was removed under reduced pressure and the residue was acidified with aqueous
25 HCl (1N). The water phase was repeatedly extracted with EtOAc, dried (Na₂SO₄) and
concentrated under reduced pressure to afford the crude product, which was used in the following
step without further purification. MS (ES⁺) *m/z* 214 (M+H)⁺

30 Step 7: methyl *N*-hex-5-en-1-yl-3-methyl-L-valyl-(4*R*)-4-[(3'-bromobiphenyl-3-yl)methoxy]-L-
prolinate **101**

N-hex-5-en-1-yl-3-methyl-L-valine (1.2 eq.), DIPEA (3.7 eq.) and HATU (1.2 eq.) were
sequentially added to a 0.10 M solution of (2*S*,4*R*)-4-[(3'-bromobiphenyl-3-yl)methoxy]-2-
(methoxycarbonyl)pyrrolidinium chloride in DMF. The reaction mixture was stirred at RT
overnight then it was diluted with H₂O/EtOAc and extracted. The collected organic layers were
35 washed with brine, dried (Na₂SO₄) and evaporated under reduced pressure. The residue was
purified by flash chromatography (SiO₂, PE:EtOAc with EtOAc from 30 to 100%) to afford the
title compound **101** as a solid (50%). ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 7.85 (bs, 1H), 7.69
(d, J 7.8, 1H), 7.66-7.58 (m, 3H), 7.51-7.43 (m, 2H), 7.37 (d, J 7.8, 1H), 5.76-5.64 (m, 1H), 4.97-
4.87 (m, 2H), 4.63 (s, 2H), 4.45 (t, J 8.6, 1H), 4.31 (bs, 1H), 4.07 (d, J 11.7, 1H), 3.66 (s, 3H),

3.73-3.55 (m, 2H), 2.50-2.41 (m, 1H), 2.40-2.32 (m, 1H), 2.31-2.23 (m, 1H), 2.08-1.96 (m, 1H), 1.94-1.85 (m, 2H), 1.34-1.18 (m, 3H), 0.96 (s, 9H), 0.94-0.85 (m, 2H). MS (ES⁺) m/z 585, 587 (M+H)⁺.

5 Step 8: methyl *N*-hex-5-en-1-yl-3-methyl-L-valyl-(4*R*)-4-[(3'-vinylbiphenyl-3-yl)methoxy]-L-prolinate **102**

Vinyltri-*n*-butyltin (1.5 eq.) was added to a 0.08 M degassed solution of methyl *N*-hex-5-en-1-yl-3-methyl-L-valyl-(4*R*)-4-[(3'-bromobiphenyl-3-yl)methoxy]-L-prolinate **101** in toluene. Tetrakis (triphenylphosphine) palladium(0) (0.15 eq.) was added and the reaction mixture was stirred in a
 10 preheated oil bath (100°C) for 2h. The crude mixture was cooled down to RT and evaporated under reduced pressure to give a residue that was purified by flash chromatography (SiO₂, PE:EtOAc=7:3) to afford the title compound **102** as a yellow oil (38 %). ¹H NMR (400 MHz, DMSO-*d*₆, 300K) δ 7.74 (bs, 1H), 7.69-7.60 (m, 2H), 7.57 (d, J 7.7, 1H), 7.52 (t, J 7.7, 1H), 7.50-7.44 (m, 2H), 7.34 (d, J 7.7, 1H), 6.86 (dd, J 17.7, 10.9, 1H), 5.97 (d, J 17.7, 1H), 5.76-5.64 (m,
 15 1H), 5.36 (d, J 10.9, 1H), 4.97-4.86 (m, 2H), 4.63 (s, 2H), 4.46 (t, J 8.6, 1H), 4.31 (bs, 1H), 3.74-3.55 (m, 2H), 3.66 (s, 3H), 2.50-2.41 (m, 1H), 2.40-2.31 (m, 1H), 2.31-2.23 (m, 1H), 1.94-1.85 (m, 2H), 1.70-1.53 (m, 3H), 1.41-1.30 (m, 4H), 1.00-0.85 (m, 8H), 0.96 (s, 9H). MS (ES⁺) m/z 533 (M+H)⁺

20 Step 9: Methyl (9*R*,11*S*,14*S*,20*E*)-14-*tert*-butyl-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-1(26),2(28),3,5,20,22,24-heptaene-11-carboxylate **103**

Zhan catalyst I (0.15 eq.) was added to a 0.01 M solution of methyl *N*-hex-5-en-1-yl-3-methyl-L-valyl-(4*R*)-4-[(3'-vinylbiphenyl-3-yl)methoxy]-L-prolinate **102** in DCM containing trifluoroacetic acid (1.3 eq.). The reaction mixture was stirred under microwave irradiation at 100°C for 20 min.
 25 The crude material was evaporated under reduced pressure affording a black residue which was used without further purification. MS (ES⁺) m/z 505 (M+H)⁺.

Step 10: methyl (9*R*,11*S*,14*S*)-14-*tert*-butyl-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-1(26),2(28),3,5,22,24-hexaene-11-carboxylate **104**

30 Pd/C 10% (20% w/w) was added to a 0.025 M solution of methyl (9*R*,11*S*,14*S*,20*E*)-14-*tert*-butyl-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-1(26),2(28),3,5,20,22,24-heptaene-11-carboxylate **103** in MeOH containing trifluoroacetic acid (1.0 eq.). The reaction mixture was stirred under a hydrogen atmosphere for 6h. Solids were filtered off and the resulting solution was evaporated under reduced pressure. The residue was used without further purification in the
 35 following step. MS (ES⁺) m/z 507 (M+H)⁺.

Step 11: (9*R*,11*S*,14*S*)-14-*tert*-butyl-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-1(26),2(28),3,5,22,24-hexaene-11-carboxylic acid **105**

LiOH (3.0 eq.) was added to a 0.05 M solution of methyl (9*R*,11*S*,14*S*)-14-*tert*-butyl-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-1(26),2(28),3,5,22,24-hexaene-11-carboxylate **104** in a mixture of THF:EtOH:H₂O (2:1:1). The reaction mixture was stirred at 40°C for 2 h then the solvent was evaporated under reduced pressure. Aqueous HCl (1N) was added to reach pH = 6 and the mixture was evaporated to dryness to yield a dark solid which was used without further purification. MS (ES⁺) m/z 493 (M+H)⁺.

Step 12: (9*R*,11*S*,14*S*)-14-*tert*-butyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-
1(26),2(28),3,5,22,24-hexaene-11-carboxamide **142**

(1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropanaminium chloride **48**

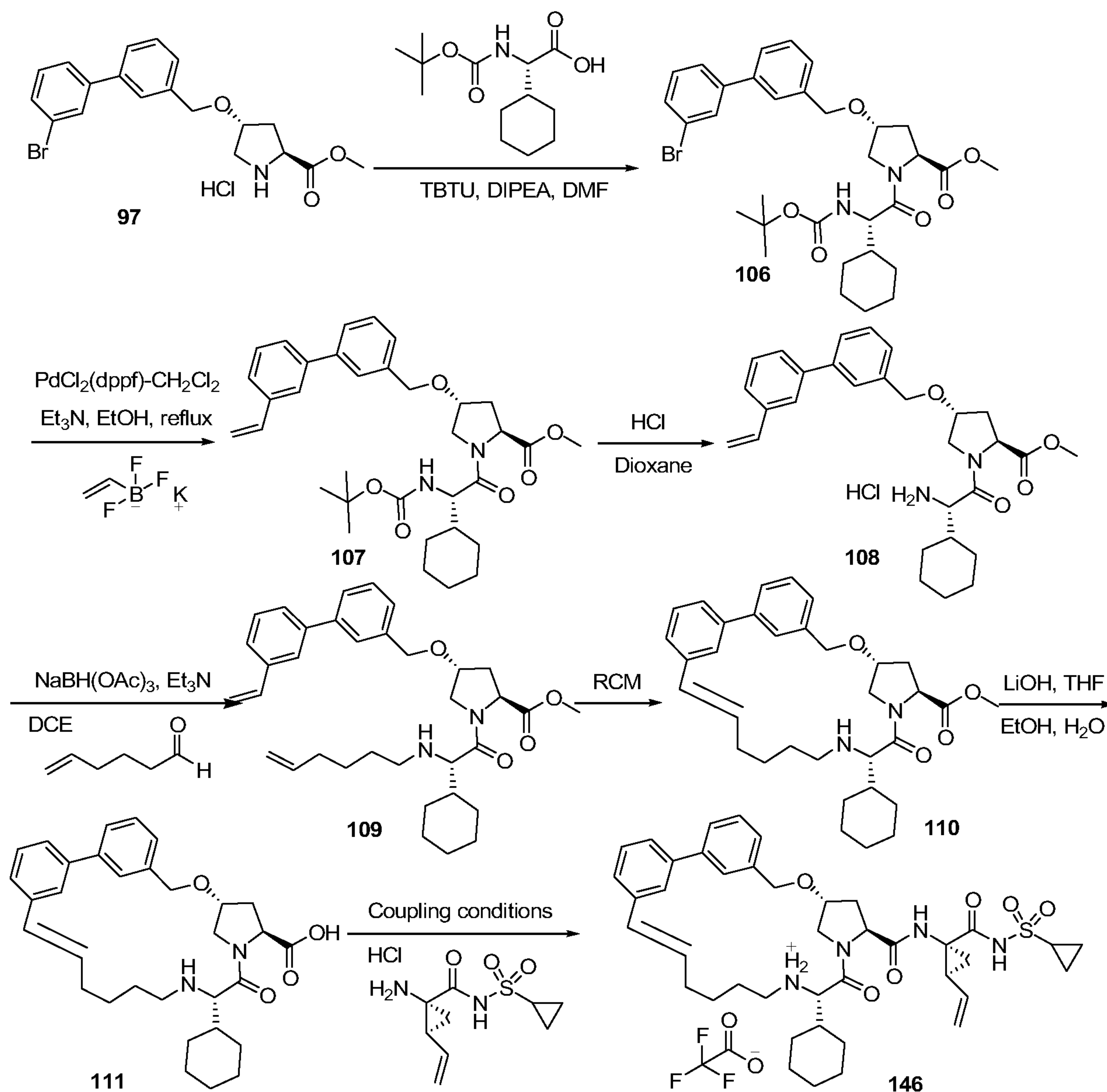
(prepared as described in WO 03/099274) (1.2 eq.) and HATU (1.2 eq.) were added to a 0.1M solution of (9*R*,11*S*,14*S*)-14-*tert*-butyl-13-oxo-8-oxa-12,15-

diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-1(26),2(28),3,5,22,24-hexaene-11-carboxylic acid **105** in

DMF containing DIPEA (4.0 eq.). The reaction mixture was stirred at RT overnight. The reaction mixture was concentrated to dryness, dissolved in DMSO and purified by RP-HPLC (stationary phase: column Waters XTerra C₁₈, 5μm, 19x150. Mobile phase: MeCN/H₂O buffered with 0.1% TFA from 30% to 90 % of MeCN in 14 minutes, run time 18 minutes). Fractions containing the pure compound were combined and freeze dried to afford compound **142** (TFA salt) as an off white

solid (30 % over 4 steps). ¹H NMR (400 MHz, DMSO-d₆, 300 K) δ 10.65 (s, 1H), 8.89 (s, 1H), 8.65-8.49 (bs, 1H), 8.25-8.11 (bs, 1H), 7.62-7.56 (m, 2H), 7.51-7.38 (m, 4H), 7.31 (d, J 7.3, 1H), 7.24 (d, J 7.3, 1H), 5.69-5.53 (m, 1H), 5.24 (d, J 17.2, 1H), 5.14 (d, J 11.9, 1H), 4.71 (d, J 12.4, 1H), 4.61 (d, J 12.4, 1H), 4.31 (bt, 1H), 4.37 (bs, 1H), 4.16 (d, J 8.8, 1H), 4.04 (d, J 11.9, 1H), 3.79 (dd, J 11.5, 3.9, 1H), 3.00-2.91 (m, 1H), 2.91-2.81 (m, 1H), 2.80-2.68 (m, 2H), 2.22 (q, J 17.5, 8.8, 1H), 2.02-1.91 (m, 1H), 1.83-1.69 (m, 2H), 1.68-1.56 (m, 2H), 1.41-1.24 (m, 5H), 1.22-1.02 (m, 13H), 0.91 (t, J 7.3, 4H). MS (ES⁺) m/z 705 (M+H)⁺.

Scheme 17



Compound 146: (9*R*,11*S*,14*S*,20*E*)-14-cyclohexyl-*N*-((1*R*,2*S*)-1-[(cyclopropylsulfonyl)amino]carbonyl)-2-vinylcyclopropyl)-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacosa-1(26),2(28),3,5,20,22,24-heptaene-11-carboxamide

Step 1: methyl (4*R*)-4-[(3'-bromobiphenyl-3-yl)methoxy]-1-[(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-2-cyclohexylacetyl]-*L*-prolinate 106

- 10 (2*S*)-[[(*tert*-butoxycarbonyl)amino](cyclohexyl)acetic acid (1.05 eq.), DIPEA (3.2 eq.) and TBTU (1.1 eq.) were added to a 0.12M solution of methyl (4*R*)-4-[(3'-bromobiphenyl-3-yl)methoxy]-*L*-prolinate hydrochloride **97** in DMF. The reaction mixture was stirred at RT for 2h then it was diluted with EtOAc:H₂O and acidified with aqueous (1N) HCl. The phases were separated and the organic layer was washed sequentially with aqueous (1N) HCl, aqueous (2N) NaOH and brine,

dried (Na₂SO₄) and evaporated under reduced pressure to afford the title compound **106** (95 % crude yield) as a pale yellow foam which was used without further purification. ¹H NMR (400 MHz, DMSO-d₆, 300 K) δ 7.86 (s, 1H), 7.70 (d, J 7.8, 1H), 7.66-7.57 (m, 3H), 7.54-7.33 (m, 3H), 6.94 (d, J 8.6, 1H), 4.65 (d, J 11.6, 1H), 4.58 (d, J 11.6, 1H), 4.36 (t, J 8.5, 1H), 4.32 (bs, 1H), 4.19 (d, J 11.1, 1H), 4.11 (t, J 11.1, 1H), 3.74-3.66 (m, 1H), 3.65 (s, 3H), 2.48-2.35 (m, 1H), 2.08-1.97 (m, 1H), 1.83-1.55 (m, 6H), 1.44-1.37 (m, 1H), 1.34 (s, 9H), 1.22-1.09 (m, 2H), 1.08-0.93 (m, 2H). MS (ES⁺) m/z 629, 631 (M+H)⁺

Step 2: methyl (4R)-1-[(2S)-2-[(*tert*-butoxycarbonyl)amino]-2-cyclohexylacetyl]-4-[(3'-vinylbiphenyl-3-yl)methoxy]-L-prolinate **107**

Potassium vinyltrifluoroborate (2.0 eq.), Et₃N (2.0 eq.) and PdCl₂(dppf)-DCM adduct (0.05 eq.) were sequentially added to a 0.12 M solution of methyl (4R)-4-[(3'-bromobiphenyl-3-yl)methoxy]-1-[(2S)-2-[(*tert*-butoxycarbonyl)amino]-2-cyclohexylacetyl]-L-prolinate **106** in EtOH. The reaction mixture was stirred with heating at reflux for 3 h then it was cooled down to RT and diluted with H₂O:EtOAc. The phases were separated and the organic layer was washed with brine, dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO₂, PE:EtOAc=8:2) to afford the title compound **107** (72%) as a foam. ¹H NMR (400 MHz, DMSO-d₆, 300 K) δ 7.75 (s, 1H), 7.71-7.61 (m, 2H), 7.59 (d, J 7.3, 1H), 7.56-4.43 (m, 3H), 7.39 (d, J 7.3, 1H), 6.94 (d, J 8.6, 1H), 6.86 (dd, J 17.7, 10.9, 1H), 5.98 (d, J 17.7, 1H), 5.36 (d, J 10.9, 1H), 4.66 (d, J 11.7, 1H), 4.58 (d, J 11.7, 1H), 4.36 (t, J 8.6, 1H), 4.32 (bs, 1H), 4.19 (d, J 10.9, 1H), 4.15-4.07 (m, 1H), 3.73-3.66 (m, 1H), 3.65 (s, 3H), 2.46-2.35 (m, 1H), 2.07-1.98 (m, 1H), 1.82-1.57 (m, 6H), 1.42-1.36 (m, 1H), 1.34 (s, 9H), 1.20-1.12 (m, 2H), 1.07-0.94 (m, 2H). MS (ES⁺) m/z 577 (M+H)⁺

Step 3: methyl (4R)-1-[(2S)-2-amino-2-cyclohexylacetyl]-4-[(3'-vinylbiphenyl-3-yl)methoxy]-L-prolinate hydrochloride **108**

Methyl (4R)-1-[(2S)-2-[(*tert*-butoxycarbonyl)amino]-2-cyclohexylacetyl]-4-[(3'-vinylbiphenyl-3-yl)methoxy]-L-prolinate **107** was suspended in 4M solution of HCl in dioxane (final conc. 1.3 M) and stirred at RT for 2 h. The solvent was removed under reduced pressure, the residue was taken up with Et₂O and evaporated to dryness to afford the title compound **108** (95% crude yield) as a white foam. ¹H NMR (400 MHz, DMSO-d₆, 300 K) δ 8.15 (bs, 3H), 7.46 (s, 1H), 7.72-7.64 (m, 2H), 7.60 (d, J 7.6, 1H), 7.57-7.46 (m, 3H), 7.40 (d, J 7.6, 1H), 6.87 (dd, J 17.7, 11.1, 1H), 5.98 (d, J 17.7, 1H), 5.37 (d, J 11.1, 1H), 4.65 (s, 2H), 4.46 (t, J 8.5, 1H), 4.36 (bs, 1H), 4.25-4.18 (m, 1H), 4.10 (d, J 11.4, 1H), 3.72-3.65 (m, 1H), 3.68 (s, 3H), 2.60-2.55 (m, partially obscured by residual DMSO-d₆, 1H), 2.11-2.00 (m, 1H), 1.89-1.61 (m, 6H), 1.32-1.02 (m, 5H). MS (ES⁺) m/z 477 (M+H)⁺

Step 4: methyl (4R)-1-[(2S)-2-cyclohexyl-2-(hex-5-en-1-ylamino)acetyl]-4-[(3'-vinylbiphenyl-3-yl)methoxy]-L-prolinate **109**

Et₃N (2.0 eq.), hex-5-enal (1.0 eq.) (obtained from hex-5-en-1-ol *via* a PCC oxidation and sodium triacetoxyborohydride (1.3 eq.) were sequentially added to a 0.07 M solution of methyl (4*R*)-1-[(2*S*)-2-amino-2-cyclohexylacetyl]-4-[(3'-vinylbiphenyl-3-yl)methoxy]-L-prolinate hydrochloride **108** in DCE. The reaction mixture was stirred at RT for 2 h then it was diluted with DCM, saturated aqueous NaHCO₃ and extracted. The collected organic layers were washed with brine, dried (Na₂SO₄) and evaporated under reduced pressure to yield a residue that was purified by flash chromatography (SiO₂, PE:EtOAc=7:3) to afford the title compound **109** (67%) as a colourless oil. ¹H NMR (400 MHz, DMSO-d₆, 300 K) δ 7.74 (s, 1H), 7.70-7.43 (m, 7H), 7.35 (d, J 7.6, 1H), 6.86 (dd, J 17.7, 10.9, 1H), 5.97 (d, J 17.7, 1H), 5.79-5.76 (m, 1H), 5.36 (d, J 10.9, 1H), 4.99-4.87 (m, 2H), 4.64 (s, 2H), 4.43 (t, J 8.3, 1H), 4.32 (bs, 1H), 4.00 (d, J 11.4, 1H), 3.64 (s, 3H), 3.64-3.57 (m, 1H), 3.21-3.13 (m, 1H), 2.49-2.34 (m, 2H), 2.33-2.22 (m, 1H), 2.06-1.97 (m, 1H), 1.97-1.83 (m, 3H), 1.75-1.57 (m, 5H), 1.34-1.06 (m, 9H). MS (ES⁺) m/z 559 (M+H)⁺

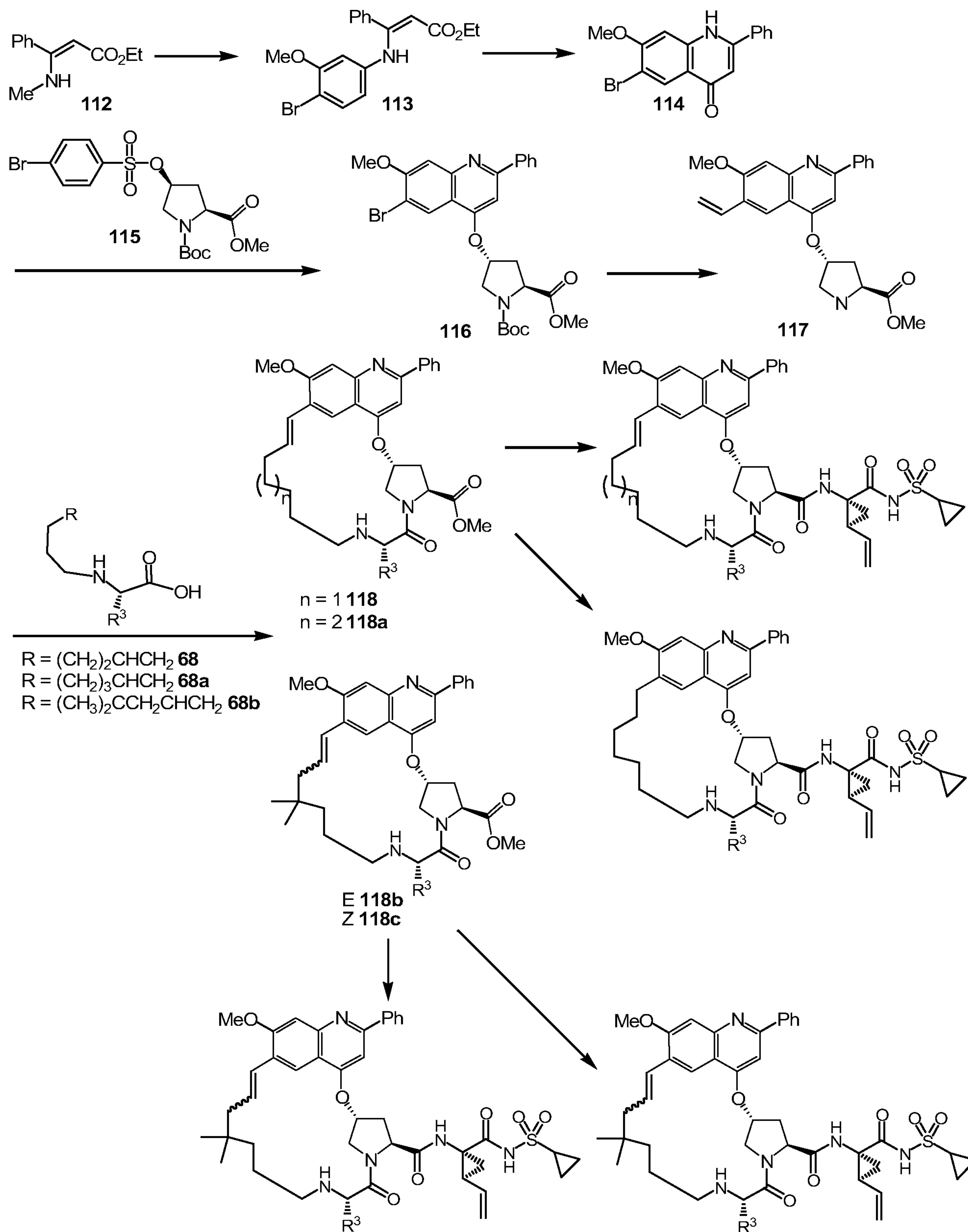
Step 5: methyl (9*R*,11*S*,14*S*,20*E*)-14-cyclohexyl-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-1(26),2(28),3,5,20,22,24-heptaene-11-carboxylate **110**
To a 0.01M solution of methyl (4*R*)-1-[(2*S*)-2-cyclohexyl-2-(hex-5-en-1-ylamino)acetyl]-4-[(3'-vinylbiphenyl-3-yl)methoxy]-L-prolinate **109** in DCM was added TFA (1.3 eq.) and Zhan I (0.15 eq.). The reaction mixture was stirred under microwave irradiation for 20 min. at 100°C. The solvent was evaporated under reduced pressure and the crude material was used in the following step without further purification. MS (ES⁺) m/z 531 (M+H)⁺

Step 6: (9*R*,11*S*,14*S*,20*E*)-14-cyclohexyl-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-1(26),2(28),3,5,20,22,24-heptaene-11-carboxylic acid **111**
LiOH (3.0 eq.) was added to a 0.04M solution of methyl (9*R*,11*S*,14*S*,20*E*)-14-cyclohexyl-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-1(26),2(28),3,5,20,22,24-heptaene-11-carboxylate **110** in a mixture of THF:EtOH:H₂O (2:1:1) and the reaction mixture was stirred at 40°C for 2 h. The solvents were removed under reduced pressure, the residue was suspended in EtOAc/H₂O, aqueous (1N) HCl was added to acidic pH and the phases separated. The collected organic layers were dried (Na₂SO₄) and evaporated under reduced pressure to afford a residue which was used without further purification. MS (ES⁺) m/z 517 (M+H)⁺

Step 7: (9*R*,11*S*,14*S*,20*E*)-14-cyclohexyl-N-((1*R*,2*S*)-1-[(cyclopropylsulfonyl)amino]carbonyl)-2-vinylcyclopropyl)-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-1(26),2(28),3,5,20,22,24-heptaene-11-carboxamide **146**
Compound **48** (1.2 eq.) and HATU (1.2 eq.) were added to a 0.12M solution of (9*R*,11*S*,14*S*,20*E*)-14-cyclohexyl-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-1(26),2(28),3,5,20,22,24-heptaene-11-carboxylic acid **111** in DMF containing DIPEA (4.0 eq.). The reaction mixture was stirred at RT overnight then it was concentrated to dryness and the residue was dissolved in DMSO and purified by RP-HPLC (stationary phase: column Waters

XBridge 19x150 mm, 5 μ m; mobile phase: MeCN/ H₂O buffered with 0.1% TFA from 50% to 90 % of MeCN in 14 min., run time 18 min.). Fractions containing the pure compound were combined and freeze dried to afford compound **146** (TFA salt) as an off white solid (4.0 % over 3 steps). ¹H NMR (400 MHz, DMSO-d₆, 300 K) δ 10.73 (s, 1H), 8.83 (s, 1H), 8.80-8.68 (m, 1H), 8.58-8.42 (m, 1H), 7.92 (s, 2H), 7.68 (d, J 7.6, 1H), 7.62 (d, J 7.6, 1H), 7.51-7.40 (m, 2H), 7.29 (t, J 8.1, 2H), 6.58 (d, J 15.7, 1H), 6.49-6.37 (m, 1H), 5.68-5.54 (m, 1H), 5.27 (d, J 16.9, 1H), 5.16 (d, J 11.6, 1H), 4.74 (d, J 11.9, 1H), 4.60 (d, J 11.9, 1H), 4.50-4.33 (m, 3H), 4.19 (d, J 11.1, 1H), 3.86 (dd, J 11.1, 3.8, 1H), 3.18-2.91 (m, 3H), 2.60-2.46 (m, partially obscured by residual DMSO-d₆, 1H), 2.43-2.24 (m, 2H), 2.19 (q, J 8.8, 1H), 2.09-1.97 (m, 1H), 1.92-1.65 (m, 9H), 1.64-1.52 (m, 1H), 1.38-1.02 (m, 11H). MS (ES⁺) m/z 729 (M+H)⁺.

Scheme 18



Compound 138: (2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-N-((1*R*,2*S*)-1-[(cyclopropylsulfonyl)amino]carbonyl)-2-vinylcyclopropyl)-23-methoxy-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13-

decahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,4-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide

(2*S*)-Cyclohexyl(hept-6-en-1-ylamino)acetic acid **68** ($R^3 = \text{cHex}$)

- 5 Following the procedure described above for Compound **19** Steps 1-2, treatment of cyclohexylglycine tert-butyl ester hydrochloride with hept-6-enal afforded the title compound **68** (76%) as an oil. MS (ES^+) m/z 254 ($\text{M}+\text{H}^+$).

Ethyl 3-(methylamino)-3-phenylacrylate (**112**)

- 10 To a solution of ethyl benzoylacetate and methylamine (2M in THF, 8 eq.) in EtOH (1 M) was added acetic acid (8 eq.). The reaction mixture was heated to reflux and stirred for three days. The reaction mixture was concentrated and partition between DCM and 1N HCl. The layers were separated and the organic layer was dried (Na_2SO_4), filtered and concentrated to give the title compound **112** (20%) which was used with no further purification.

- 15 Step 1: Ethyl 3-[(4-bromo-3-methoxyphenyl)amino]-3-phenylacrylate **113**
To a solution of compound **112** and 4-bromo-3-methoxyaniline (1 eq.) in DCM (0.15 M) was added PPTS (1 eq.). The mixture was heated to reflux and stirred for one day. The mixture was cooled and the solids were removed by filtration and washed with dichloromethane. The filtrate
20 was concentrated and purified by column chromatography (SiO_2 , PE:EtOAc with EtOAc from 1 to 15%) to give the title compound **113** (80%). ^1H NMR (CDCl_3) δ (ppm) 10.32 (br s, 1H), 7.32 (m, 5H), 7.20 (d, J 8.5, 1H), 6.19 (dd, J 8.5, 2.5, 1H), 6.11 (d, J 2.5, 1H), 5.03 (s, 1H), 4.21 (q, J 7.0, 2H), 3.50 (s, 3H), 1.32 (t, J 7.0, 3H).

- 25 Step 2: 6-Bromo-7-methoxy-2-phenylquinolin-4(1*H*)-one **114**

- Dowtherm A (0.19 M) was heated to reflux ($\sim 300^\circ\text{C}$). A mixture of the product **113** in Dowtherm A (2.5 M) was added to the heated Dowtherm A solution portionwise. The mixture was stirred at reflux for 1h after the addition was complete. The mixture was cooled to RT, filtered, and the solid was washed with hexane to give the title compound **114** (86%). ^1H NMR ($\text{DMSO}-d_6$) δ (ppm)
30 11.69 (s, 1H), 8.19 (s, 1H), 7.82 (m, 2H), 7.59 (m, 3H), 7.35 (s, 1H), 6.33 (s, 1H), 3.96 (s, 3H).

1-tert-Butyl 2-methyl (2*S*,4*S*)-4-{[(4-bromophenyl)sulfonyl]oxy}pyrrolidine-1,2-dicarboxylate **115**

- To a solution of 1-*tert*-butyl 2-methyl (2*S*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate and DABCO (1.6 eq.) in toluene (0.20 M) at 0°C was added a solution of brosyl chloride (3.14 g, 12.3 mmol) in
35 toluene (0.41 M) and stirring was continued at RT. EtOAc was added and a white precipitate formed, the reaction mixture was stirred for 20 min and filtered. The filtrate was partitioned between EtOAc and 2.5% aqueous NaHCO_3 . The layers were separated and the organic was washed with 5% aqueous potassium bisulfate and brine, dried (Na_2SO_4), filtered and concentrated. The resulting oil was triturated with hexane/ether and the resulting white solid recovered by

filtration affording the title compound **115** (67%), which was then used without further purification. MS (ES⁺) *m/z* 464 and 466 (M+H)⁺.

Step 3: 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-[(6-bromo-7-methoxy-2-phenylquinolin-4-yl)oxy]pyrrolidine-1,2-dicarboxylate **116**

To a solution of compounds **115** and **114** in N-methylpyrrolidine (0.36 M), cesium carbonate (2 eq.) was added. The reaction mixture was heated to 50°C and stirred for 3h and cooled. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NaHCO₃, water and brine, dried (Na₂SO₄), filtered and concentrated. The residue was purified by column chromatography (SiO₂, PE:EtOAc with EtOAc from 1 to 60%) to give the title compound **116** (99%) as a pale yellow solid. MS (ES⁺) *m/z* 557 and 559 (M+H)⁺.

Step 4: Methyl (4*R*)-4-[(7-methoxy-2-phenyl-6-vinylquinolin-4-yl)oxy]-L-prolinate hydrochloride **117**

Tributylvinylstannane (1.15 eq.) and tetrakis(triphenylphosphine) palladium(0) (0.07 eq.) were added to a solution of compound **116** in toluene (0.09 M) and the reaction mixture was heated at 100°C. After 20h volatiles were removed *in vacuo* and the residue was purified by column chromatography (SiO₂, PE:EtOAc with EtOAc from 1 to 60%) to give a pale yellow solid, that was taken up in a 4N solution of HCl in dioxane (0.31 M). The reaction mixture was stirred for 1h and the resulting white solid recovered by filtration, washed with EtOAc/petroleum ether affording the title compound **117** (99%) as a pale yellow solid. MS (ES⁺) *m/z* 405 (M+H)⁺.

Step 5: (2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-23-methoxy-4-(methoxycarbonyl)-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,4-*r*][1,5,8]oxadiazacyclononadecin-8-ium trifluoroacetate **118** (R³=cHex)

Following the procedure described for Compound **19** Step 3, treatment of the compounds **117** and **68** with TBTU and DIPEA afforded methyl (4*R*)-1-[(2*S*)-2-cyclohexyl-2-(hept-6-en-1-ylamino)acetyl]-4-[(7-methoxy-2-phenyl-6-vinylquinolin-4-yl)oxy]-L-prolinate (35%) as an oil. MS (ES⁺) *m/z* 640 (M+H)⁺. Treatment of this material as described for compound **19** Step 4 afforded the title compound **118** (65%) as a solid.

Step 6: (2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl) amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,4-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide **138**

Treatment of the compound **118** as described for Compound **19** Steps 6-7 afforded the title compound **138** (54%, TFA salt) as a white solid. MS (ES⁺) *m/z* 810 (M+H)⁺.

Compound 139: (2*R*,4*S*,7*S*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13,14,15-

dodecahydro-2H-16,18-etheno-2,5-methanopyrido[3,4-r][1,5,8]oxadiazacyclononadecine-4-carboxamide

Treatment of compound **118** as described for Compound **19** Steps 5-7 afforded the title compound **139** (38%, TFA salt) as a white solid. MS (ES⁺) *m/z* 812 (M+H)⁺.

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**Compound 140: (2R,4S,7S,15E)-7-cyclohexyl-N-((1R,2S)-1-
{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-24-methoxy-6-oxo-21-phenyl-
3,4,7,8, 9,10,11,12,13,14-decahydro-2H,6H-17,19-etheno-2,5-methanopyrido[3,4-
s][1,5,8]oxadiazacycloicosine-4-carboxamide**

10

N-[(*S*)-carboxy(cyclohexyl)methyl]oct-7-en-1-aminium trifluoroacetate (**68a**)

Following the procedure described above for Compound **19** Steps 1-2, treatment of cyclohexylglycine tert-butyl ester hydrochloride with oct-7-enal afforded the title compound **68a** (19%) as a white solid. MS (ES⁺) *m/z* 268 (M+H)⁺.

15

Step 5: (2R,4S,7S,15E)-7-cyclohexyl-24-methoxy-4-(methoxycarbonyl)-6-oxo-21-phenyl-
3,4,7,8,9,10,11,12,13,14-decahydro-2H,6H-17,19-etheno-2,5-methanopyrido[3,4-
s][1,5,8]oxadiazacycloicosin-8-ium trifluoroacetate **118a** (n=2, R³=cHex)

Following the procedure described for Compound **118**, treatment of compounds **68a** and **117**
20 afforded the title compound **118a** (19%) as an oil. MS (ES⁺) *m/z* 626 (M+H)⁺.

Step 6: (2R,4S,7S,15E)-7-cyclohexyl-N-((1R,2S)-1-
{[(cyclopropylsulfonyl)amino]carbonyl}-2-
vinylcyclopropyl)-24-methoxy-6-oxo-21-phenyl-3,4,7,8, 9,10,11,12,13,14-decahydro-2H,6H-
17,19-etheno-2,5-methanopyrido[3,4-s][1,5,8]oxadiazacycloicosine-4-carboxamide **140**

25 Treatment of compound **118a** as described for Compound **138** afforded the title compound **140**
(43%, TFA salt) as a solid. MS (ES⁺) *m/z* 824 (M+H)⁺.

**Compound 141: (2R,4S,7S)-7-cyclohexyl-N-((1R,2S)-1-
{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-24-methoxy-6-oxo-21-phenyl-
30 3,4,7,8,9,10,11,12,13,14,15,16-dodecahydro-2H,6H-17,19-etheno-2,5-methanopyrido[3,4-
s][1,5,8]oxa diazacycloicosine-4-carboxamide**

Treatment of compound **118a** as described for Compound **19** Steps 5-7 afforded the title compound **141** (47%, TFA salt) as a white solid. MS (ES⁺) *m/z* 826 (M+H)⁺.

35 **Compound 147: (2R,4S,7S,14E)-7-cyclohexyl-N-((1R,2S)-1-
{[(cyclopropylsulfonyl)
amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6-oxo-20-phenyl-
3,4,6,7,8,9,10,11,12,13-decahydro-2H-16,18-etheno-2,5-methanopyrido[3,4-r][1,5,8]oxadiazacyclononadecine-4-carboxamide**

(2S)-cyclohexyl[(4,4-dimethylhept-6-en-1-yl)amino]acetic acid **68b**

Following the procedure described above for Compound **19** Steps 1-2, treatment of cyclohexylglycine methyl ester hydrochloride with 4,4-dimethylhept-6-enal afforded the title compound **68b** (56%) as a solid. ¹H NMR (CD₃OD) δ (ppm) 5.84 (m, 1H), 5.06-4.99 (m, 2H), 3.28 (d, J 4.3, 1H), 2.98-2.83 (m, 2H), 1.99 (m, 2H), 1.88-1.65 (m, 8H), 1.36-1.16 (m, 7H), 1.99 (s, 6H). MS (ES⁺) *m/z* 282 (M+H)⁺.

Step 5: (2R,4S,7S,14E)-7-cyclohexyl-23-methoxy-4-(methoxycarbonyl)-12,12-dimethyl-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13-decahydro-2H-16,18-etheno-2,5-methanopyrido[3,4-*r*][1,5,8]oxadiazacyclononadecin-8-ium trifluoroacetate **118b** and (2R,4S,7S,14Z)-7-cyclohexyl-23-methoxy-4-(methoxycarbonyl)-12,12-dimethyl-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13-decahydro-2H-16,18-etheno-2,5-methanopyrido[3,4-*r*][1,5,8]oxadiazacyclononadecin-8-ium trifluoroacetate **118c**

Following the procedure described for compound **118**, treatment of compounds **117** and **68b** afforded after chromatography compounds **118b** (80%) and **118c** (2%) as oils. MS (ES⁺) *m/z* 640 (M+H)⁺.

Step 6: (2R,4S,7S,14E)-7-cyclohexyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13-decahydro-2H-16,18-etheno-2,5-methanopyrido[3,4-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide **147**

Treatment of compound **118b** following Step 6 for compound **138** afforded the title compound **147** (41%, TFA salt) as a solid. ¹H NMR (DMSO-d₆) δ (ppm) 10.78 (br s, 1H), 8.93-8.68 (br m, 2H), 8.66 (s, 1H), 8.30-8.20 (m, 2H), 8.11 (s, 1H), 7.67-7.54 (m, 5H), 7.47 (s, 1H), 6.76 (d, J 15.7, 1H), 6.33-6.23 (m, 1H), 5.76 (br s, 1H), 5.56 (dt, J 17.1, 9.5, 1H), 5.18 (d, J 17.1, 1H), 5.09 (d, J 11.9, 1H), 4.63 (d, J 11.9, 1H), 4.50-4.40 (m, 2H), 4.00 (s, 3H), 4.01-3.90 (m, 1H), 3.23-3.12 (m, 1H), 2.90 (m, 1H), 2.81-2.68 (m, 2H), 2.26-2.06 (m, 4H), 2.00-1.66 (m, 8H), 1.32-0.95 (m, 12H), 0.93 (s, 3H), 0.91 (s, 3H). MS (ES⁺) *m/z* 838 (M+H)⁺.

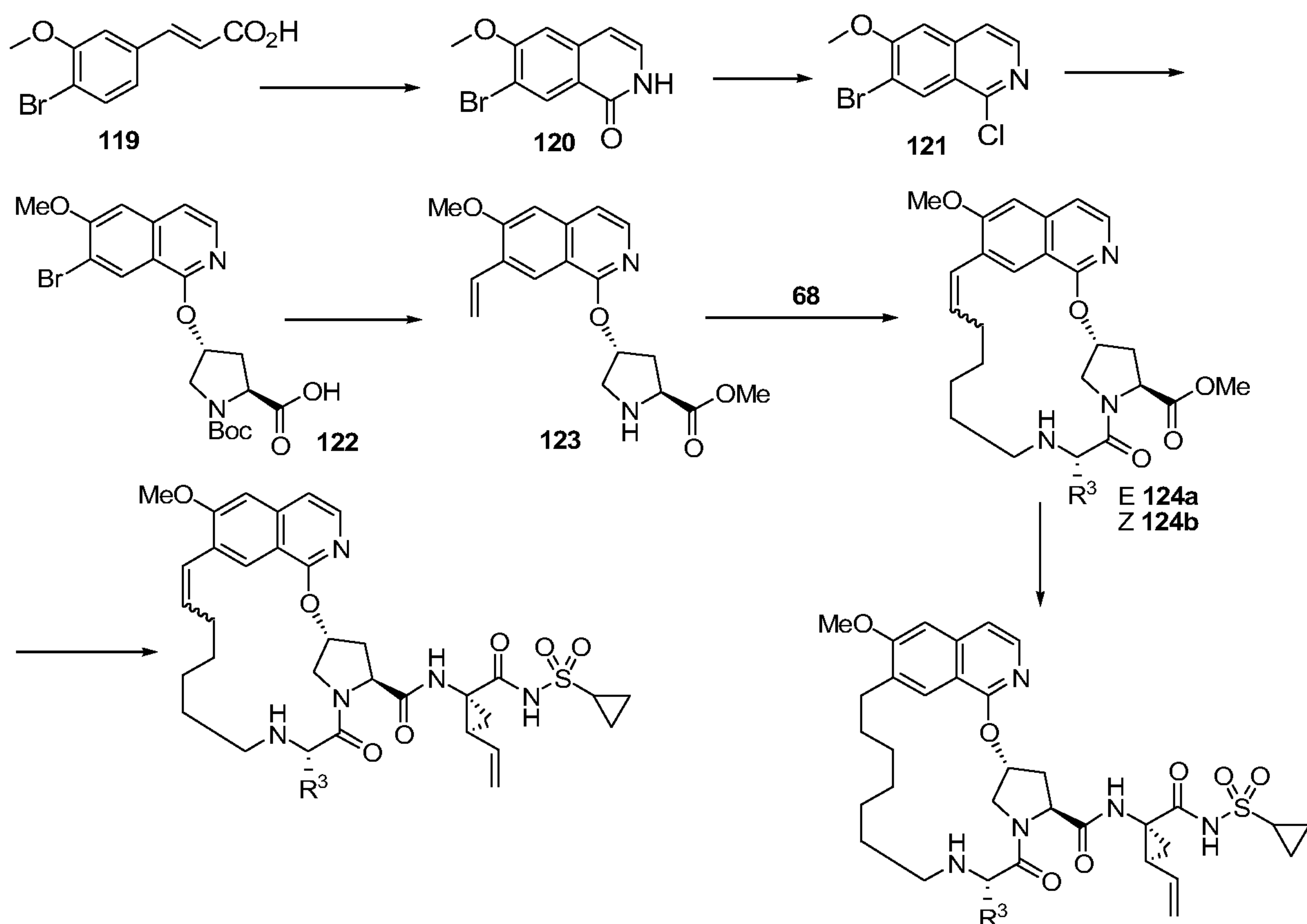
Compound 148: (2R,4S,7S)-7-cyclohexyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2H-16,18-etheno-2,5-methanopyrido[3,4-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide

Treatment of compound **118c** as described for Compound **19** Steps 5-7 afforded the title compound **148** (37%, TFA salt) as a white solid. ¹H NMR (DMSO-d₆) δ (ppm) 10.83 (br s, 1H), 8.79 (s, 1H), 8.65-8.55 (br s, 1H), 8.51-8.41 (br s, 1H), 8.28-8.20 (m, 2H), 7.83 (s, 1H), 7.67-7.54 (m, 5H), 7.47 (s, 1H), 5.85 (br s, 1H), 5.58 (dt, J 16.7, 9.5, 1H), 5.22 (d, J 16.7, 1H), 5.12 (d, J 11.6, 1H), 4.63 (dd, J 9.2, 8.2, 1H), 4.41 (d, J 12.1, 1H), 4.38-4.31 (br m, 1H), 3.98 (s, 3H), 4.01-3.89 (m, 1H), 2.97-2.84 (m, 3H), 2.80-2.73 (m, 1H), 2.68-2.57 (m, 2H), 2.35-2.25 (m, 1H), 2.14 (q, J

5

Treatment of compound **118c** as described for Compound **19** Steps 6-7 afforded the title compound **149** (24%, TFA salt) as a white solid. MS (ES⁺) *m/z* 838 (M+H)⁺.

Scheme 19



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(2*E*)-3-(4-Bromo-3-methoxyphenyl)acrylic acid **119**

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and stirred overnight. The solid was filtered and washed with 1:1 EtOH: hexane to give the desired product **119**. LRMS ESI⁺ (M+H)⁺ 257.0.

Step 1: 7-Bromo-6-methoxyisoquinolin-1(2H)-one **120**

5 Compound **119** was azeotroped with benzene, suspended in benzene (0.5 M) with TEA (1.4 eq.), diphenylphosphoryl azide (1 eq.) was added and the reaction mixture stirred at RT for 1h. The mixture was filtered through a pad of silica and eluted with toluene, the volatiles evaporated, the residue resuspended in diphenylmethane (0.5 M) and the mixture heated to reflux for 3h (internal temperature 250°C). The reaction mixture was allowed to cool to RT, stirred overnight, filtered
10 and the solid washed with hexanes to give a tan solid (60%). LRMS ESI⁺ (M+H)⁺ 254.1.

Step 2: 7-Bromo-1-chloro-6-methoxyisoquinoline **121**

A mixture of compound **120** in phosphorus oxychloride (0.6 M) was heated to reflux for 2h, cooled to RT, the volatiles evaporated and the residue partitioned between 3N NaOH and DCM. The
15 organic phase was dried (Na₂SO₄), solvent evaporated and the solid triturated with Et₂O and filtered to give a solid (74%). LRMS ESI⁺ (M+H)⁺ 274.0.

Step 3: (4R)-4-[(7-bromo-6-methoxyisoquinolin-1-yl)oxy]-1-(tert-butoxycarbonyl)-L-proline **122**

To a solution of *trans* 4-hydroxy L-BOC-proline in DMSO (0.23 M) at RT potassium t-butoxide (3
20 eq.) was added. The reaction mixture was stirred at RT for 30 min, cooled to 15 °C and compound **121** (1 eq) was added as a solution DMSO (0.9 M), the reaction mixture was allowed to warm to RT and stirred for 30 min. The reaction mixture was quenched with ice-cold 10% citric acid solution and partitioned with EtOAc. The organic layer was washed with aqueous citric acid solution, water and brine and the aqueous phases back extracted with EtOAc. The combined
25 organic phases were dried (Na₂SO₄) and the solvent evaporated. LRMS ESI⁺ (M+H-tBu)⁺ 411.2.

Step 4: (2S,4R)-2-(methoxycarbonyl)-4-[(6-methoxy-7-vinylisoquinolin-1-yl)oxy]pyrrolidinium chloride **123**

To a solution of compound **122** in MeOH (0.1 M) was added TMS-diazomethane (4.2 eq.) and the
30 mixture was stirred at RT for 20 min. Volatiles were evaporated and the crude purified by chromatography to obtain 1-*tert*-butyl 2-methyl (2S,4R)-4-[(7-bromo-6-methoxyisoquinolin-1-yl)oxy]pyrrolidine-1,2-dicarboxylate as a pale orange foam (79%). To the previous compound dissolved in toluene (0.1 M) tetrakis-(triphenylphospin)-palladium(0) (0.1 eq.) and vinyltri-N-butyltin (1 eq) were added and the mixture was heated at 100°C for 20h. Volatiles were evaporated
35 and the residue purified by chromatography to obtain 1-*tert*-butyl 2-methyl (2S,4R)-4-[(6-methoxy-7-vinylisoquinolin-1-yl)oxy]pyrrolidine-1,2-dicarboxylate as a pale yellow foam (45%) that was treated with HCl 4N in dioxane (26 eq) at RT. After 30 min volatiles were evaporated to obtain the title compound **123** in quantitative yield. MS (ES⁺) *m/z* 329 (M+H)⁺.

Step 5: (2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-23-methoxy-4-(methoxycarbonyl)-6-oxo-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecin-8-ium trifluoroacetate **124a** (11% yield) and (2*R*,4*S*,7*S*,14*Z*)-7-cyclohexyl-23-methoxy-4-(methoxycarbonyl)-6-oxo-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecin-8-ium trifluoroacetate **124b**

Following the procedure described for compound **19** Step 3, treatment of compound **123** and **68** ($R^3 = \text{cHex}$) with TBTU and DIPEA afforded methyl (4*R*)-1-[(2*S*)-2-cyclohexyl-2-(hept-6-en-1-ylamino)acetyl]-4-[(6-methoxy-7-vinylisoquinolin-1-yl)oxy]-L-prolinate (57%) as a oil. Treatment of this material as described for Compound **19** Step 4 afforded after purification by preparative RP-HPLC (stationary phase: column Waters XBridgeTM C18, 19x100mm, mobile phase MeCN/water buffered with 0.1% TFA) the two title compounds: **124a** (first eluted, 59% yield) and **124b** (second eluted, 11% yield). MS (ES^+) m/z 536 ($M+H$)⁺.

Step 6: (2*R*,4*S*,7*S*,14*Z*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl) amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6-oxo-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido [3,2-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide **143**

Treatment of compound **124b** as described for compound **138** Step 6 afforded the title compound **143** (23%, TFA salt) as a solid. MS (ES^+) m/z 734 ($M+H$)⁺.

Compound 144: (2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl) amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6-oxo-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido [3,2-*r*][1,5,8]oxadiazacyclo nonadecine-4-carboxamide

Treatment of ((2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-23-methoxy-4-(methoxycarbonyl)-6-oxo-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecin-8-ium trifluoroacetate as described for Compound **138** Step 6 afforded the title compound **144** (25%, TFA salt) as a solid. MS (ES^+) m/z 734 ($M+H$)⁺.

Compound 145: (2*R*,4*S*,7*S*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6-oxo-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido [3,2-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide

Treatment of compound **124a** as described for Compound **19** Steps 5-7 afforded the title compound **145** (25%, TFA salt) as a white solid. MS (ES^+) m/z 736 ($M+H$)⁺.

Compound 150: (2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl) amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6-oxo-

3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide

Following the procedures described for compound **143** Steps 5-6, treatment of (2*S*,4*R*)-2-(methoxycarbonyl)-4-[(6-methoxy-7-vinylisoquinolin-1-yl)oxy]pyrrolidinium chloride with compound **68b** afforded the title compound **150** (14%, TFA salt) as a white solid. MS (ES⁺) *m/z* 762 (M+H)⁺.

Compound 134 : (3*S*,3*aR*,6*S*,8*R*)-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3-methyl-4,10-dioxo-2,3,3*a*,4,7,8,12,17,18,19,20,21,22,23-tetradecahydro-1*H*,6*H*-5,8:11,13-dimethanopyrrolo [2,1-*j*][4,2,8,11]benzoxatriazacycloicosine-6-carboxamide

(3*S*)-1-hept-6-en-1-yl-3-methyl-L-proline **125**

Following the procedure described above for Compound **19** Steps 1-2, treatment of methyl (3*S*)-3-methyl-L-prolinate with hept-6-enal afforded the title compound **125** (80 %) as an oil. ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 5.78 (m, 1H), 5.03-4.92 (m, 2H), 3.58-3.48 (m, 2H), 3.19-3.01 (m, 2H), 3.07-2.95 (m, 1H), 2.34-2.22 (m, 1H), 2.12-2.00 (m, 3H), 1.69-1.55 (m, 3H), 1.41-1.22 (m, 4H), 1.18 (d, *J* 8.8, 3H).

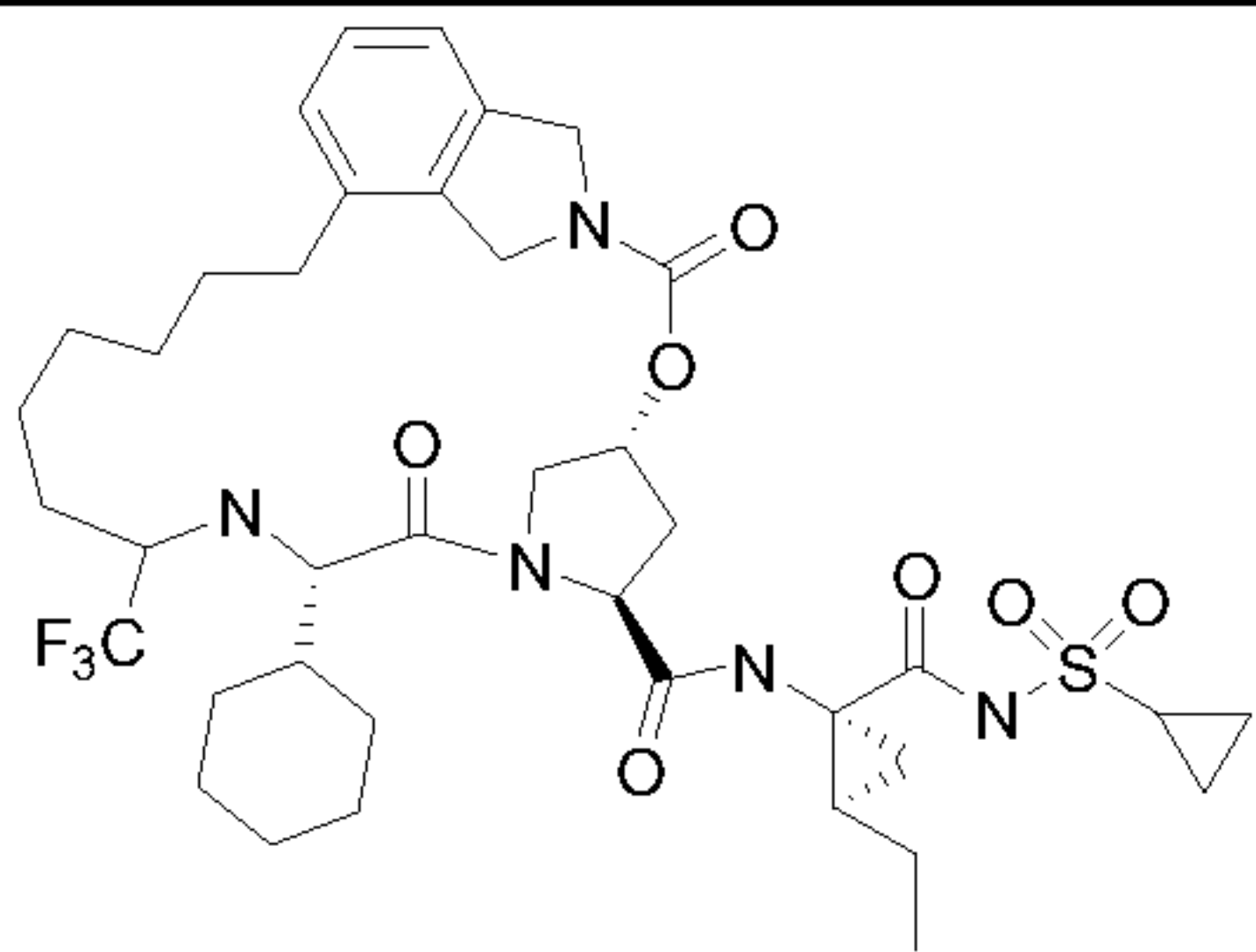
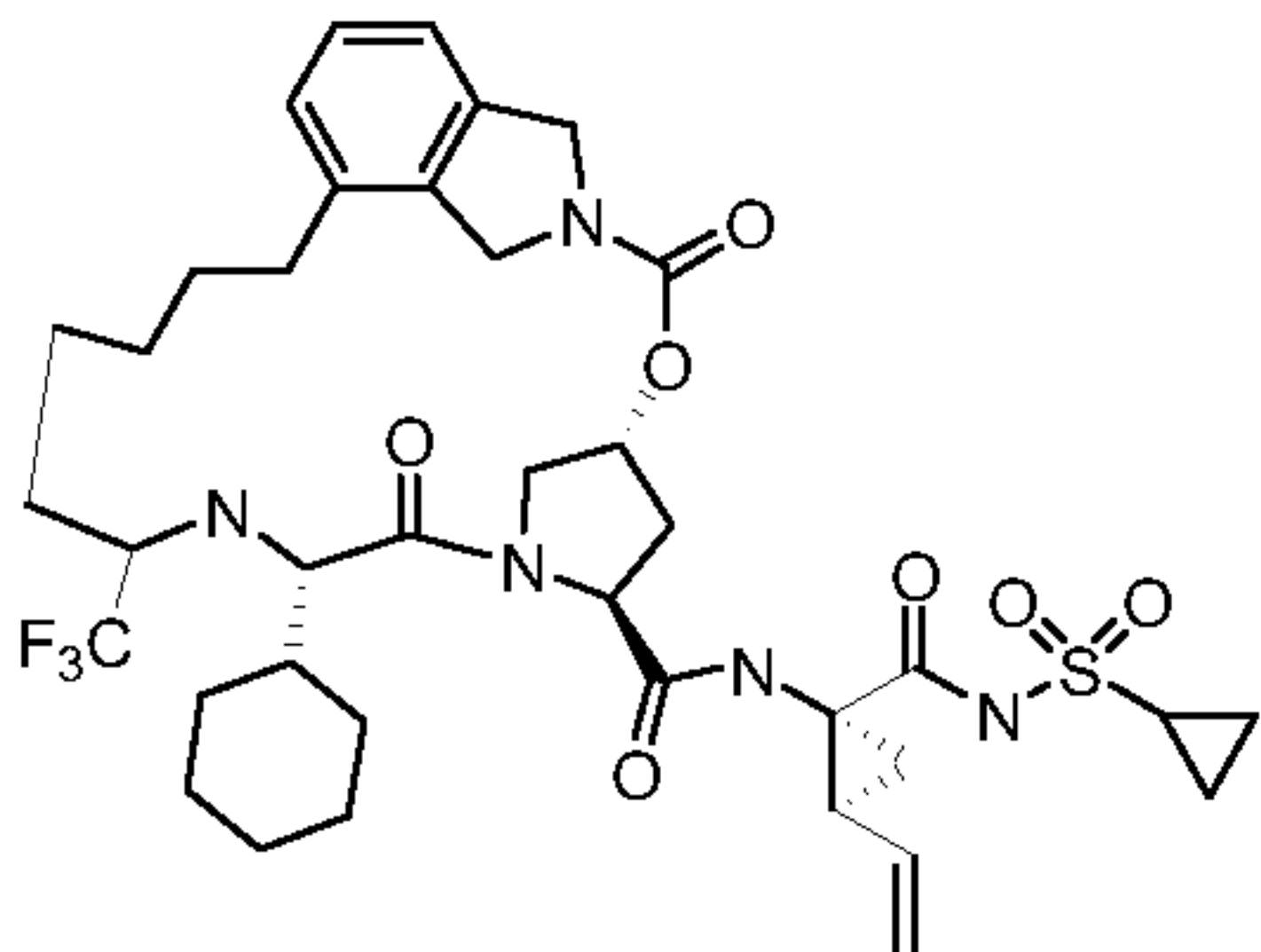
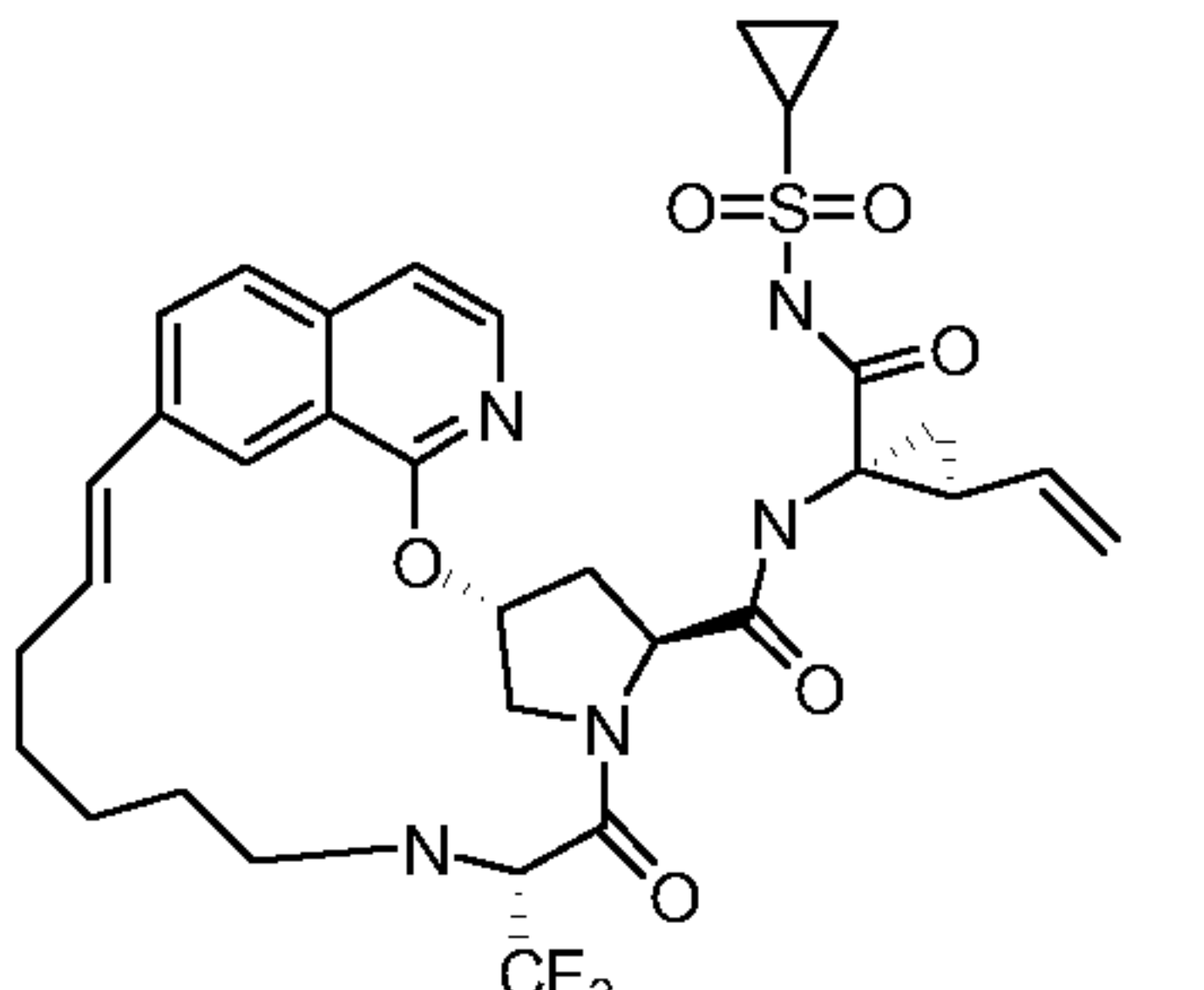
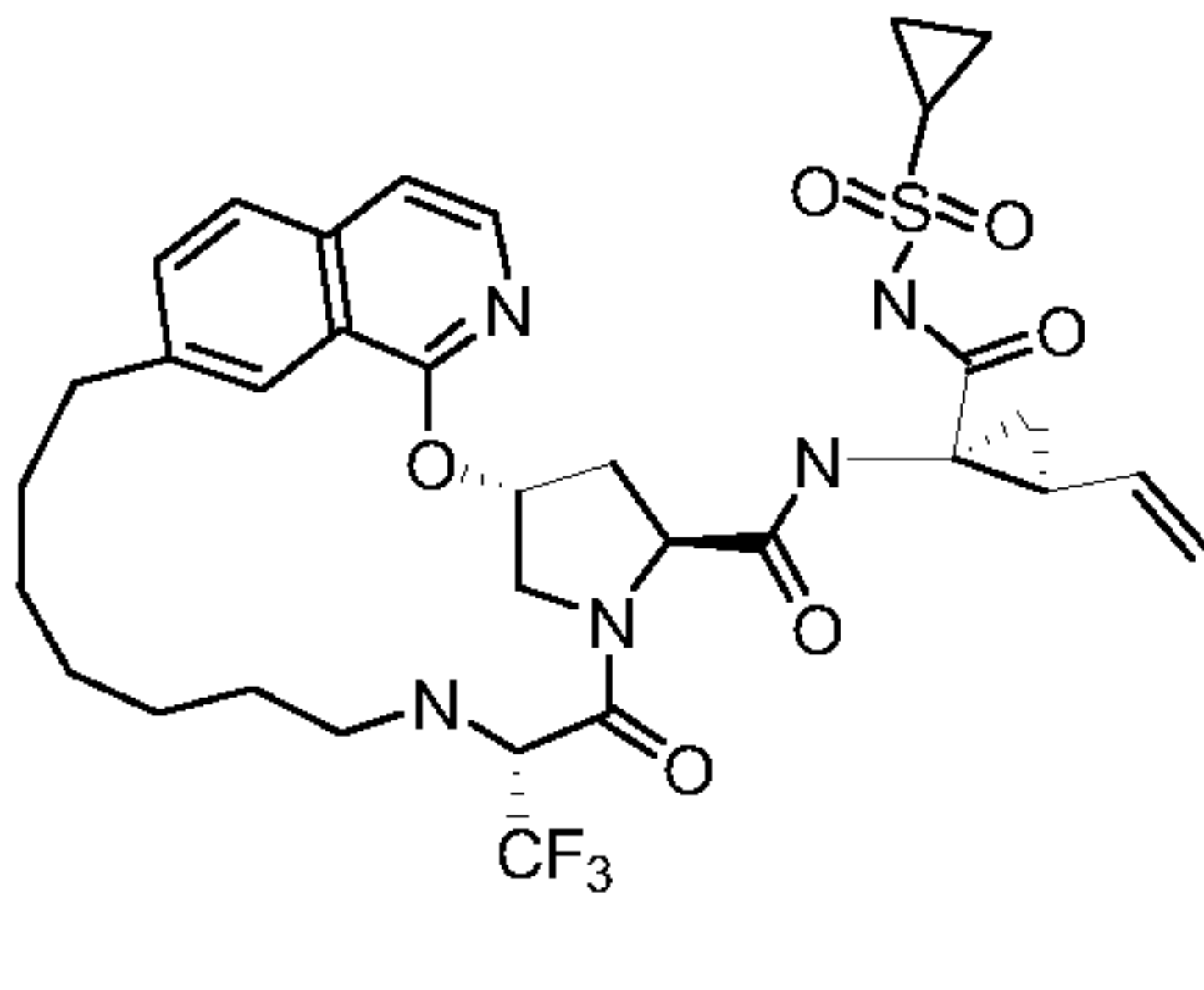
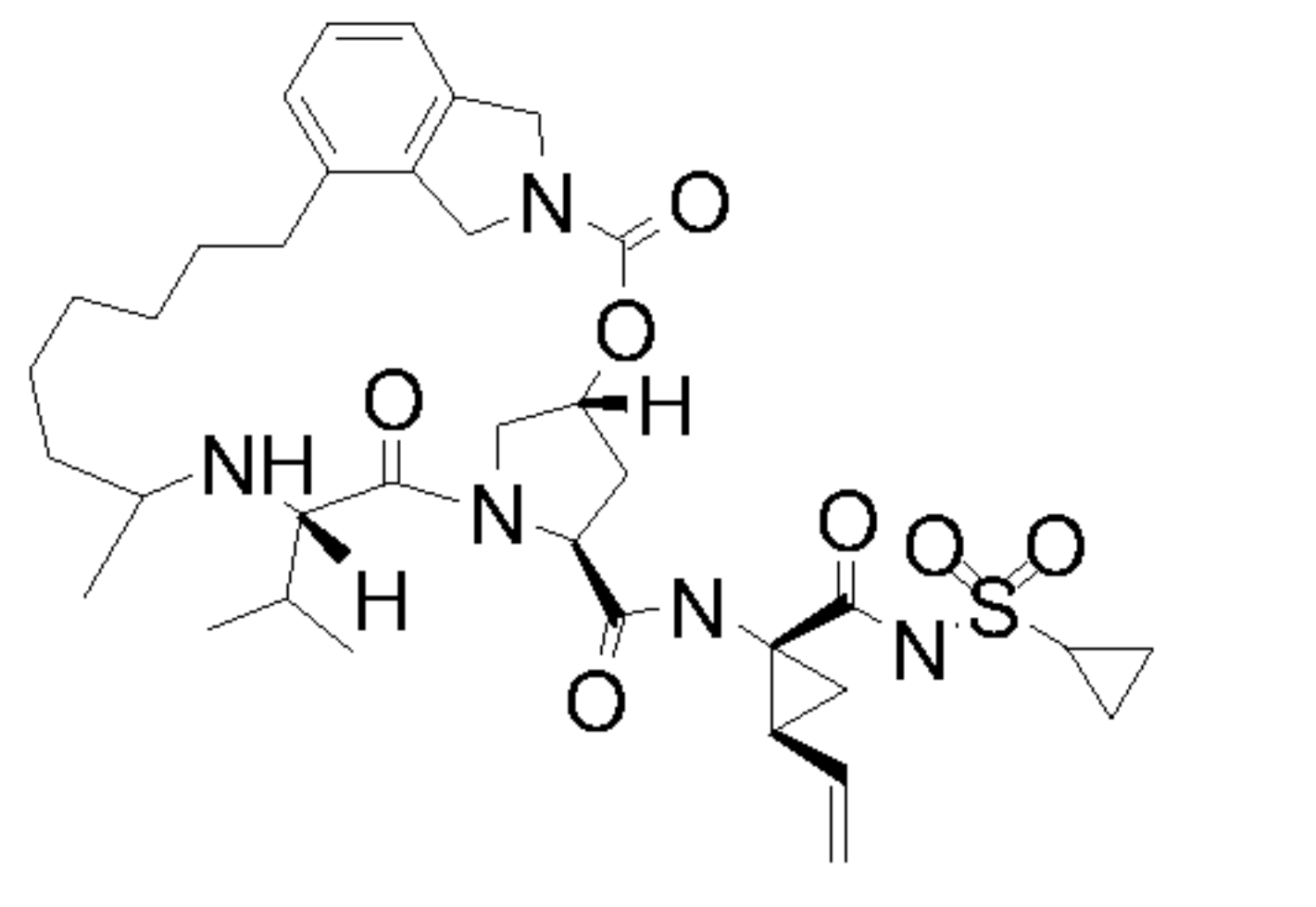
(3*S*,3*aS*,6*S*,8*R*)-6-{[((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)amino]carbonyl}-3-methyl-4,10-dioxo-2,3,3*a*,4,7,8,12,17,18,19,20,21,22,23-tetradecahydro-1*H*,6*H*-5,8:11,13-dimethanopyrrolo[2,1-*j*][4,2,8,11]benzoxatriazacycloicosin-24-ium trifluoroacetate

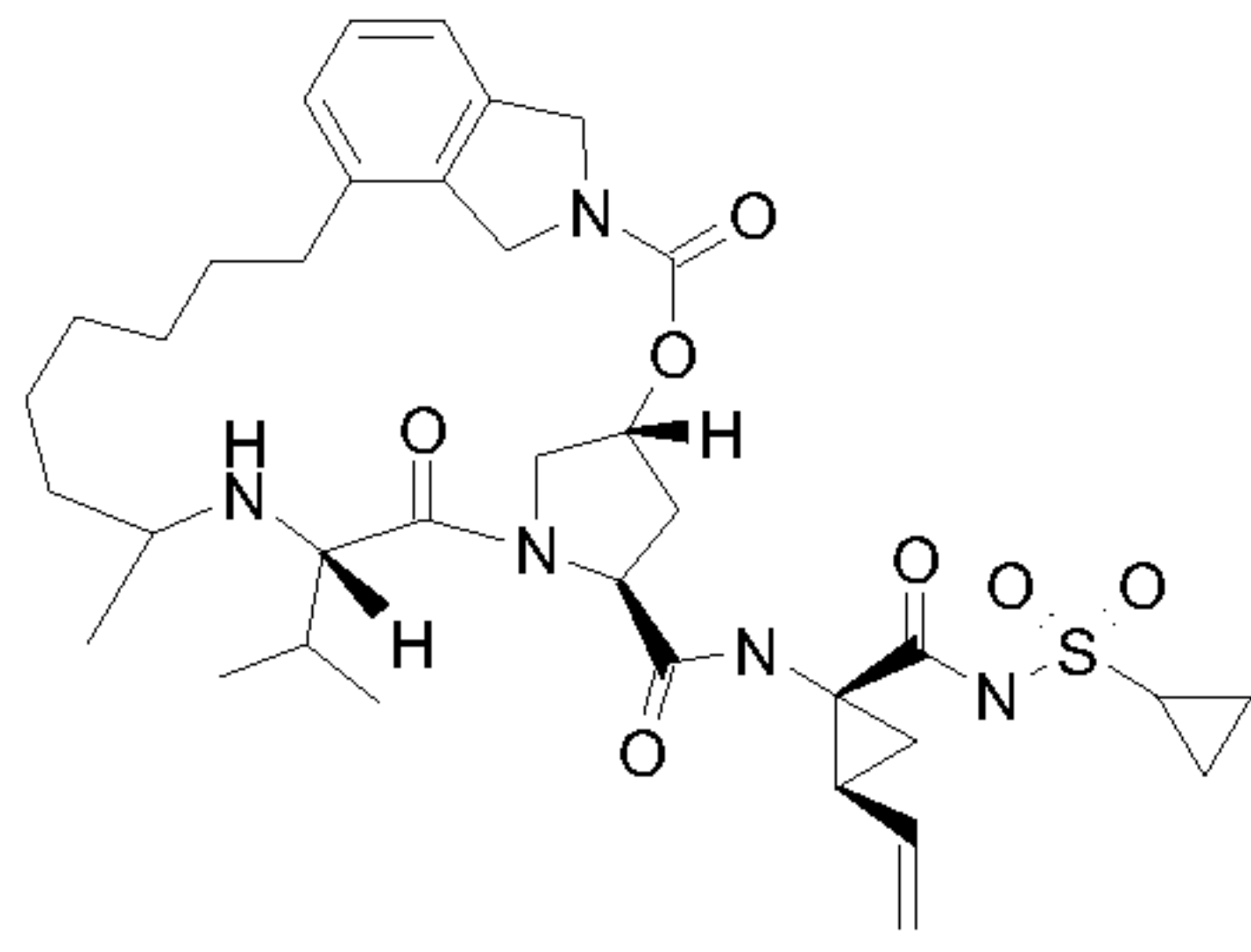
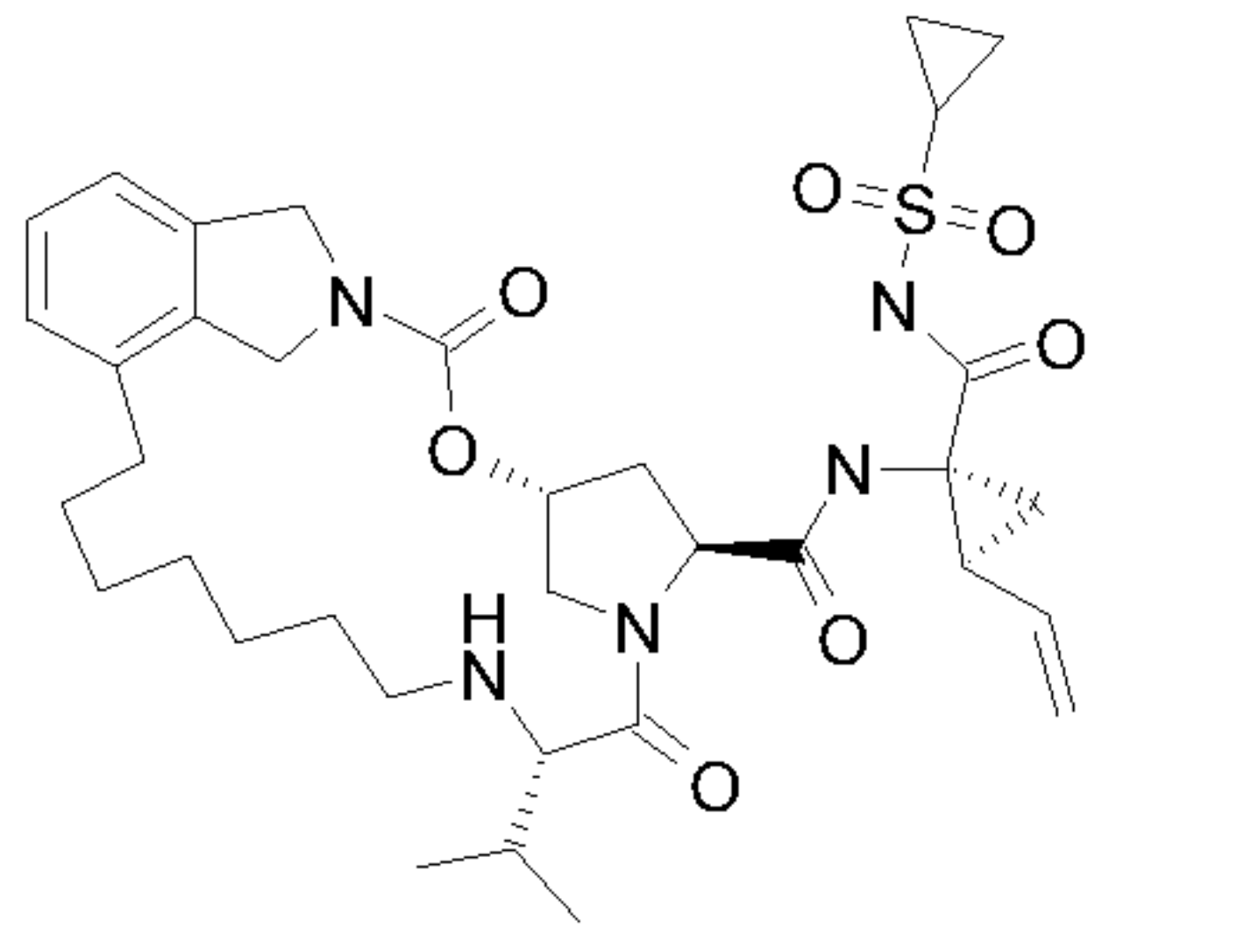
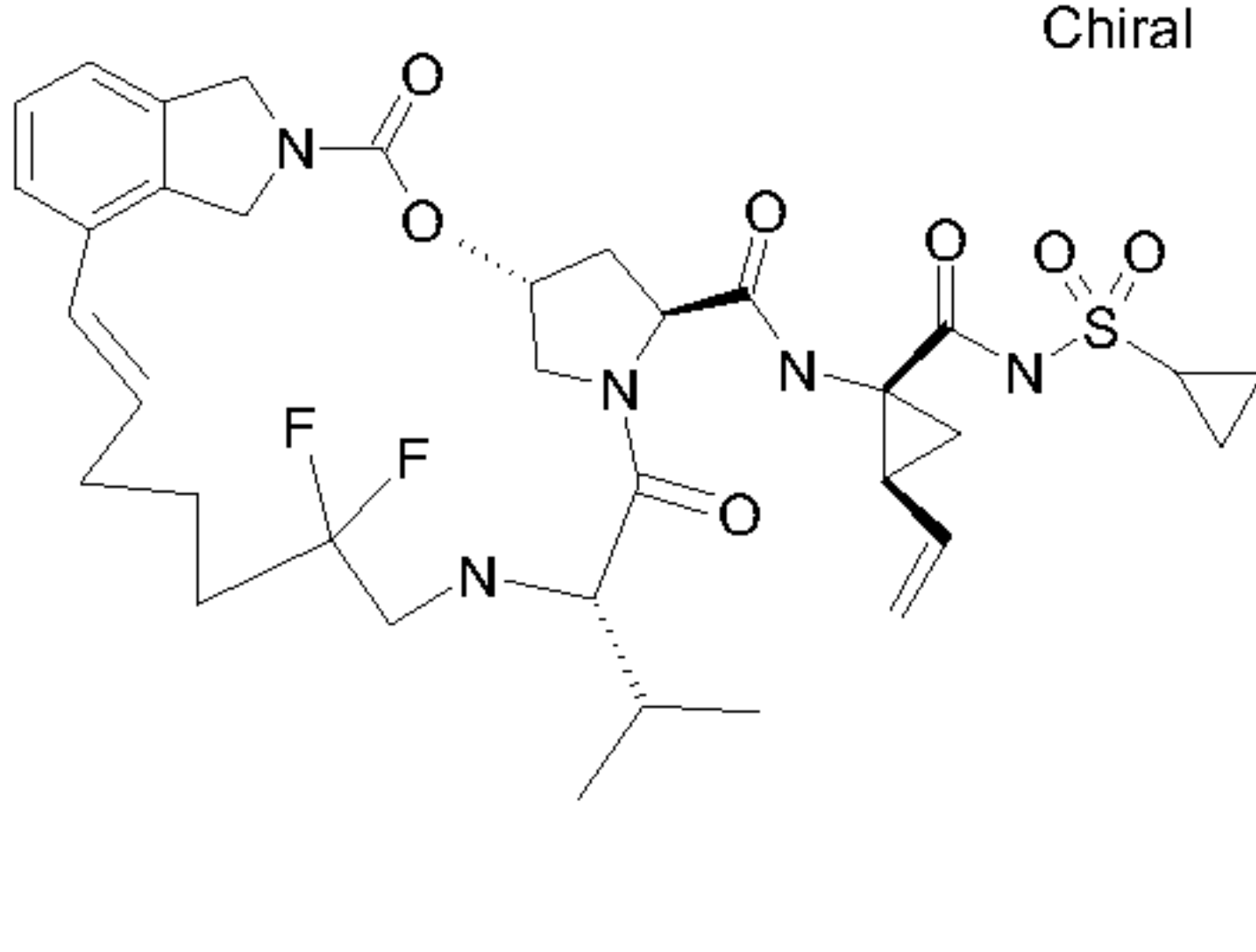
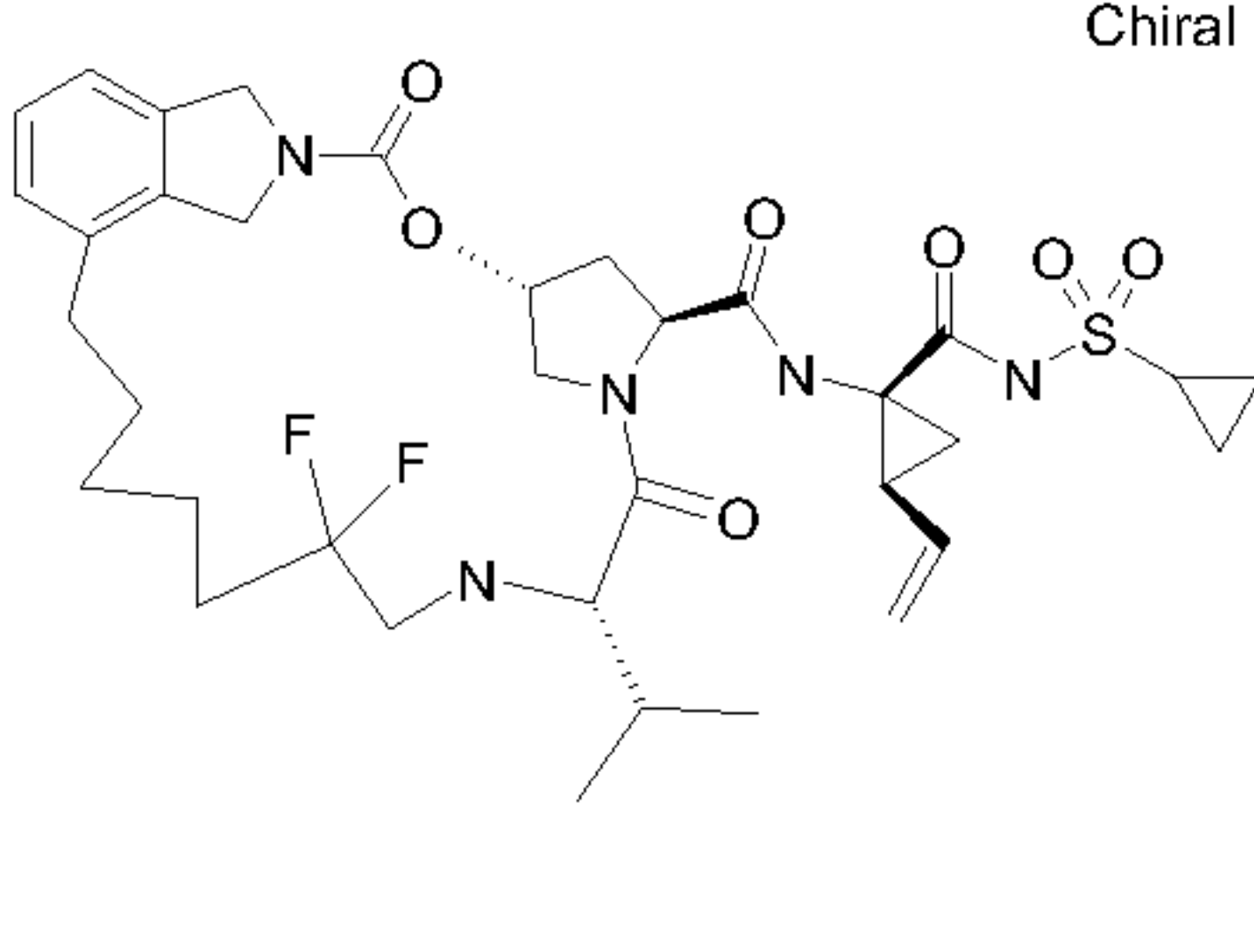
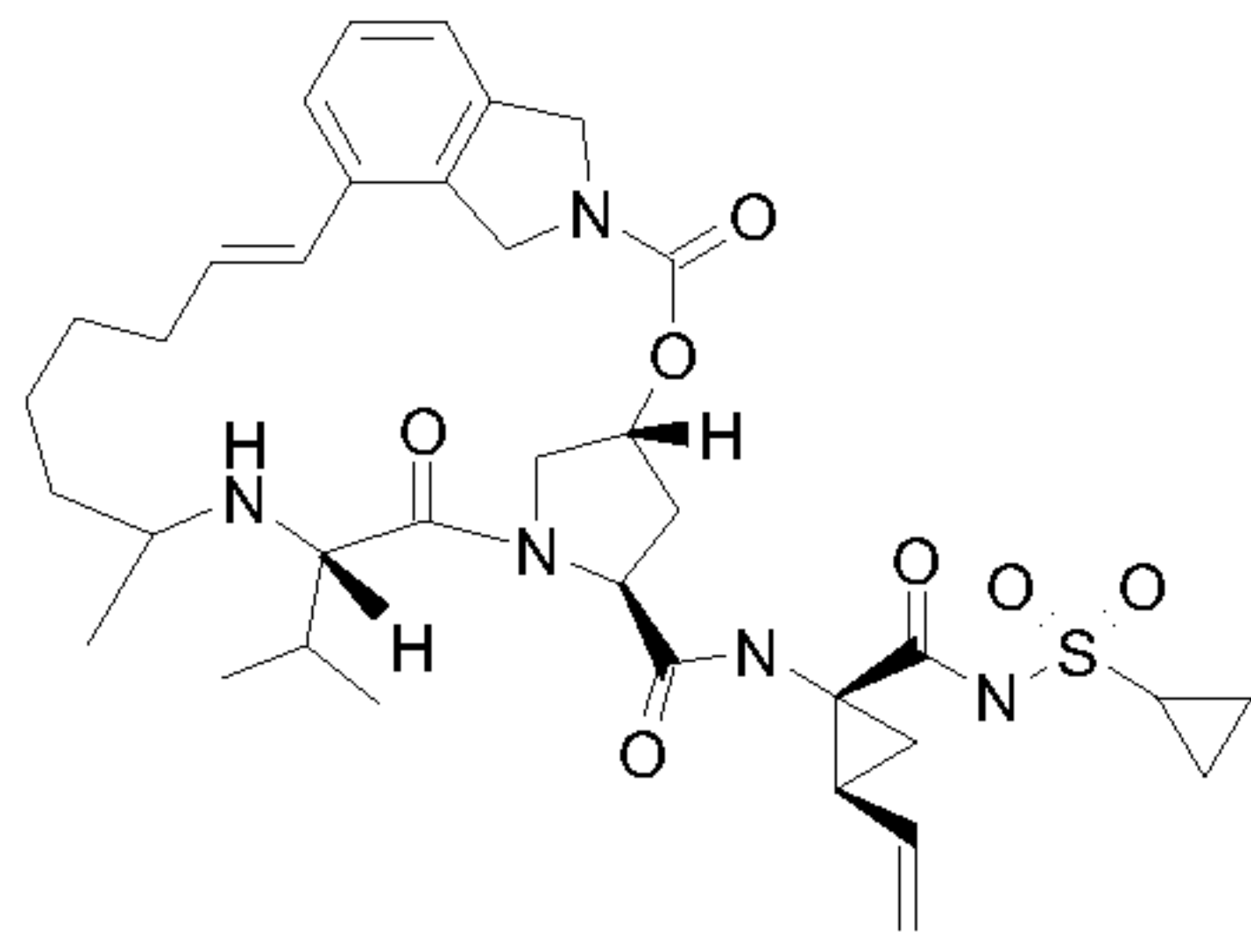
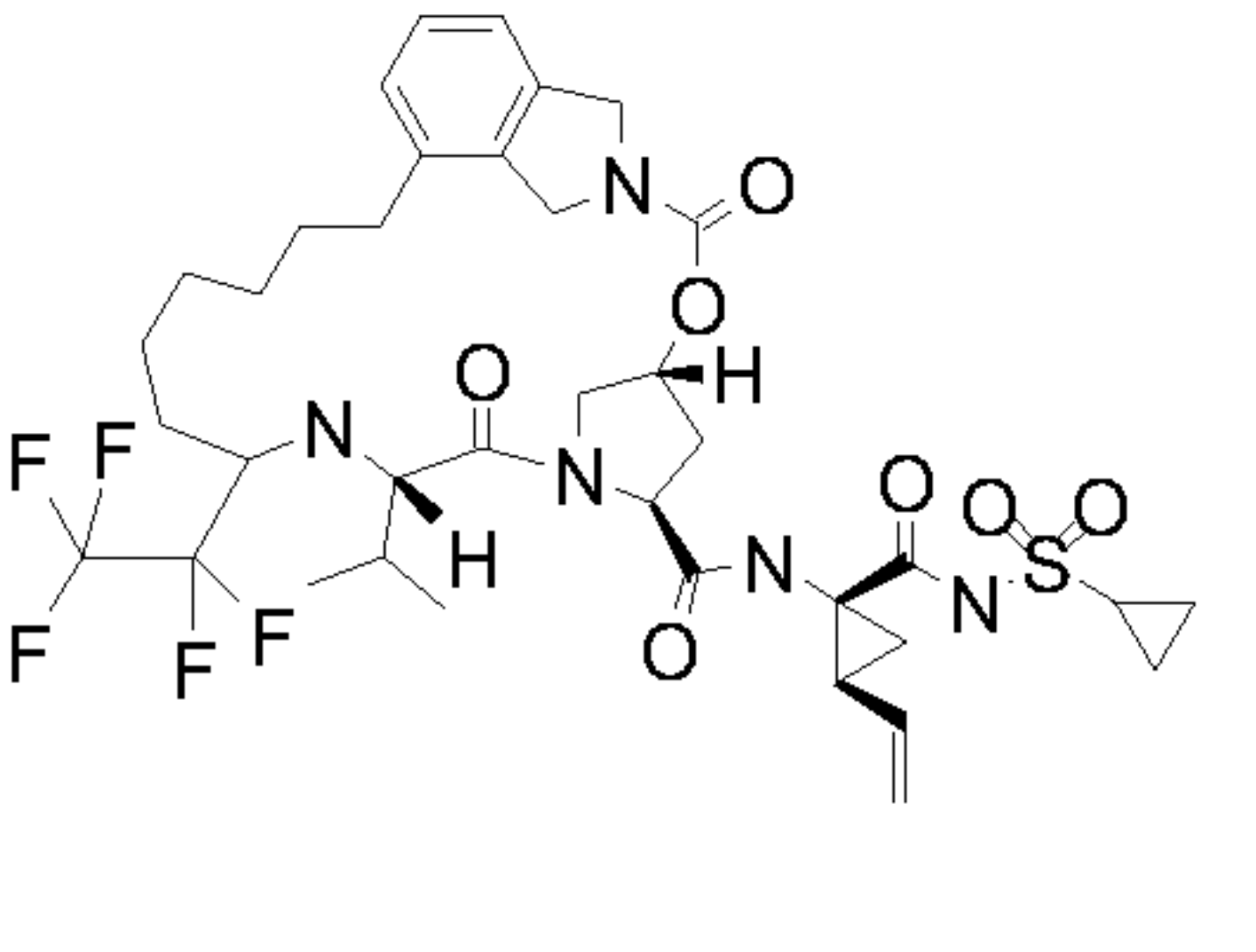
Following the procedures described for Compound **19**, Steps 3-7, treatment of compound **125** with (2*S*,4*R*)-2-(methoxycarbonyl)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}pyrrolidinium chloride afforded the title compound **134** (24 %, TFA salt) as a solid. MS (ES⁺) *m/z* 696 (M+H)⁺.

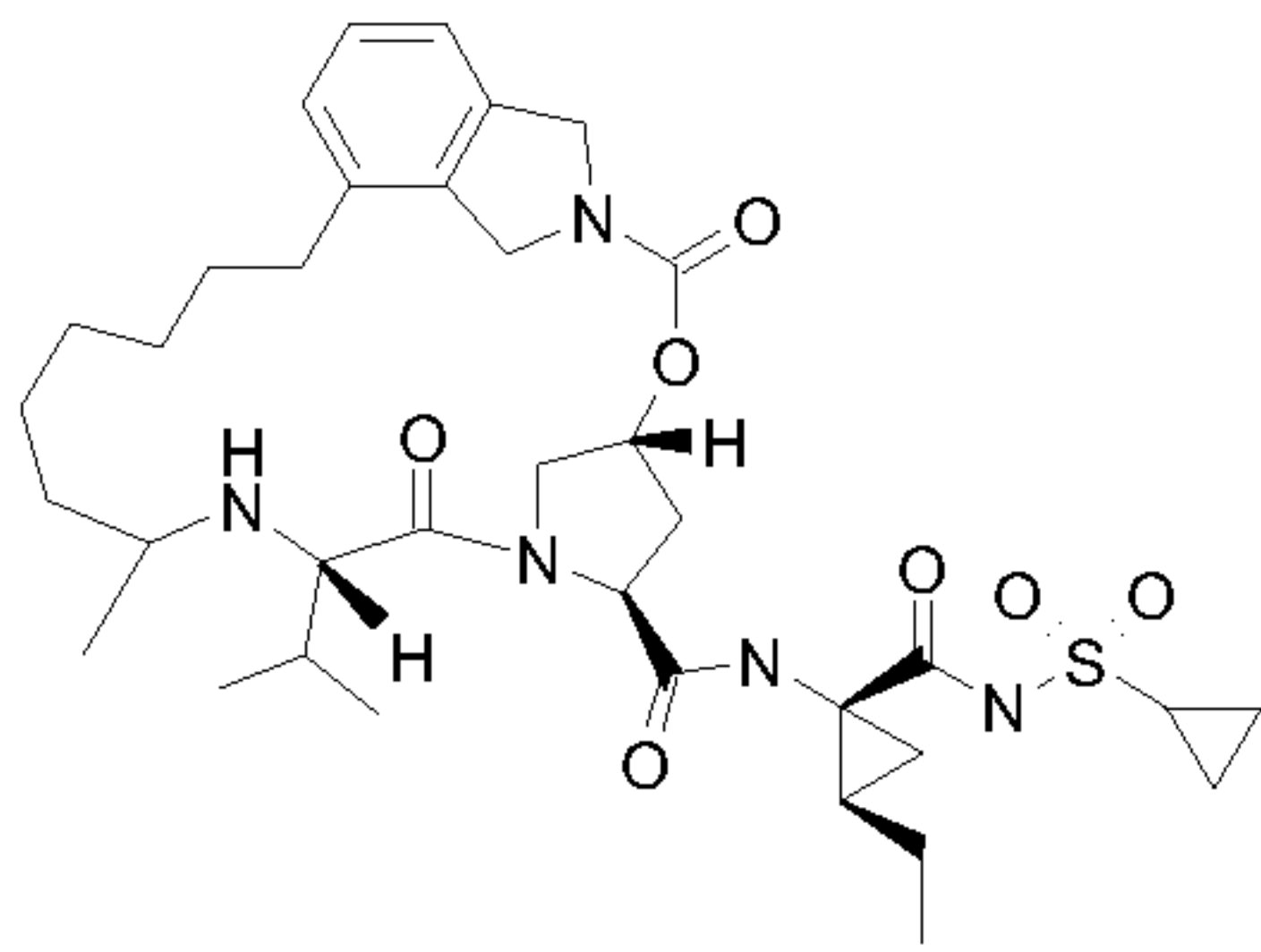
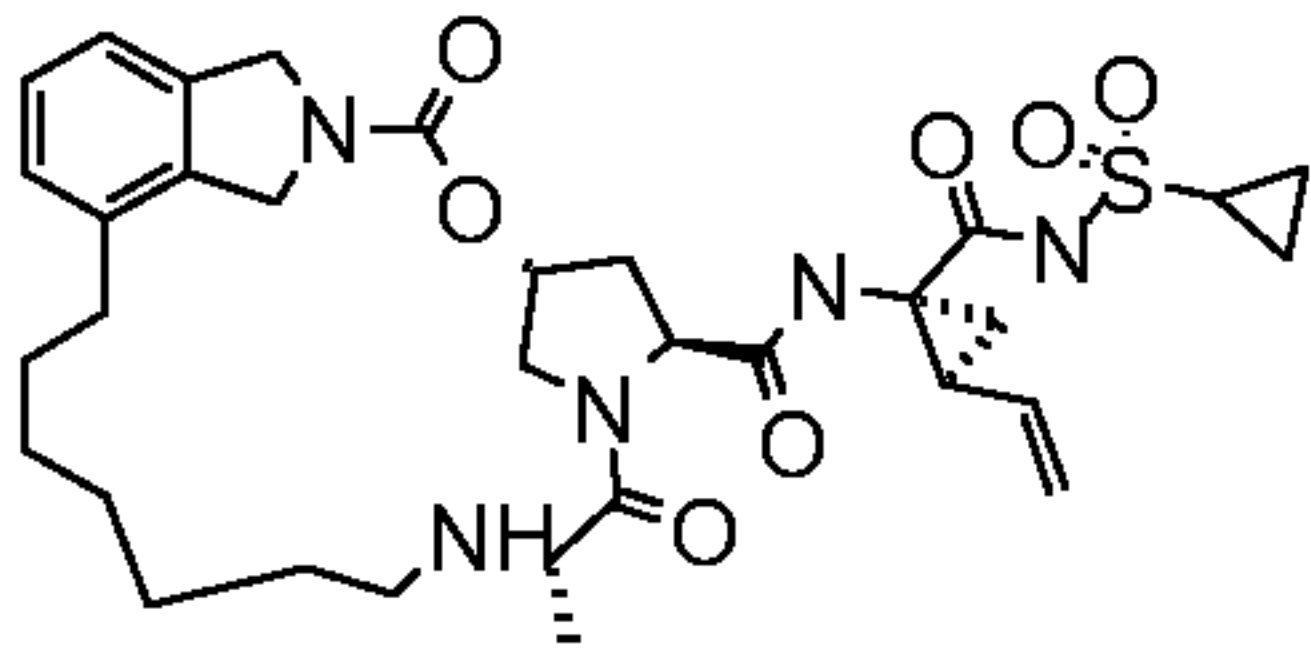
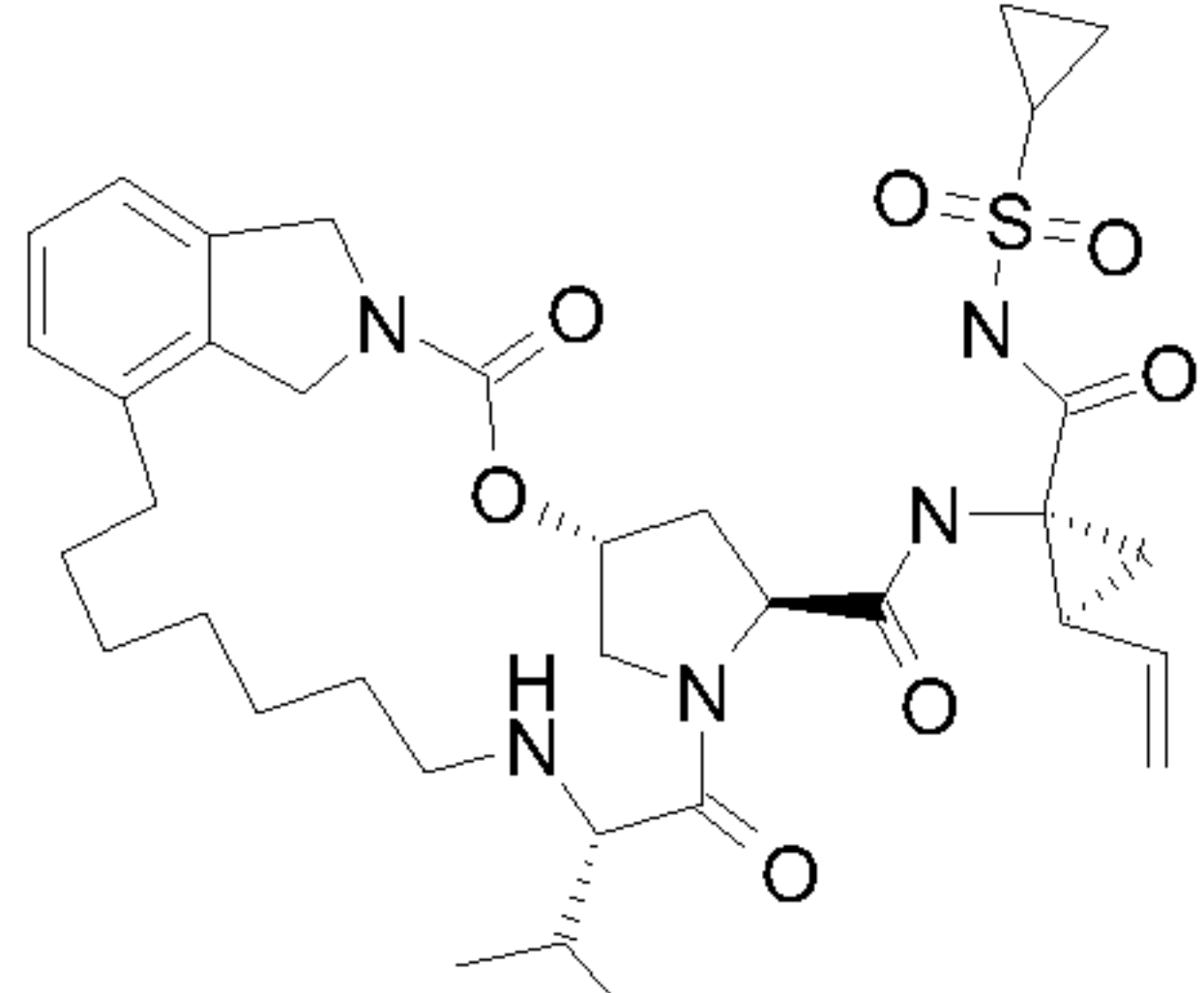
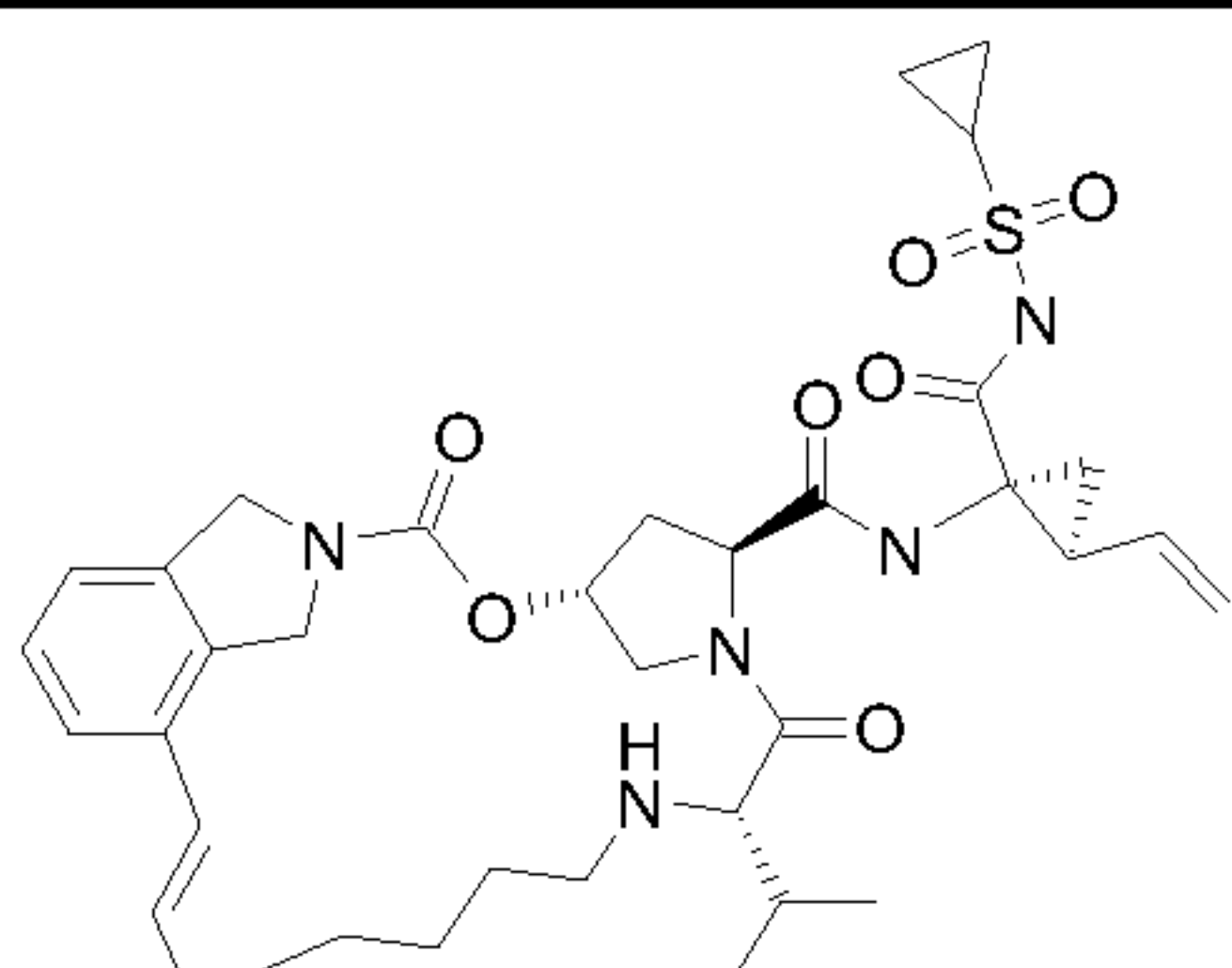
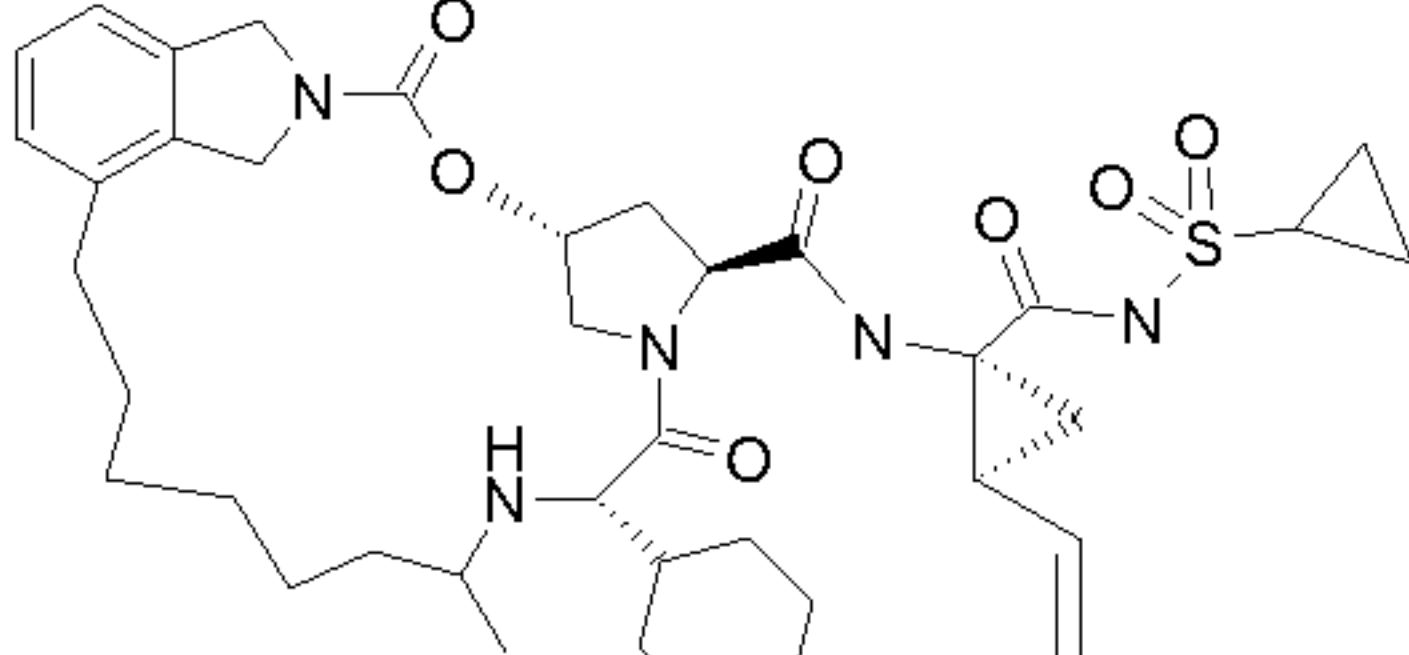
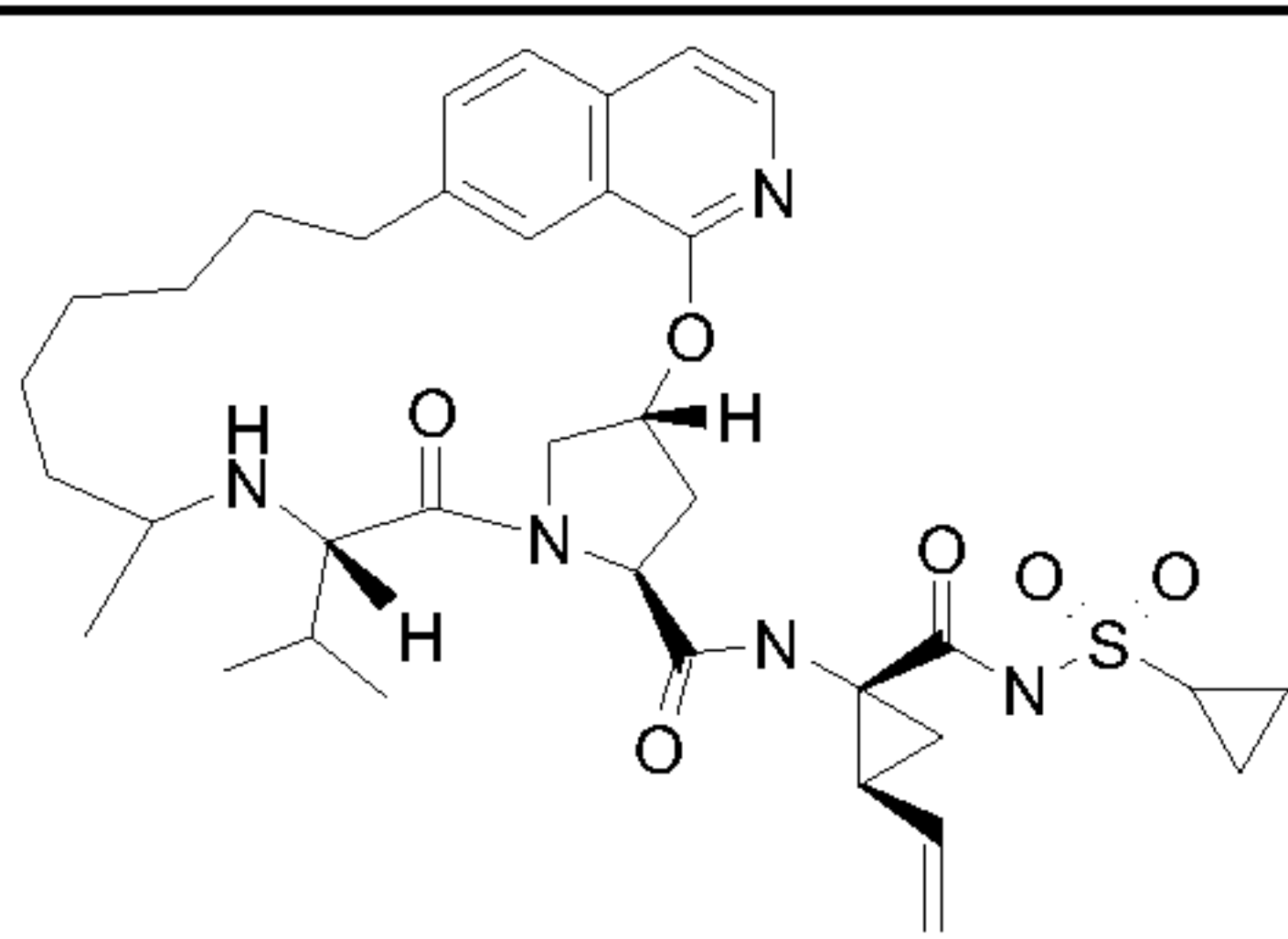
Table 1 lists specific compounds of the present invention including the compounds described in the experimental section. The table provides the structure and name of each compound and the mass of its molecular ion plus 1 (M+1) as determined *via* mass spectrometry (ES-MS). The synthetic scheme employed to prepare the compound is indicated in the last column.

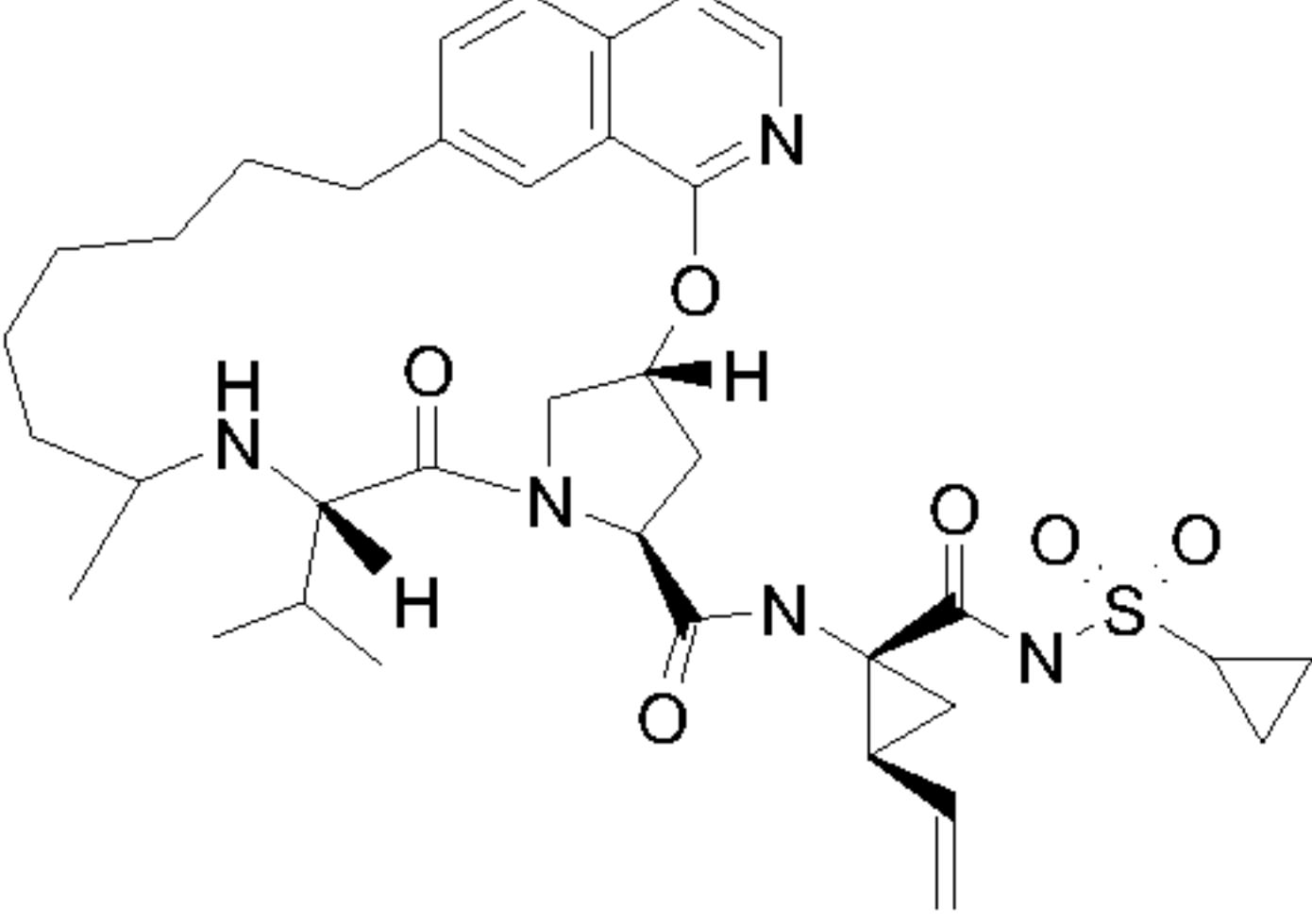
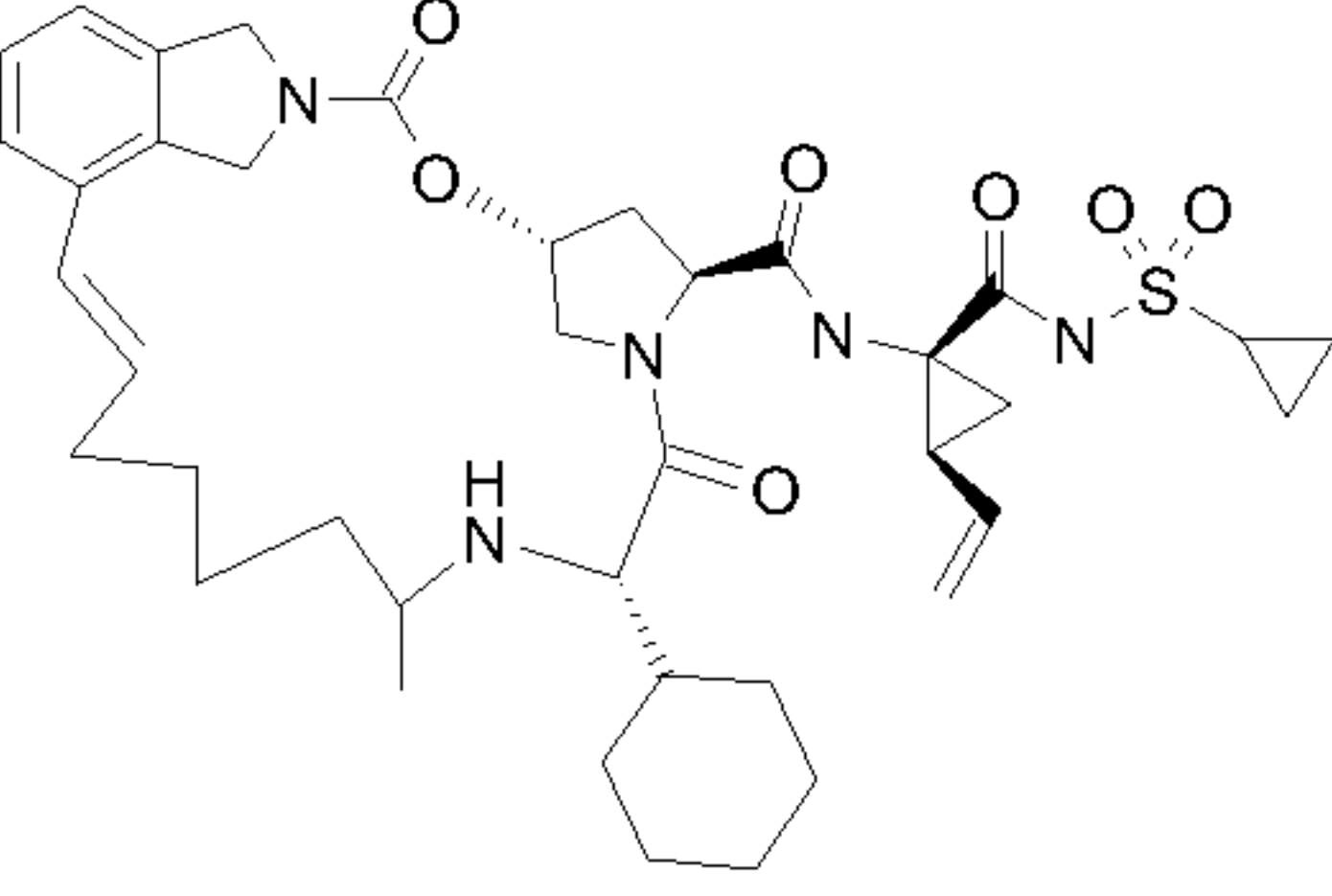
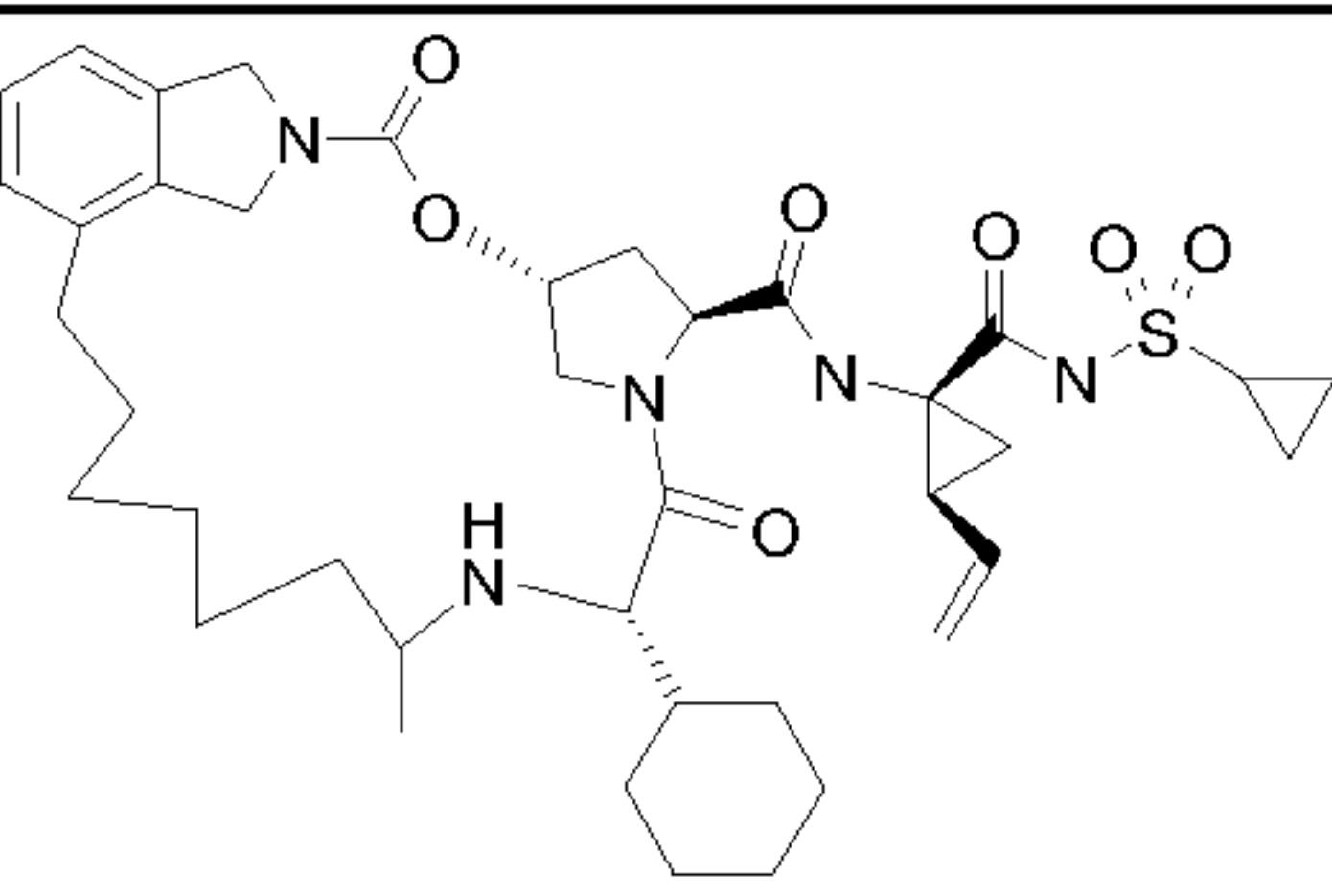
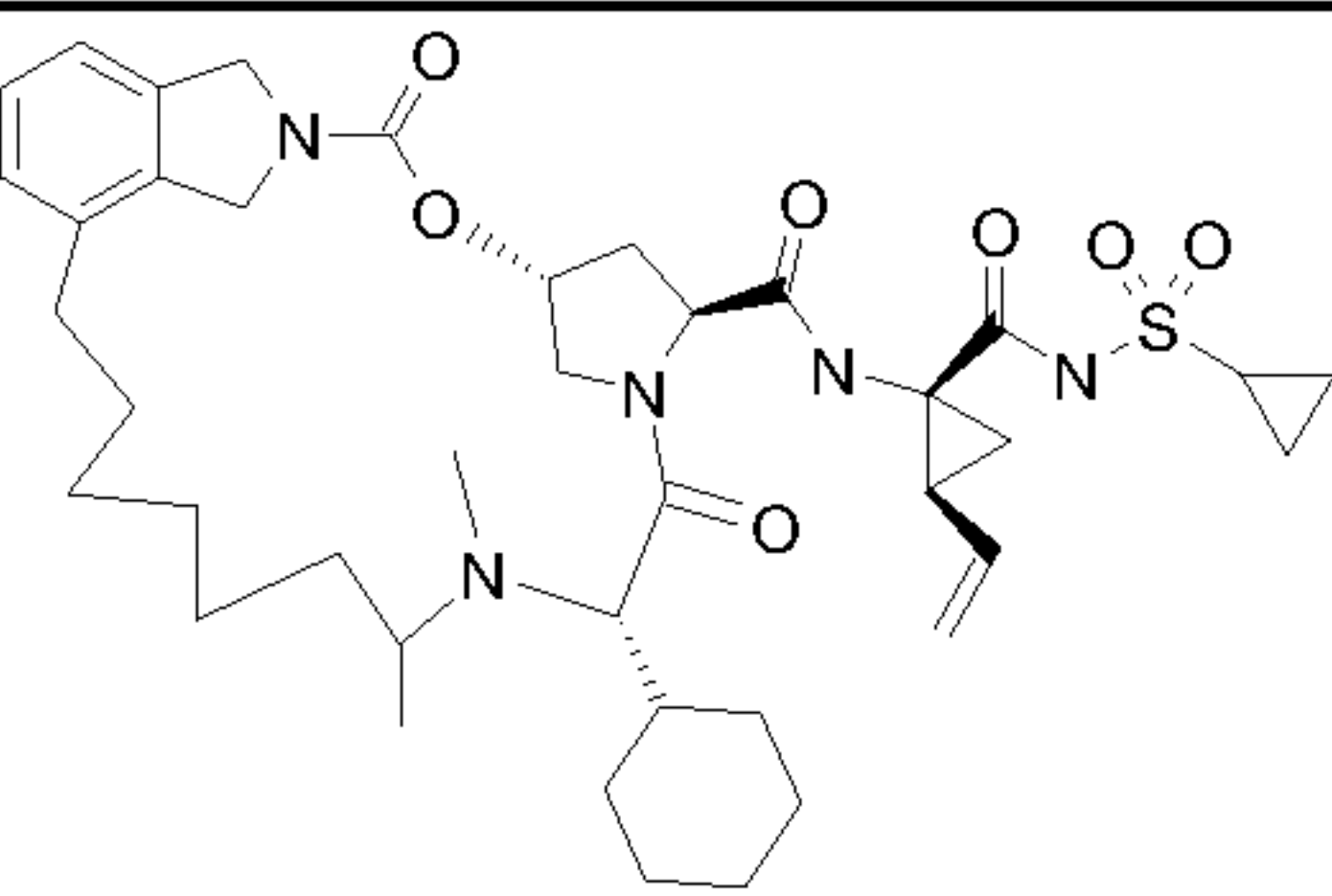
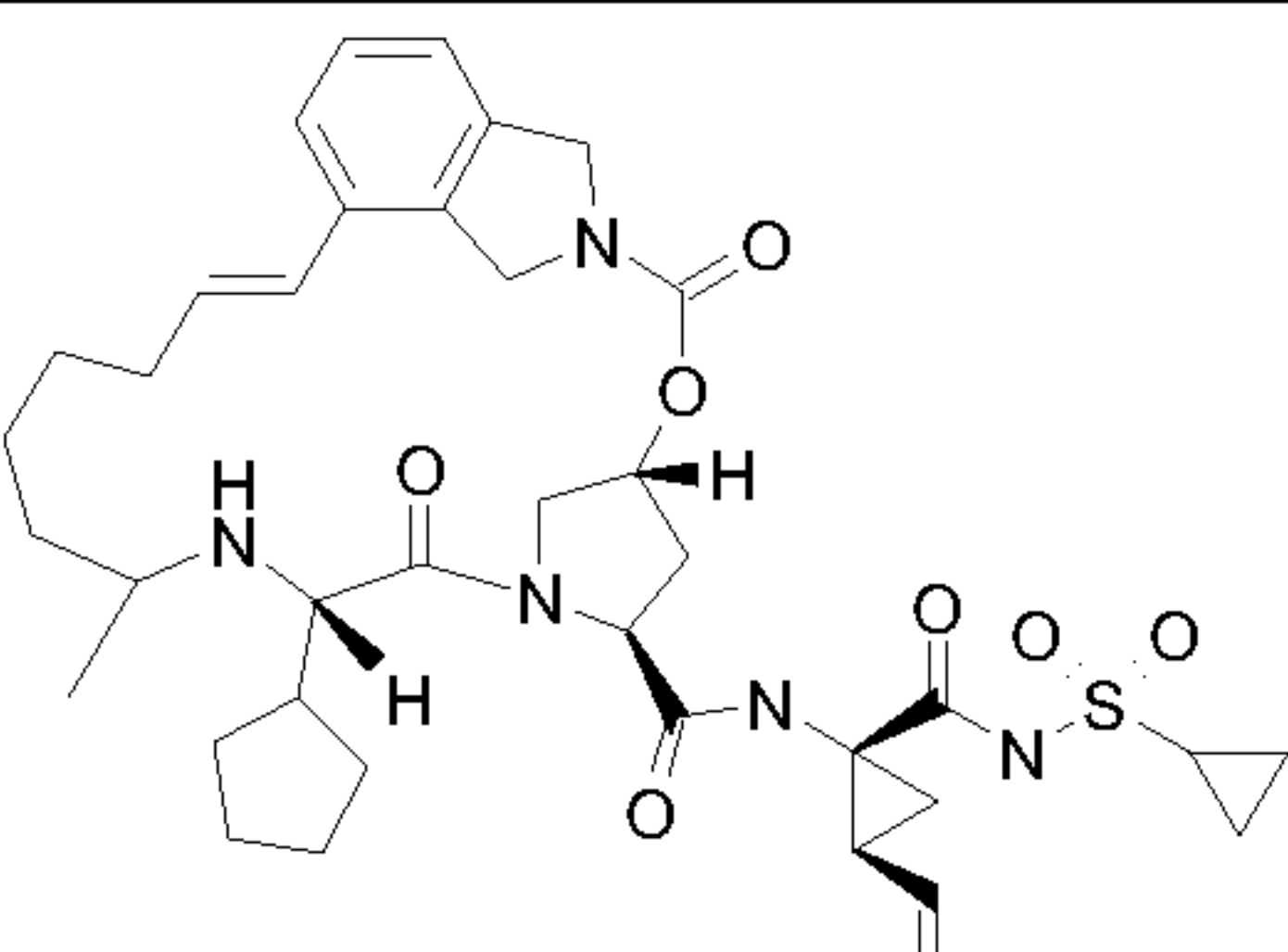
Table 1

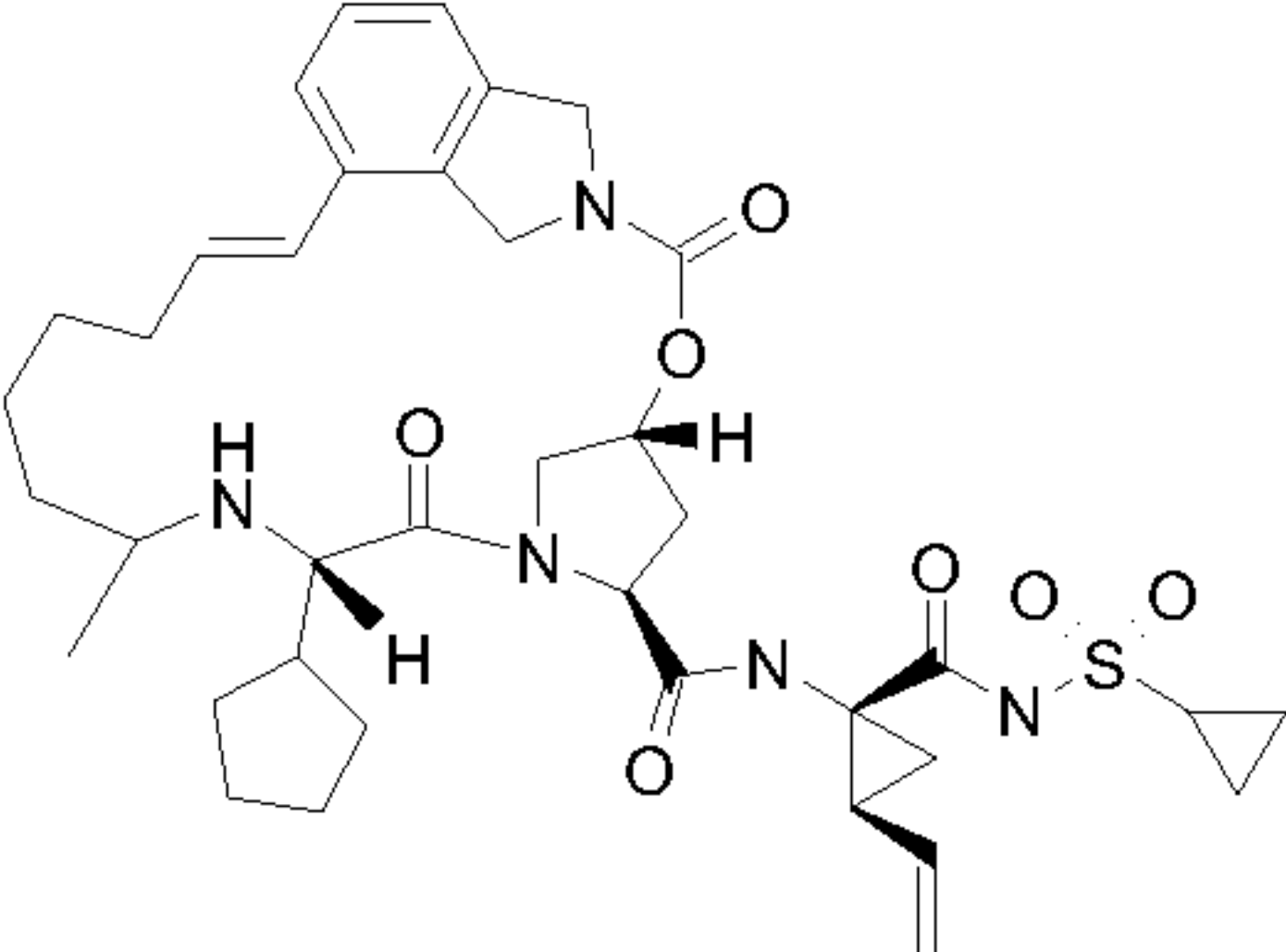
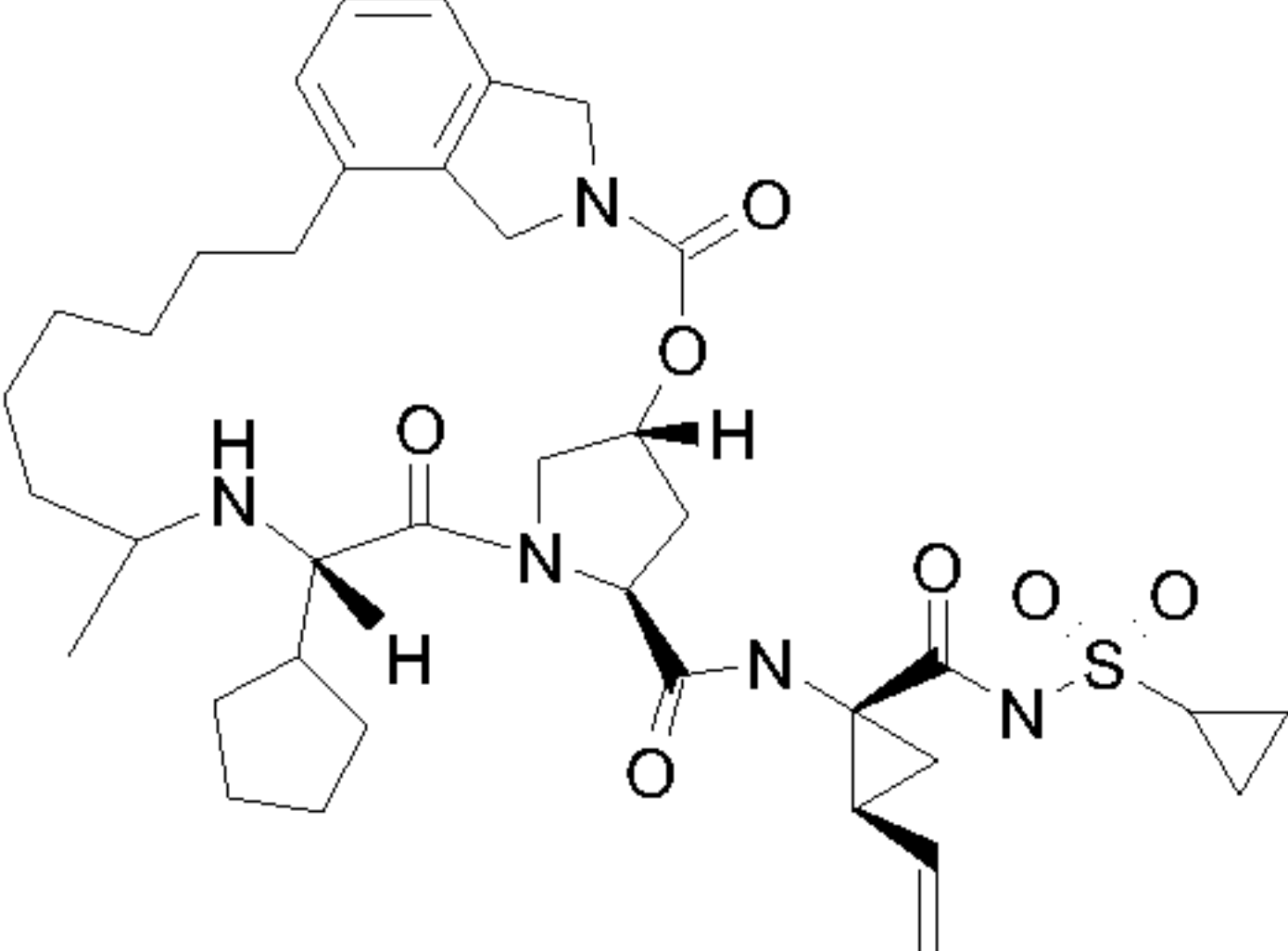
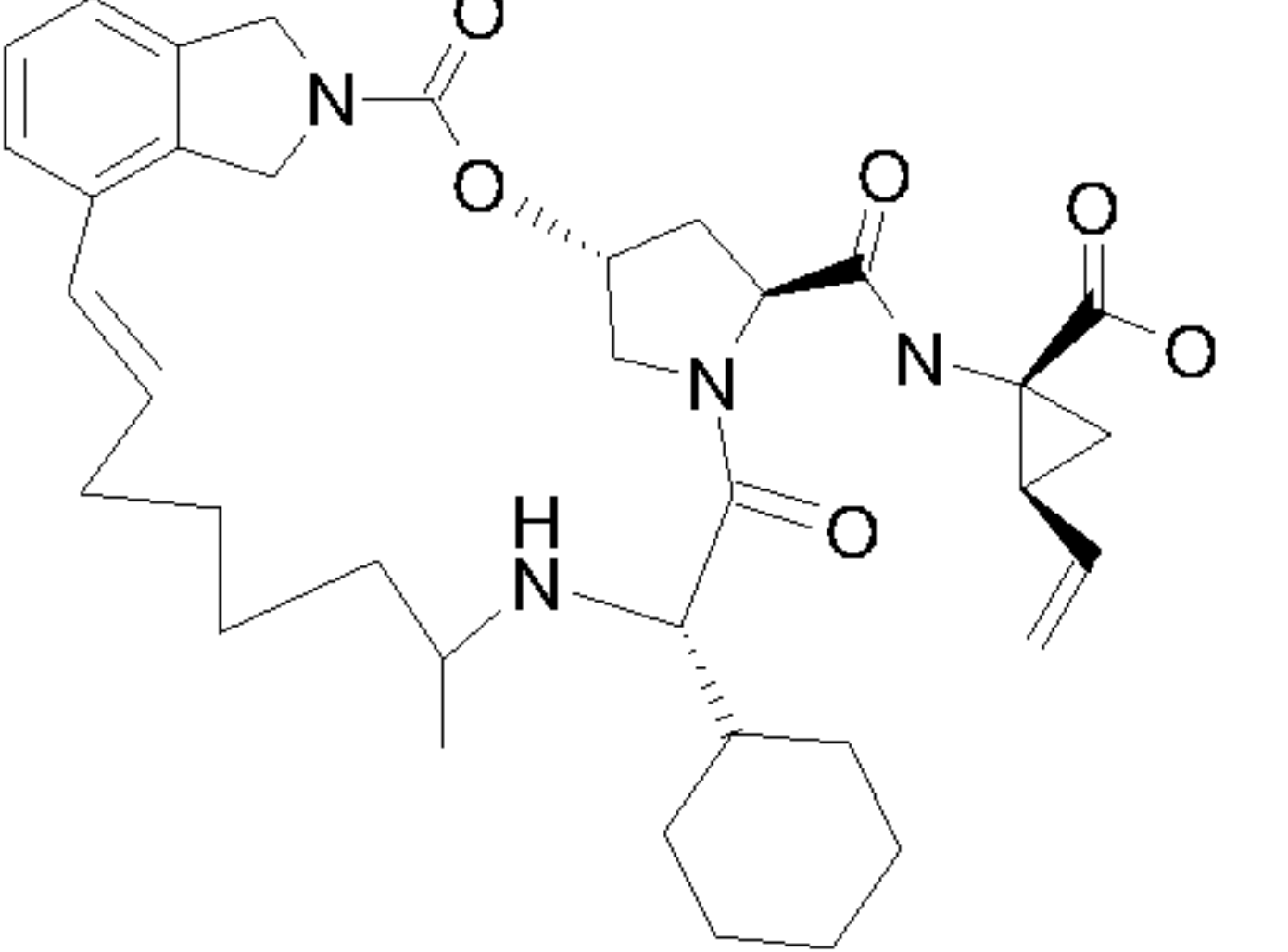
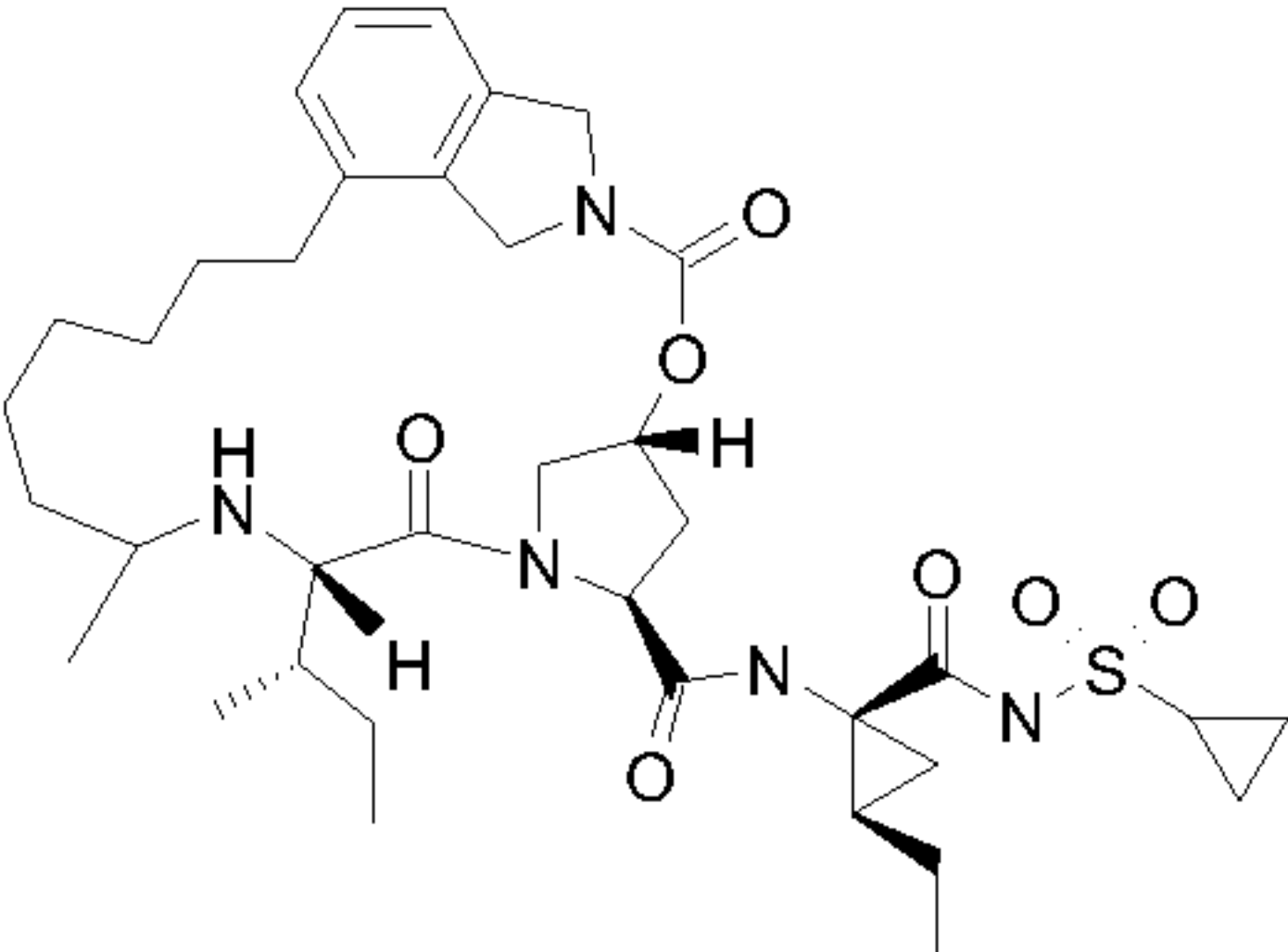
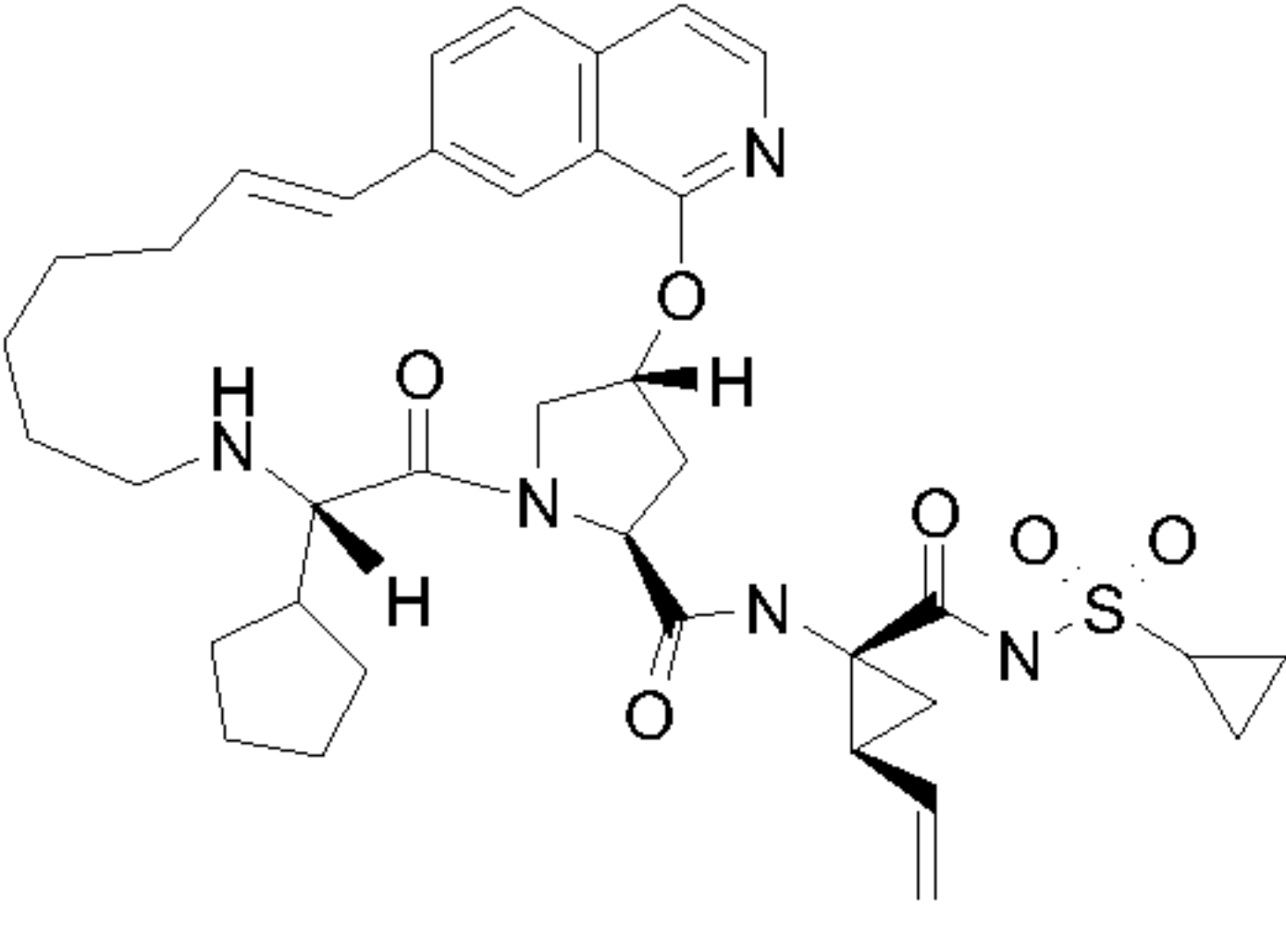
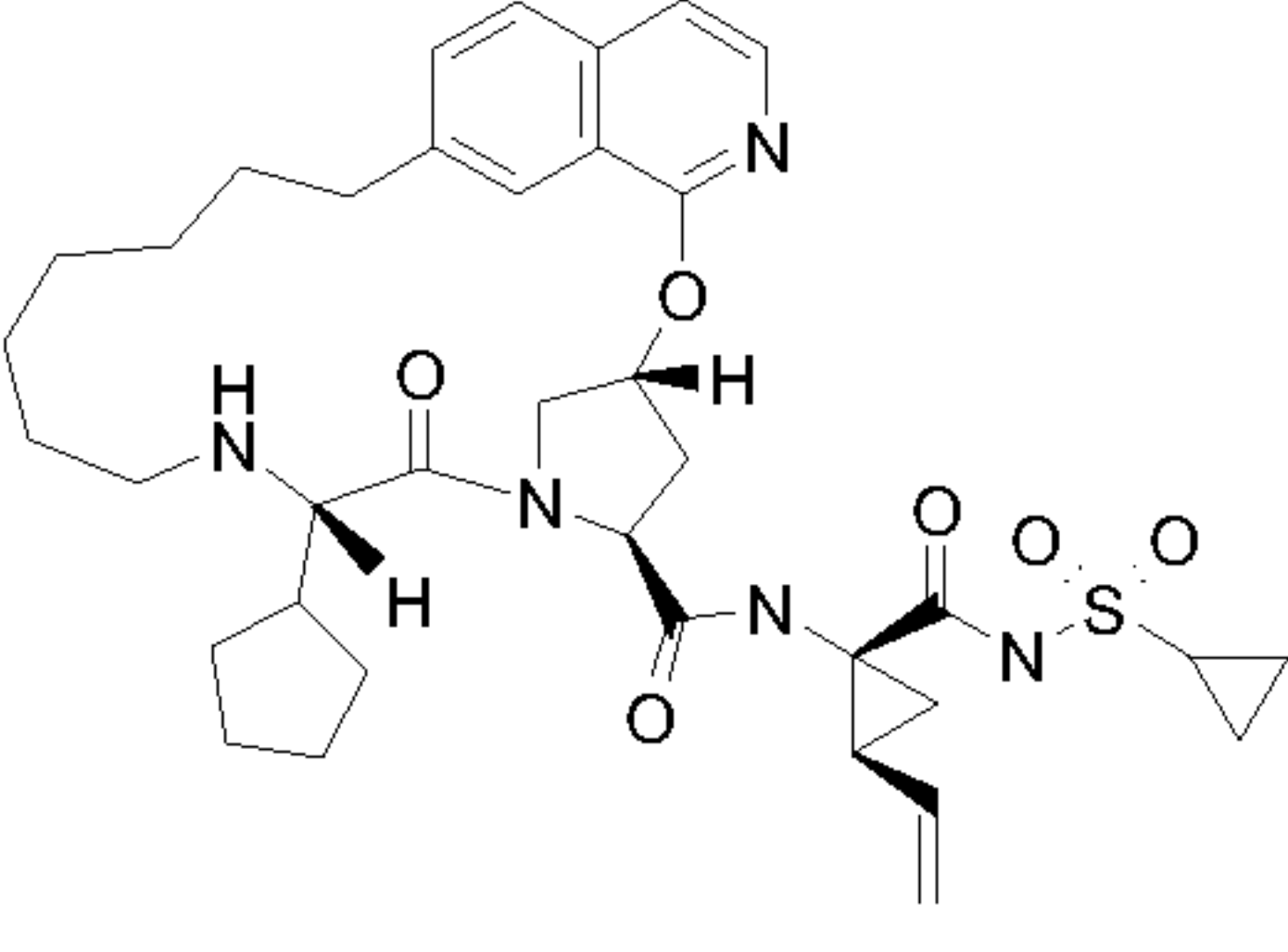
Cmp no.	Chemical name	Structure	Mass spec. (M+1)	Procedure (Scheme no.)
1	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i>)-N-((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-10-isopropyl- 3,9-dioxo-12-(trifluoromethyl)- 6,7,9,10,11,12,13,14,15,16,17,18- dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide		752	1
2	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i> ,9 <i>R</i> or <i>S</i>)-N-((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-7-isopropyl-6- oxo-9-(trifluoromethyl)- 3,4,6,7,8,9,10,11,12,13,14,15- dodecahydro-2 <i>H</i> -16,18- (ethanediylidene)-2,5-methanopyrido [3,2- <i>r</i>][1,5,8]oxadiazacyclonona decine-4-carboxamide		734	3
3	(5 <i>R</i> ,7 <i>S</i> ,10 <i>R</i> ,17 <i>E</i>)-N-((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-3,9-dioxo-10- (trifluoromethyl)-6,7,9,10,11,12,13, 14,15,16-decahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatriaza cycl icosine-7-carboxamide		708	4
4	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i>)-N-((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-10-isopropyl- 3,9-dioxo-12-(trifluoromethyl)- 6,7,9,10,11,12,13,14,15,16,17,18- dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide		752	1
5	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i>)-10-cyclohexyl- N-((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)- 3,9-dioxo-12-(trifluoromethyl)- 6,7,9,10,11,12,13,14,15,16,17,18- dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide		792	1

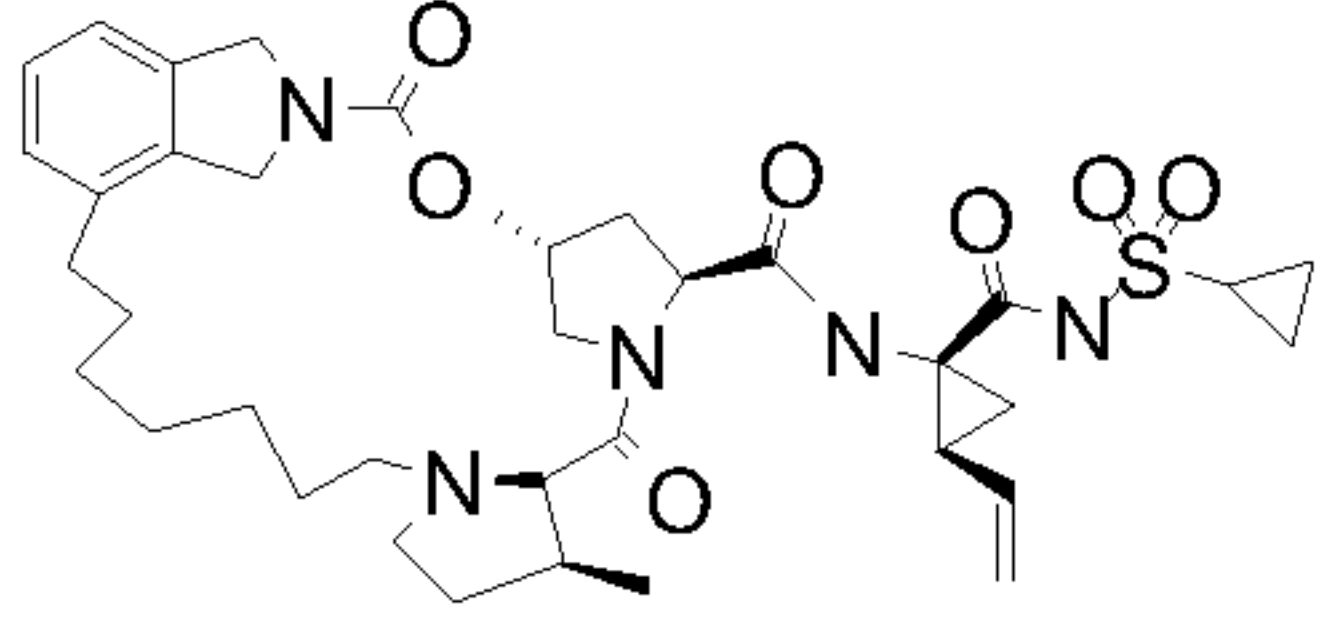
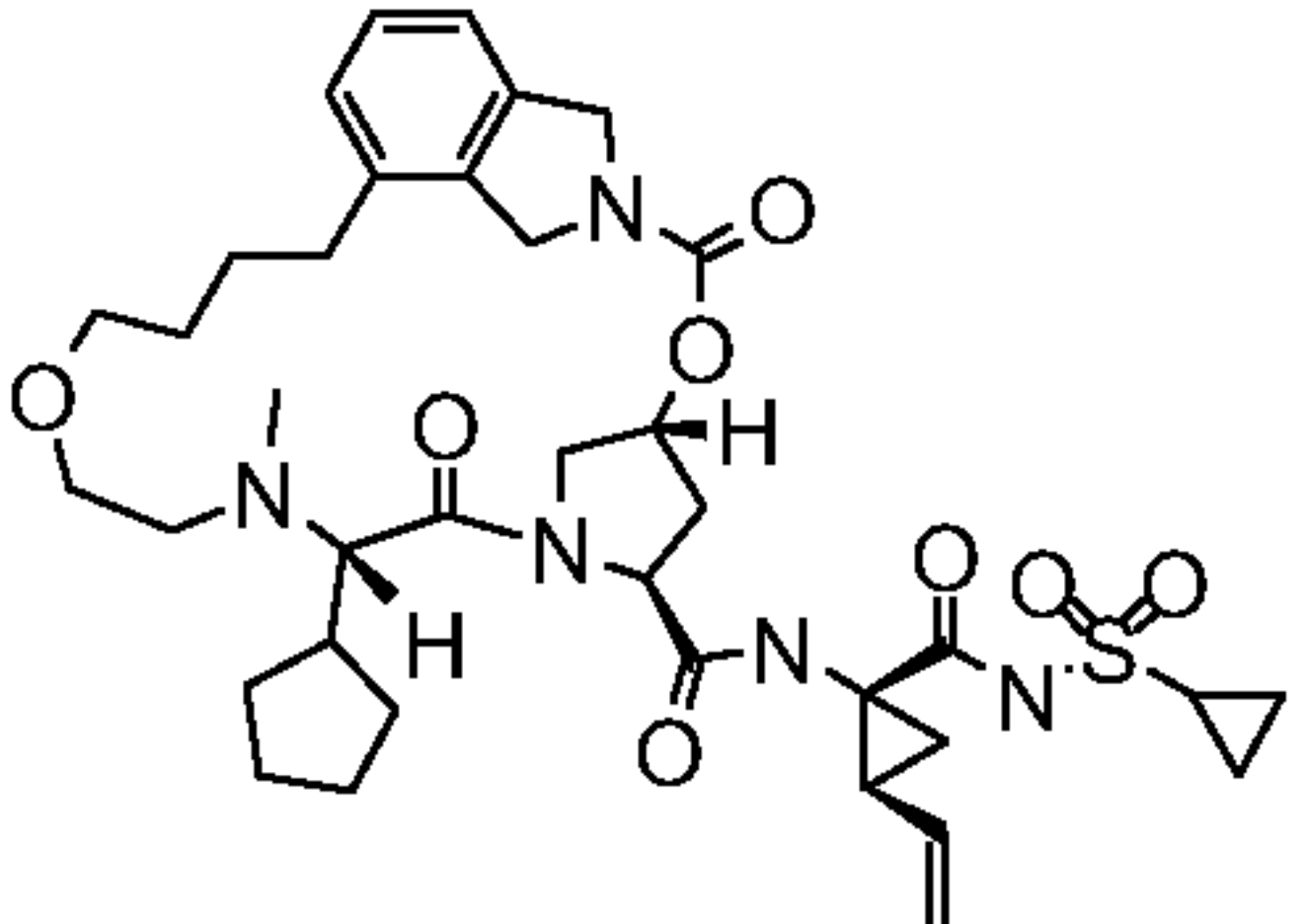
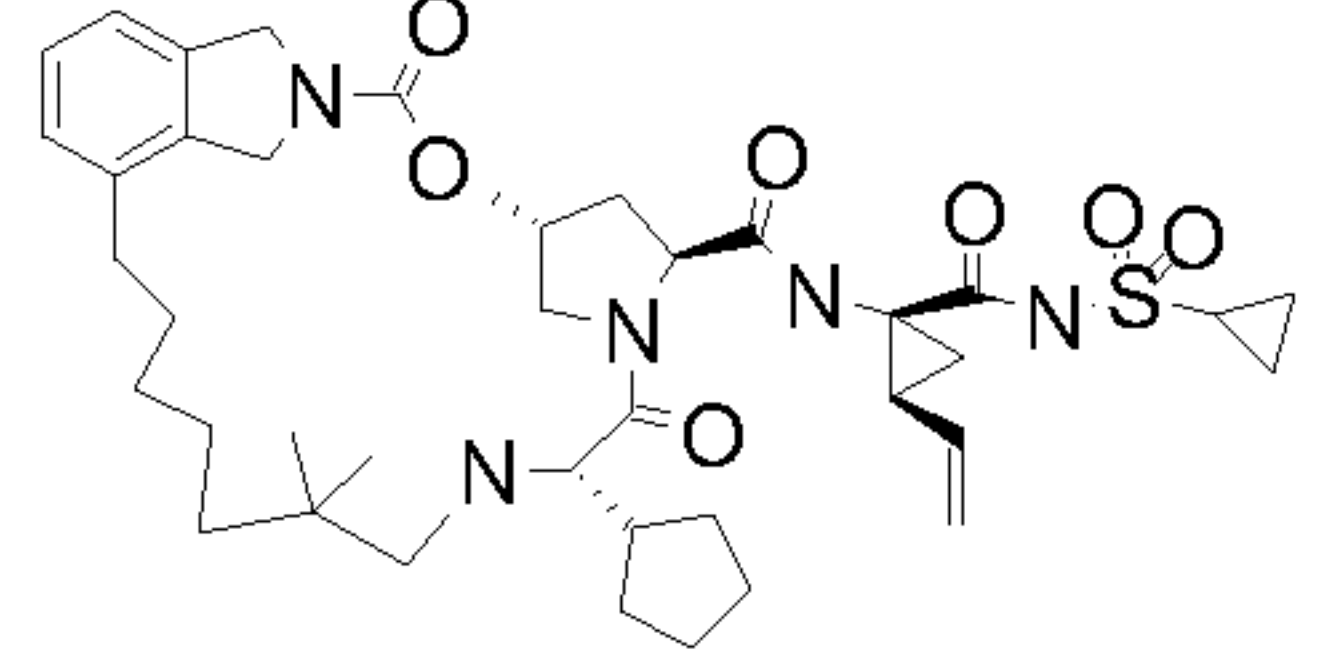
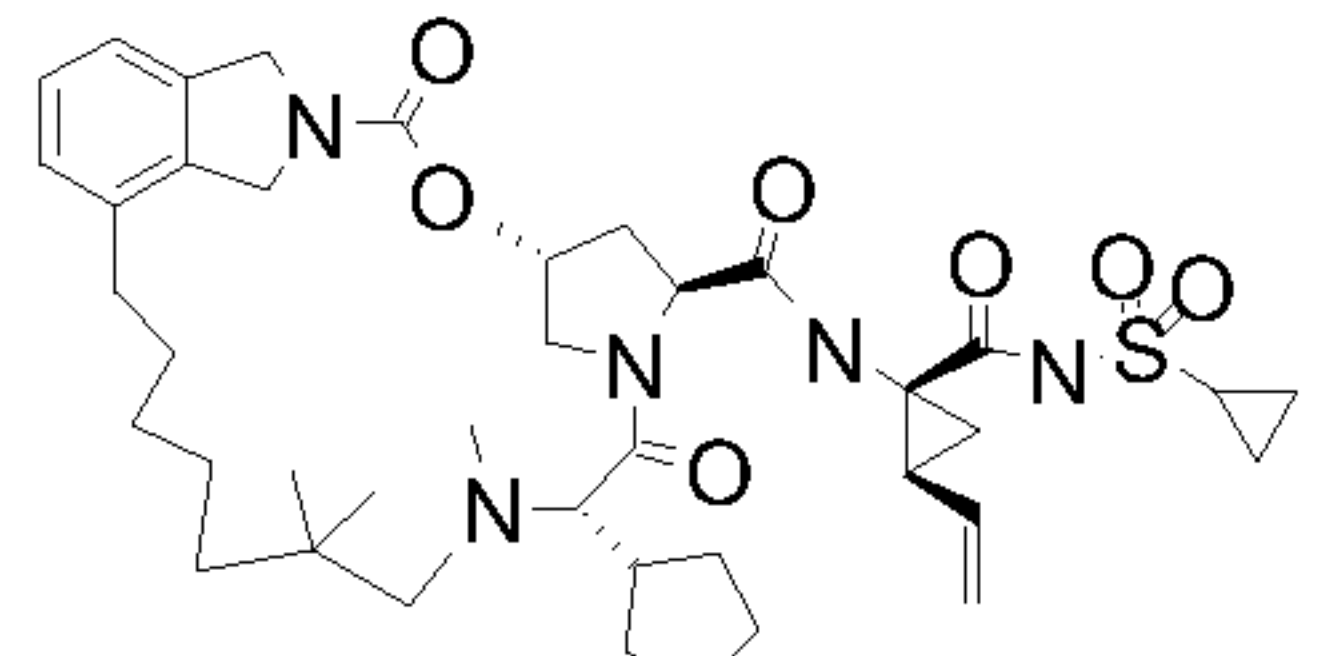
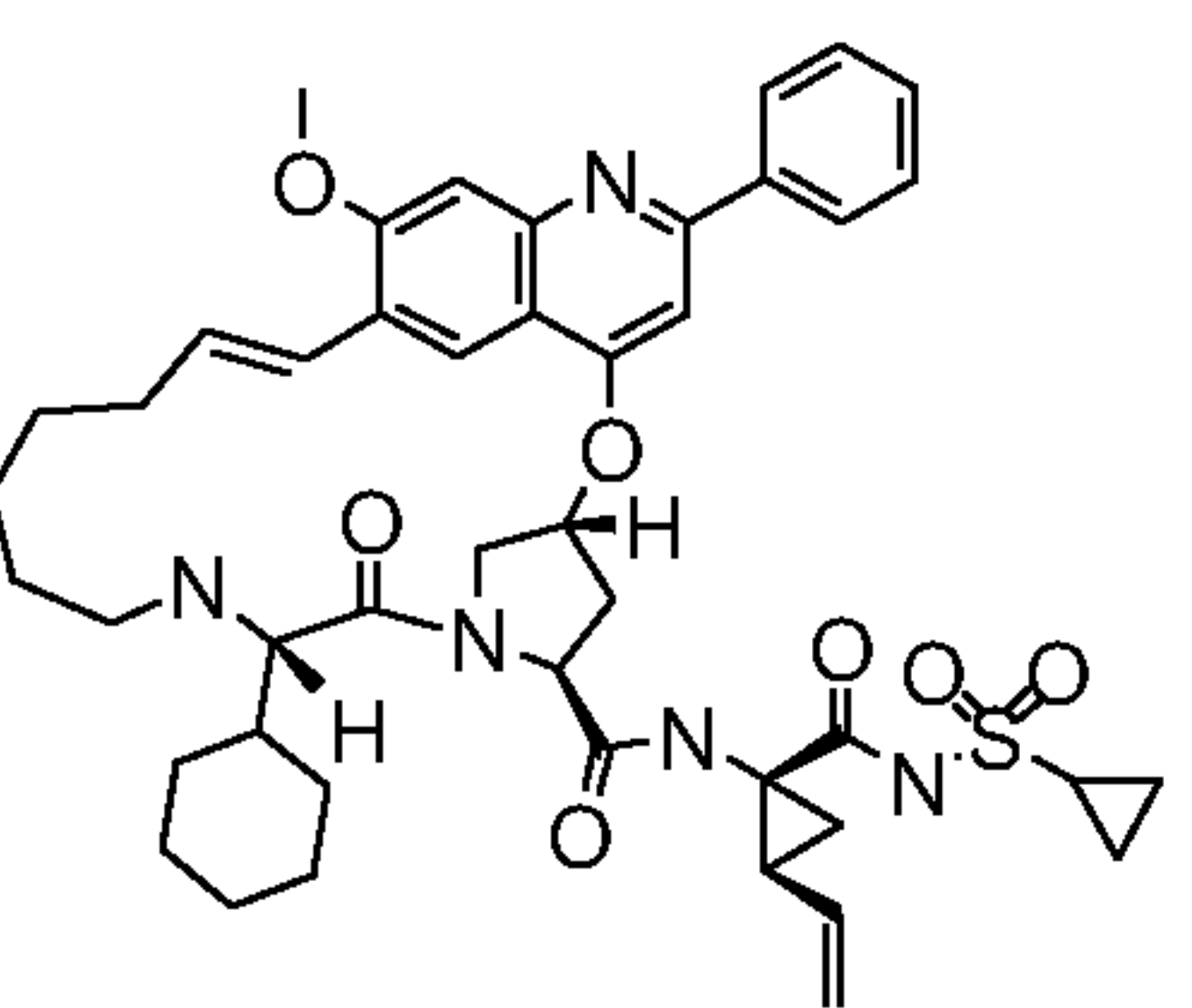
6	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i>)-10-cyclohexyl-N-((1 <i>R</i> ,2 <i>R</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3,9-dioxo-12-(trifluoromethyl)-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8-dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide		794	2
7	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i>)-10-cyclohexyl-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,9-dioxo-12-(trifluoromethyl)-1,6,7,9,10,11,12,13,14,15,16,17-dodecahydro-5 <i>H</i> -2,21:5,8-dimethano-4,2,8,11-benzoxatriazacyclononadecine-7-carboxamide		778	1
8	(2 <i>R</i> ,4 <i>S</i> ,7 <i>R</i> ,14 <i>E</i>)-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6-oxo-7-(trifluoromethyl)-3,4,6,7,8,9,10,11,12,13-decahydro-2 <i>H</i> -16,18-(ethanediylidene)-2,5-methanopyrido[3,2- <i>r</i>][1,5,8]oxadiazacyclononadecine-4-carboxamide		690	5
9	(2 <i>R</i> ,4 <i>S</i> ,7 <i>R</i>)-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6-oxo-7-(trifluoromethyl)-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2 <i>H</i> -16,18-etheno-2,5-methanopyrido[3,2- <i>r</i>][1,5,8]oxadiazacyclononadecine-4-carboxamide		692	5
10	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i>)-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-isopropyl-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide		698	6

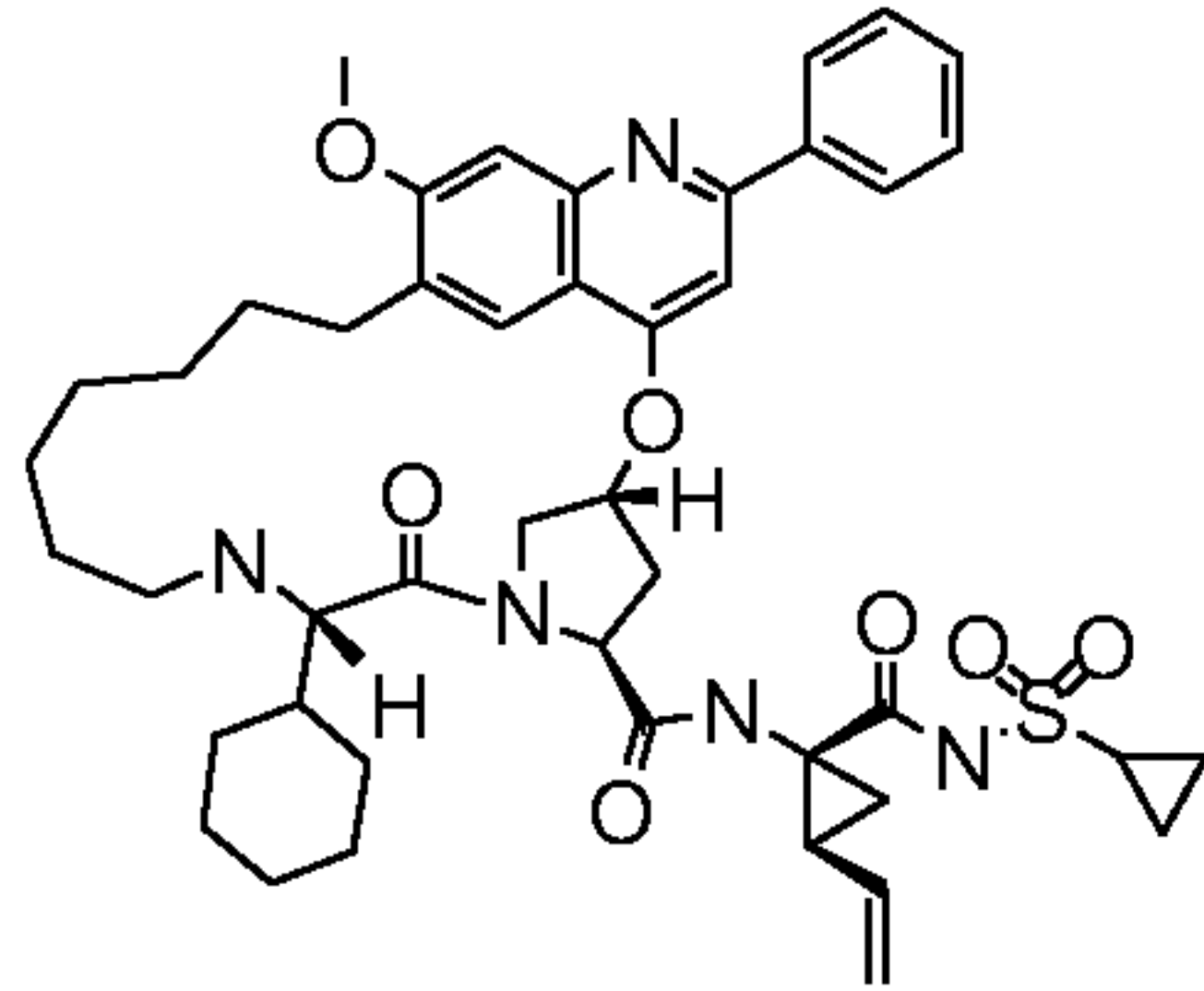
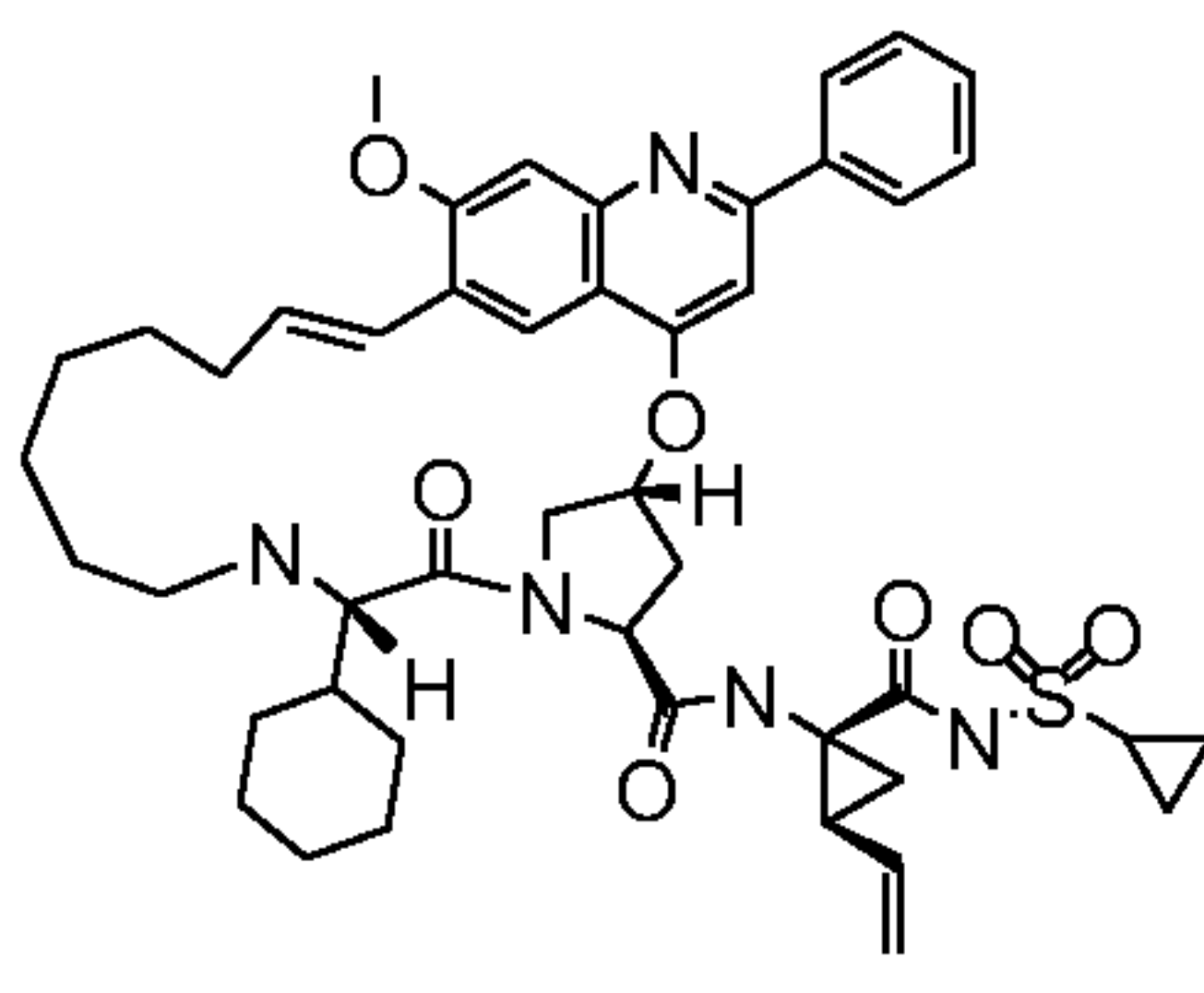
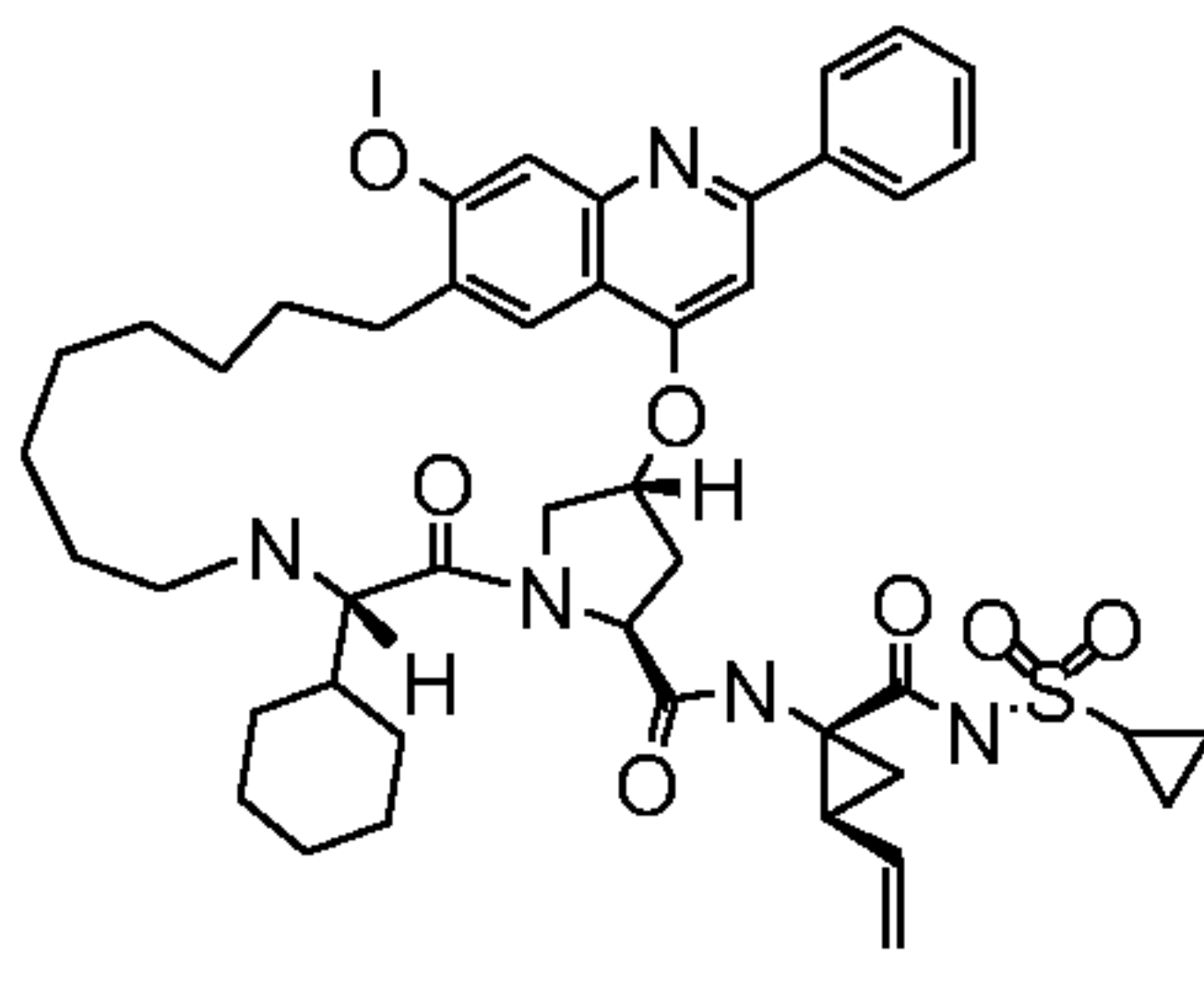
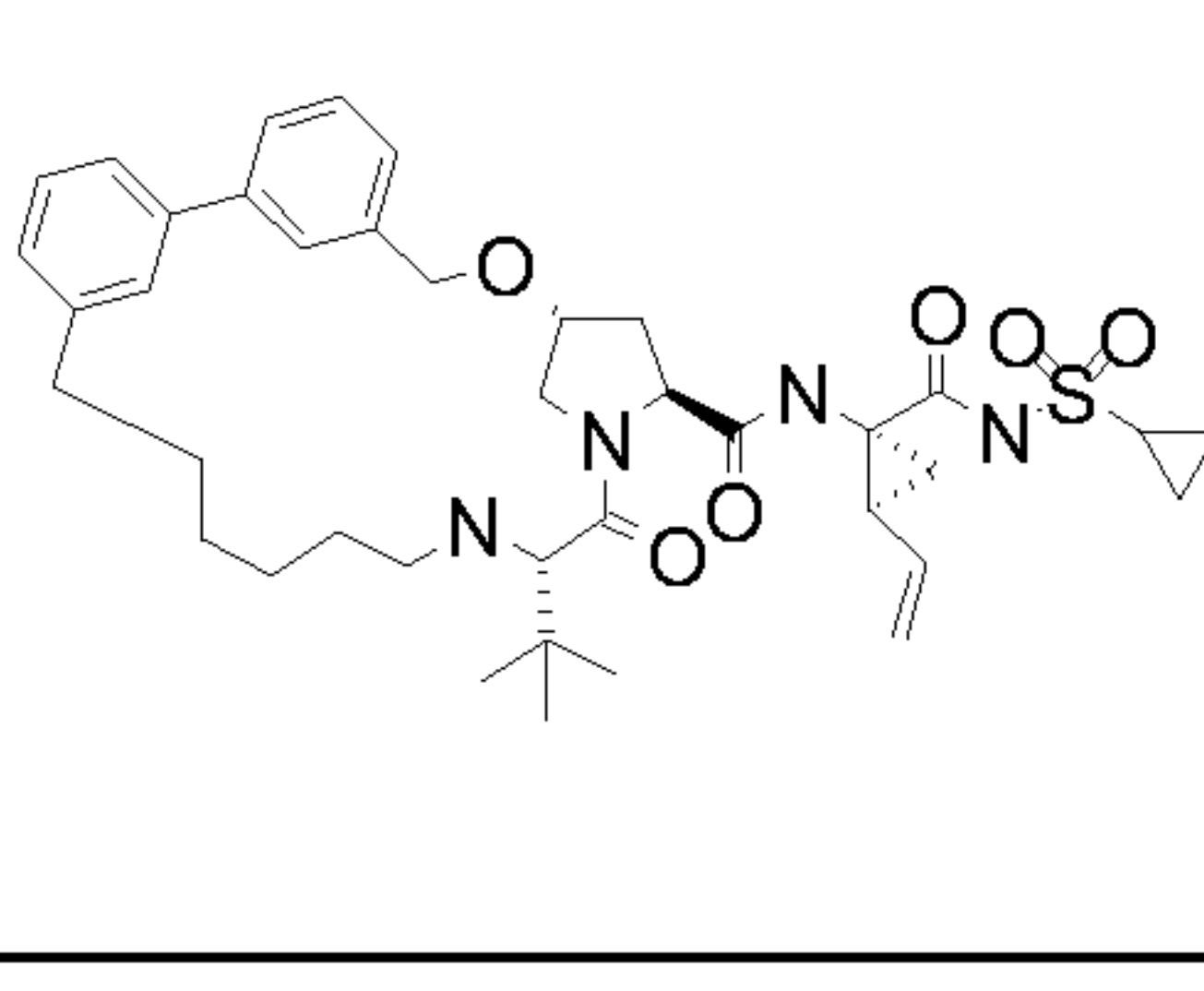
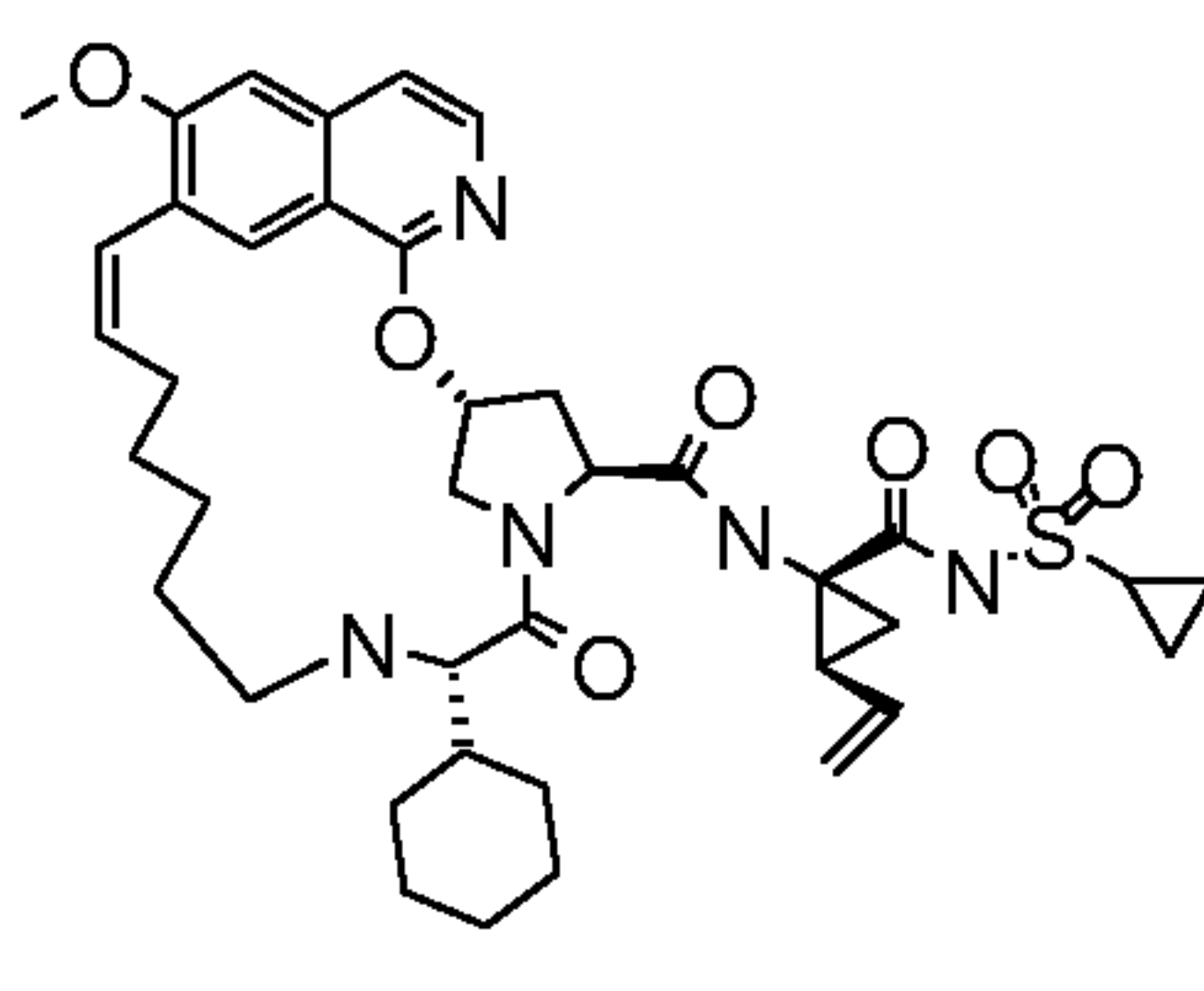
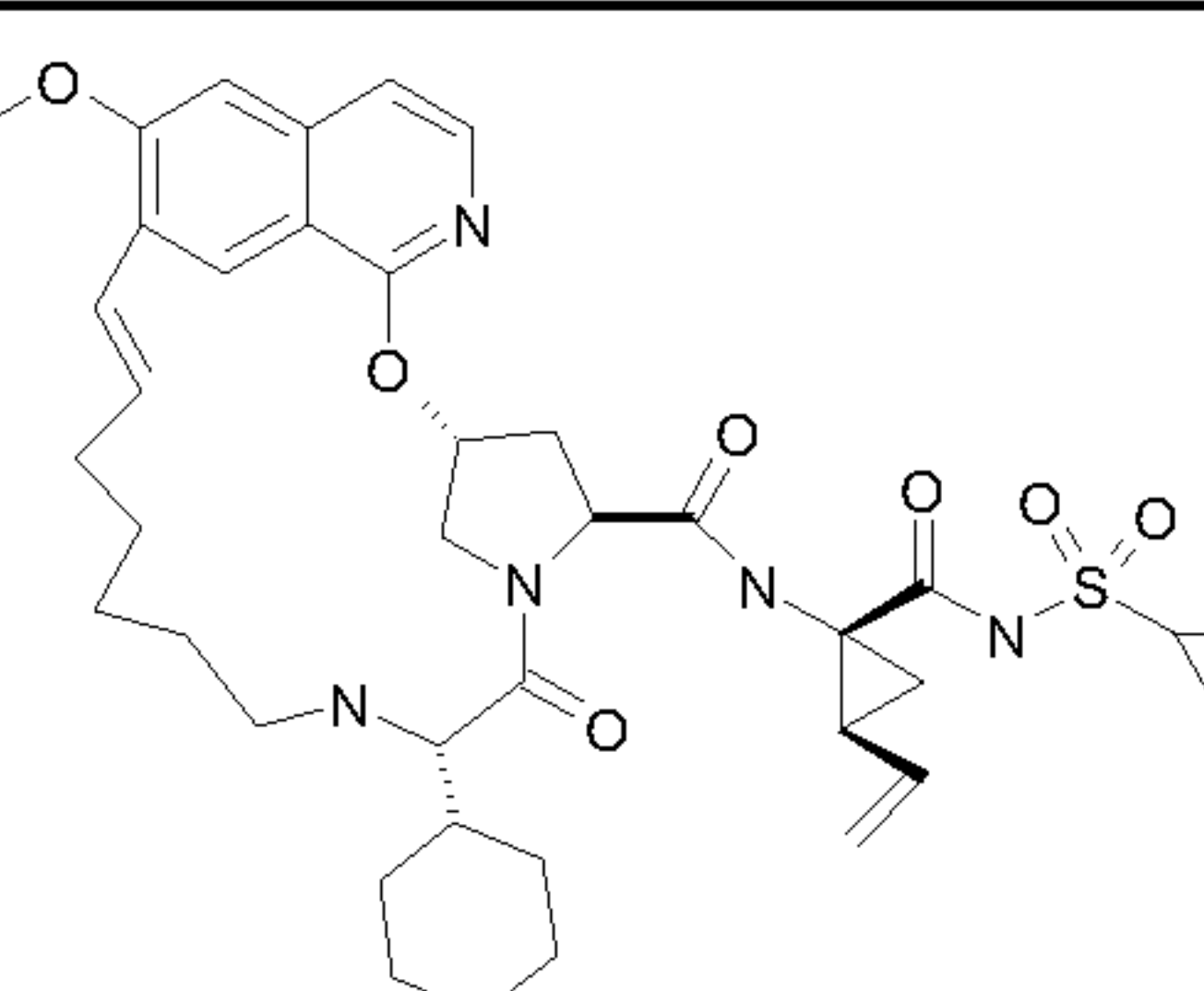
11	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-10-isopropyl-12- methyl-3,9-dioxo-6,7,9,10,11,12,13, 14,15,16,17,18-dodecahydro-1 <i>H</i> ,5 <i>H</i> - 2,22:5,8-dimethano-4,2,8,11- benzoxatriazacycloicosine-7- carboxamide		698	6
12	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,17 <i>E</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-10-methyl-3,9- dioxo-6,7,9,10,11,12,13,14,15,16- decahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8-dimethano- 4,2,8,11-benzoxatriazacycloicosine-7- carboxamide		684	8
13	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,17 <i>E</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-13,13-difluoro- 10-isopropyl-3,9-dioxo-6,7,9,10,11,12, 13,14,15,16-decahydro-1 <i>H</i> ,5 <i>H</i> - 2,22:5,8-dimethano-4,2,8,11- benzoxatriazacyclo icosine-7- carboxamide		718	10
14	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-13,13-difluoro- 10-isopropyl-3,9-dioxo- 6,7,9,10,11,12,13,14,15,16,17,18- dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide		720	10
15	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i> ,17 <i>E</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)- 1-{[(cyclopropylsulfonyl)amino] carbonyl}-2-vinylcyclopropyl)-10- isopropyl-12-methyl-3,9-dioxo- 6,7,9,10,11,12,13,14, 15,16- decahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8-dimethano- 4,2,8,11-benzoxatriazacycloicosine-7- carboxamide		696	6
16	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-10-isopropyl- 3,9-dioxo-12-(pentafluoroethyl)- 6,7,9,10,11,12,13,14,15,16,17,18- dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatriaza		802	1

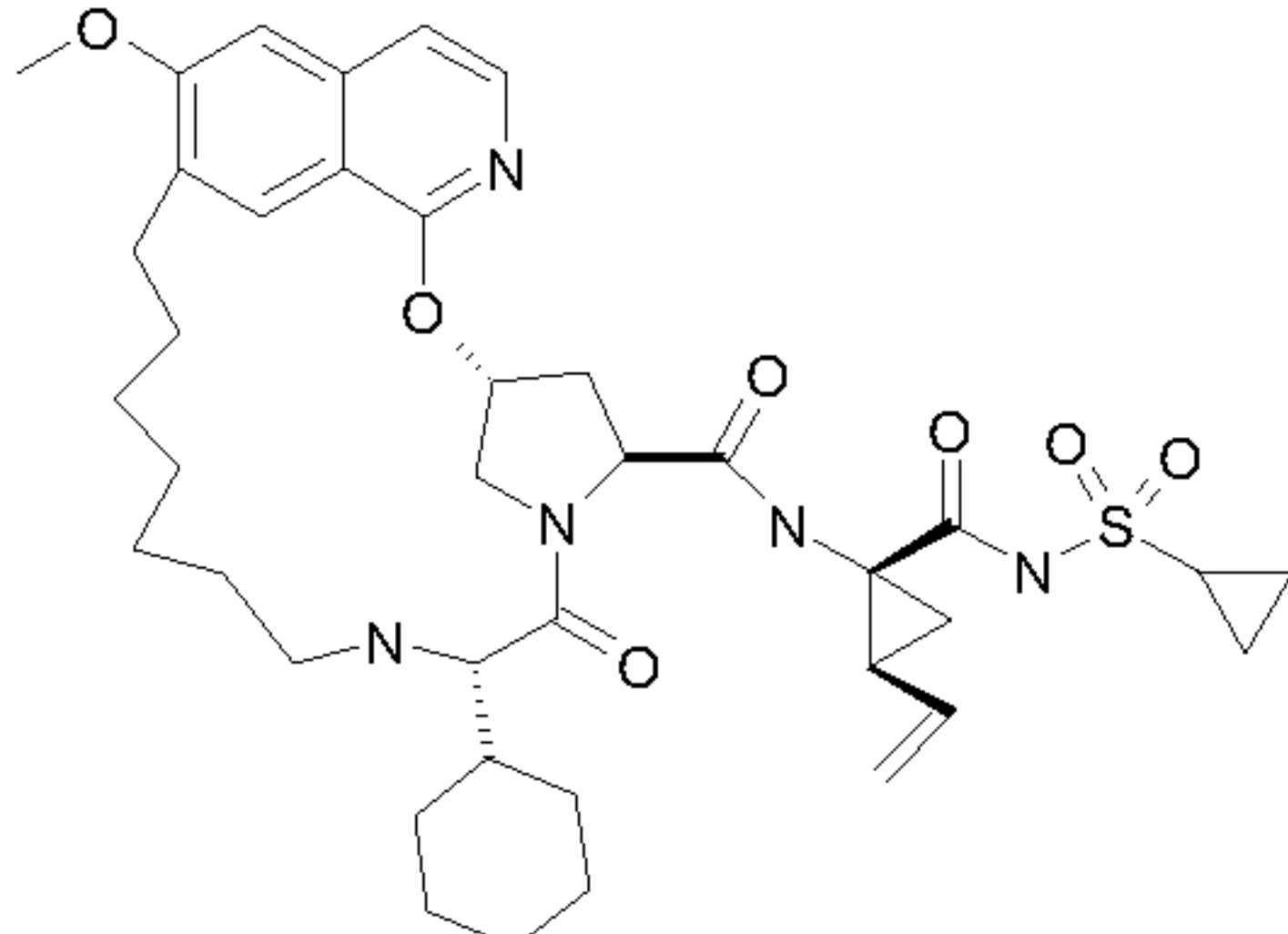
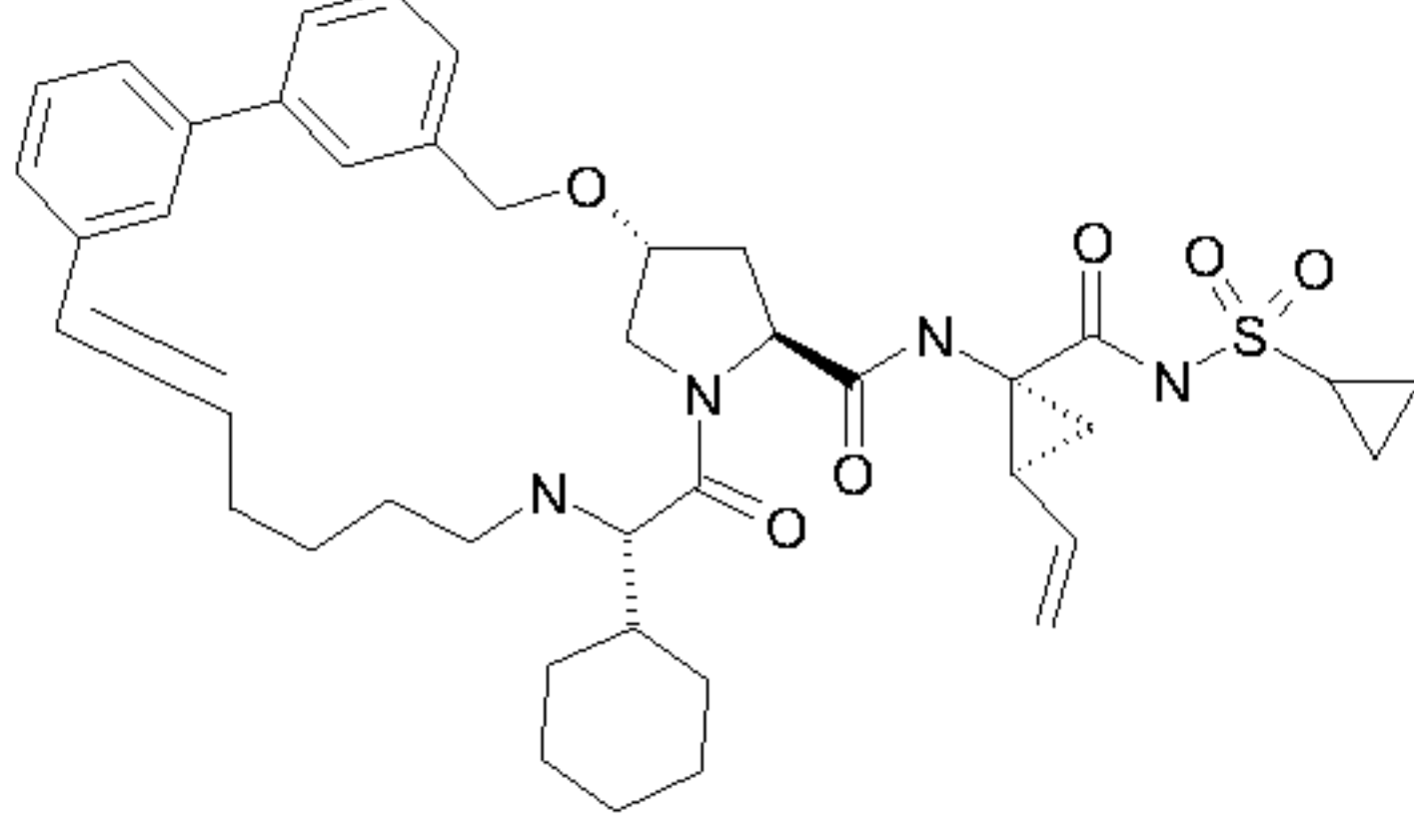
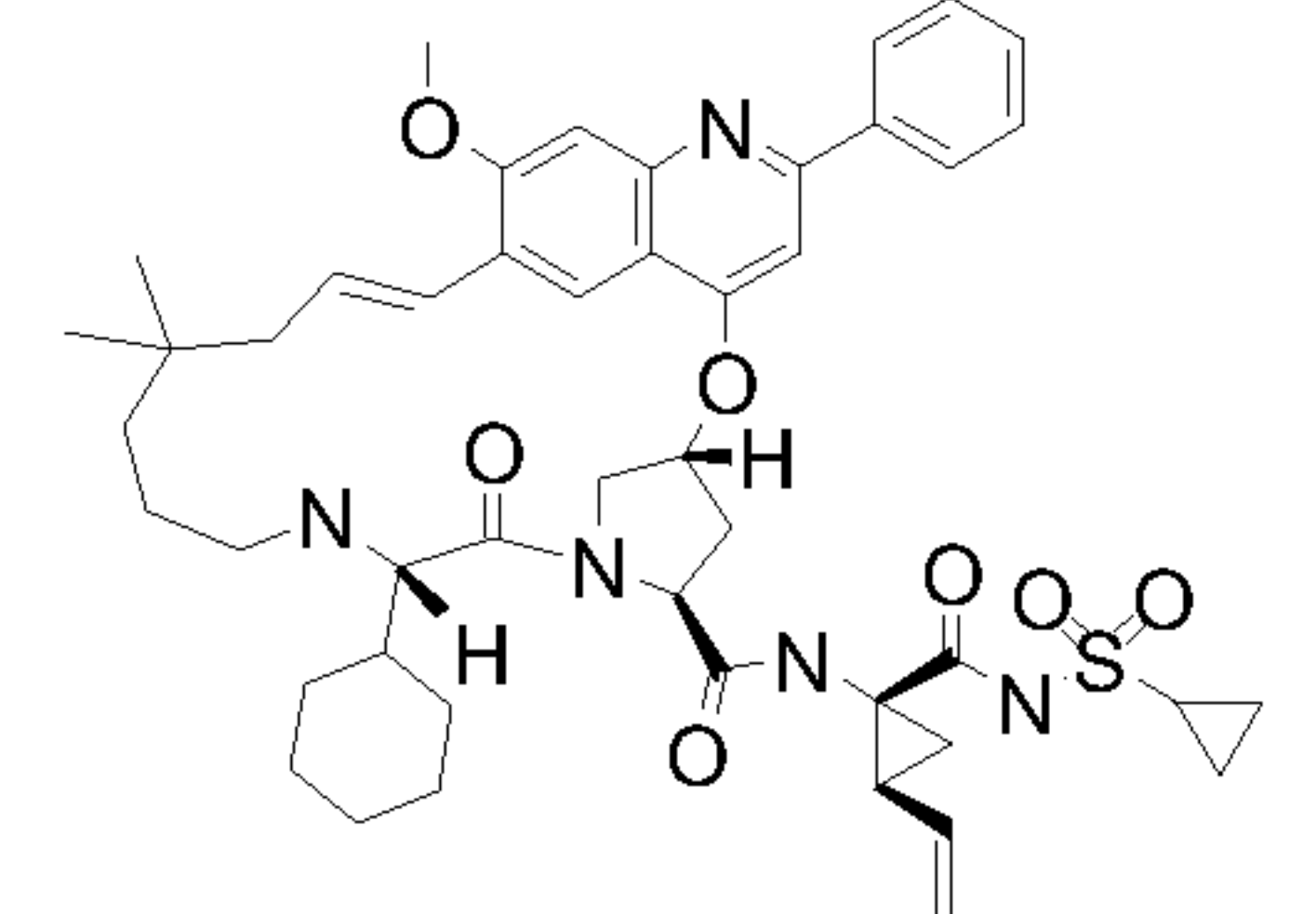
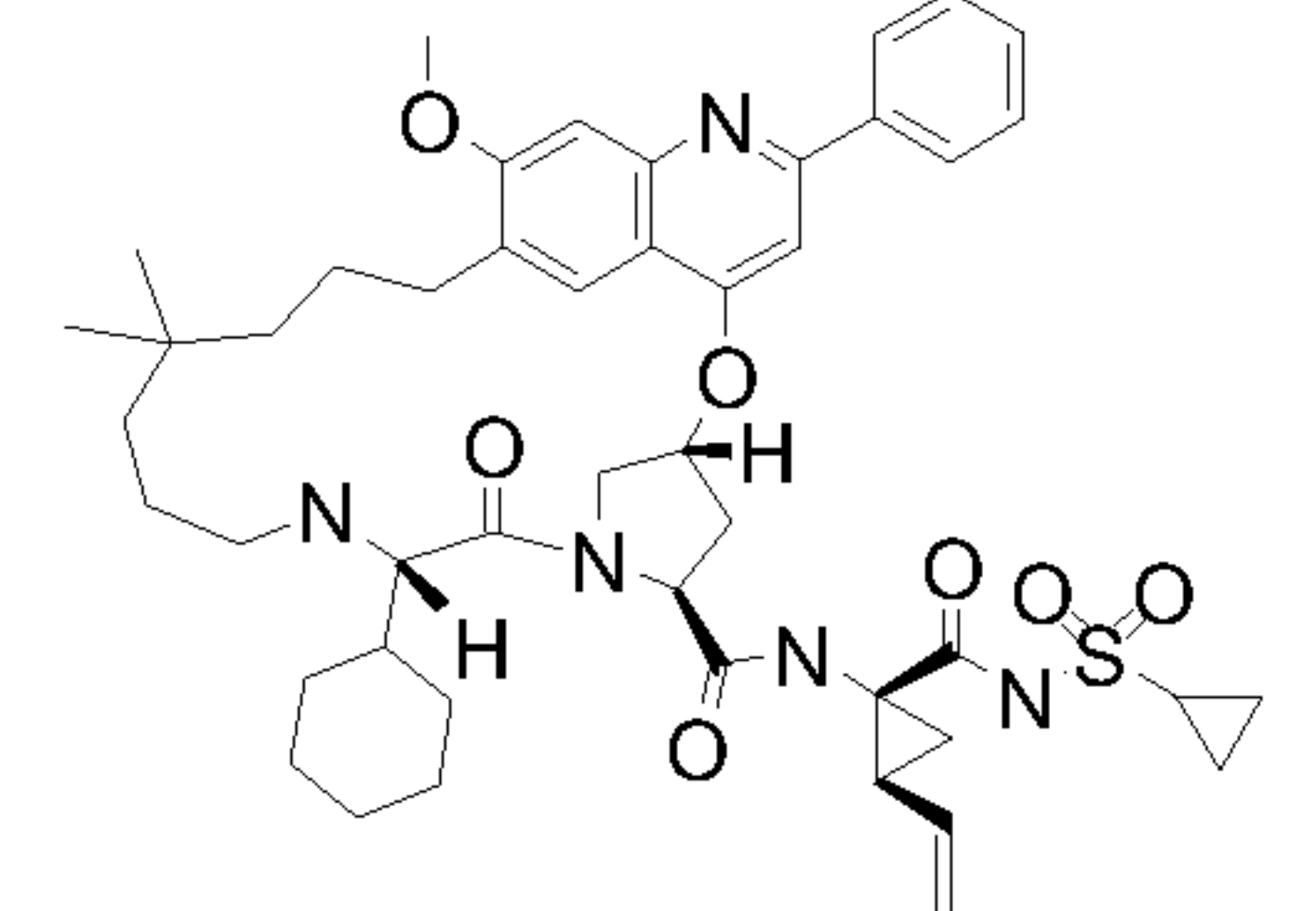
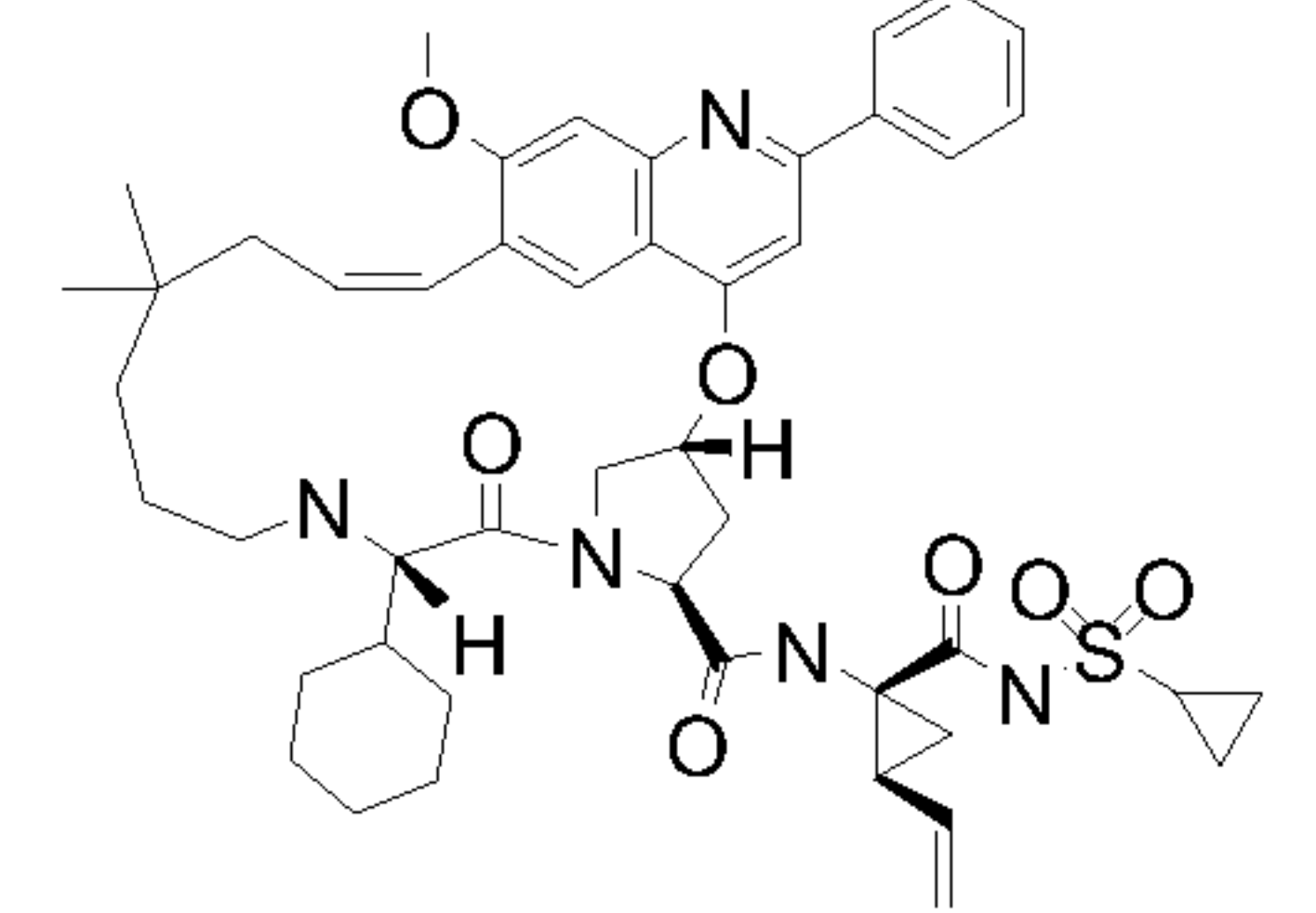
	cycloicosine-7-carboxamide			
17	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-ethylcyclopropyl)-10-isopropyl-12- methyl-3,9-dioxo- 6,7,9,10,11,12,13,14, 15,16,17,18- dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide		700	6
18	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-10-methyl-3,9- dioxo-6,7,9,10,11,12,13,14,15,16,17, 18-dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide		656	8
19	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-10-isopropyl- 3,9-dioxo- 6,7,9,10,11,12,13,14,15,16,17, 18- dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide		684	8
20	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,17 <i>E</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-10-isopropyl- 3,9-dioxo-6,7,9,10,11,12,13,14,15,16- decahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8-dimethano- 4,2,8,11-benzoxatriazacycloicosine-7- carboxamide		682	8
21	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i>)-10-cyclohexyl- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl) amino]carbonyl}-2-vinylcyclopropyl)- 12-methyl-3,9-dioxo- 6,7,9,10,11,12,13,14,15,16,17,18- dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide		738	6
22	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i> ,9 <i>R</i> or <i>S</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-7-isopropyl-9- methyl-6-oxo-3,4,6,7,8,9,10,11,12,13, 14,15-dodecahydro-2 <i>H</i> -16,18-etheno- 2,5-methanopyrido[3,2- <i>r</i>][1,5,8]oxa diazacyclononadecine-4-carboxamide		680	14

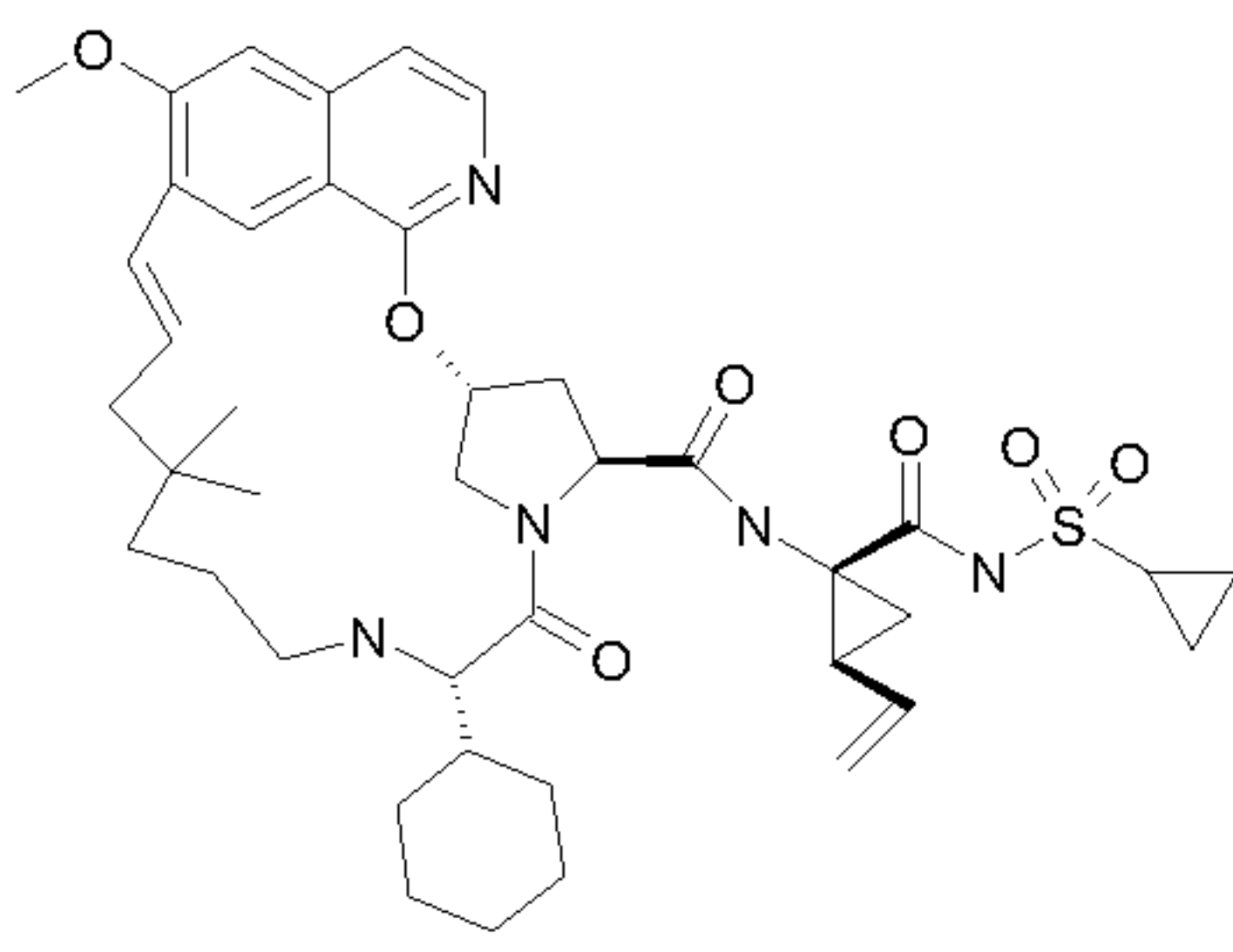
23	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i> ,9 <i>S</i> or <i>R</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-7-isopropyl-9- methyl-6-oxo-3,4,6,7,8,9,10,11,12,13, 14,15-dodecahydro-2 <i>H</i> -16,18-etheno- 2,5-methanopyrido[3,2- <i>r</i>][1,5,8]oxa diazacyclononadecine-4-carboxamide		680	14
24	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i> ,7 <i>E</i>)-10- cyclohexyl- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino] carbonyl}-2-vinylcyclopropyl)-12- methyl-3,9-dioxo-6,7,9,10,11,12,13, 14,15,16-decahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide		736	6
25	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i>)-10-cyclohexyl- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl) amino]carbonyl}-2-vinylcyclopropyl)- 12-methyl-3,9-dioxo- 6,7,9,10,11,12,13,14,15,16,17,18- dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxa triazacycloicosine-7-carboxamide		738	6
26	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i>)-10-cyclohexyl- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl) amino]carbonyl}-2-vinylcyclopropyl)- 11,12-dimethyl-3,9-dioxo- 6,7,9,10,11,12,13,14,15,16,17,18- dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide		752	9
27	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i> ,17 <i>E</i>)-10- cyclopentyl- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-12-methyl-3,9- dioxo-6,7,9,10,11,12,13,14,15,16- decahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8-dimethano- 4,2,8,11-benzoxatriazacycloicosine-7- carboxamide		722	6

28	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i> ,17 <i>E</i>)-10-cyclopentyl-N-((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-vinylcyclopropyl)-12-methyl-3,9- dioxo-6,7,9,10,11,12,13,14,15,16- decahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8-dimethano- 4,2,8,11-benzoxatriazacycloicosine-7- carboxamide		722	6
29	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i>)-10-cyclopentyl- N-((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl) amino]carbonyl}-2-vinylcyclopropyl)- 12-methyl-3,9-dioxo- 6,7,9,10,11,12,13,14,15,16,17,18- dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatria- cycloicosine-7-carboxamide		724	6
30	(1 <i>R</i> ,2 <i>S</i>)-1-({[(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i> ,17 <i>E</i>)-10-cyclohexyl-12-methyl-3,9- dioxo-6,7,9,10,11,12,13,14,15,16- decahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8-dimethano- 4,2,8,11-benzoxatriazacycloicosin-7- yl]carbonyl} amino)-2- vinylcyclopropanecarboxylic acid		633	6
31	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i> ,12 <i>R</i> or <i>S</i>)-N-((1 <i>R</i> ,2 <i>R</i>)-1- {[(cyclopropylsulfonyl)amino]carbonyl }-2-ethylcyclopropyl)-12-methyl-10- [(1 <i>S</i>)-1-methylpropyl]-3,9-dioxo- 6,7,9,10,11,12,13,14,15,16,17,18- dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatria- cycloicosine-7-carboxamide		714	7
32	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i> ,14 <i>E</i>)-7-cyclopentyl-N- ((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl) amino]carbonyl}-2-vinylcyclopropyl)- 6-oxo-3,4,6,7,8,9,10,11,12,13- decahydro-2 <i>H</i> -16,18-etheno-2,5- methanopyrido [3,2- r][1,5,8]oxadiazacyclononadecine-4- carboxamide		690	15
33	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i>)-7-cyclopentyl-N-((1 <i>R</i> ,2 <i>S</i>)- 1- {[(cyclopropylsulfonyl)amino] carbonyl}-2-vinylcyclopropyl)-6-oxo- 3,4,6,7,8,9,10,11,12,13,14,15- dodecahydro-2 <i>H</i> -16,18-etheno-2,5- methanopyrido[3,2-r][1,5,8]oxadiaz- acyclononadecine-4-carboxamide		692	15

134	(3 <i>S</i> ,3 <i>aR</i> ,6 <i>S</i> ,8 <i>R</i>)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino] carbonyl}-2-vinylcyclopropyl)-3- methyl-4,10-dioxo-2,3,3 <i>a</i> ,4,7,8,12,17, 18,19,20,21,22,23-tetradecahydro- 1 <i>H</i> ,6 <i>H</i> -5,8:11,13-dimethanopyrrolo [2,1- <i>j</i>][4,2,8,11]benzoxatriazacyclo icosine-6-carboxamide		695	8
135	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i>)-10-cyclopentyl- <i>N</i> - ((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino] carbonyl}-2-vinylcyclopropyl)- 11-methyl-3,9-dioxo- 6,7,10,11,12,13,15,16,17,18- decahydro-1 <i>H</i> ,5 <i>H</i> ,9 <i>H</i> -2,22:5,8- dimethano-4,14,2,8,11-benzodioxatriazacycloicosine-7-carboxamide		725	9
136	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i>)-10-cyclopentyl- <i>N</i> - ((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino] carbonyl}-2-vinylcyclopropyl)-13,13- dimethyl-3,9-dioxo-6,7,9,10,11,12,13, 14,15,16,17,18-dodecahydro-1 <i>H</i> ,5 <i>H</i> - 2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide		737	18
137	(5 <i>R</i> ,7 <i>S</i> ,10 <i>S</i>)-10-cyclopentyl- <i>N</i> - ((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino] carbonyl}-2-vinylcyclopropyl)- 11,13,13-trimethyl-3,9-dioxo- 6,7,9,10,11,12,13,14,15,16,17,18- dodecahydro-1 <i>H</i> ,5 <i>H</i> -2,22:5,8- dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide		751	9
138	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i> ,14 <i>E</i>)-7-cyclohexyl- <i>N</i> - ((1 <i>R</i> ,2 <i>S</i>)-1- {[(cyclopropylsulfonyl)amino] carbonyl}-2-vinylcyclopropyl)- 23-methoxy-6-oxo-20-phenyl- 3,4,6,7,8,9,10,11,12,13-decahydro- 2 <i>H</i> -16,18-etheno-2,5- methanopyrido[3,4- <i>r</i>][1,5,8]oxadiazacyclononadecine-4-carboxamide		810	18

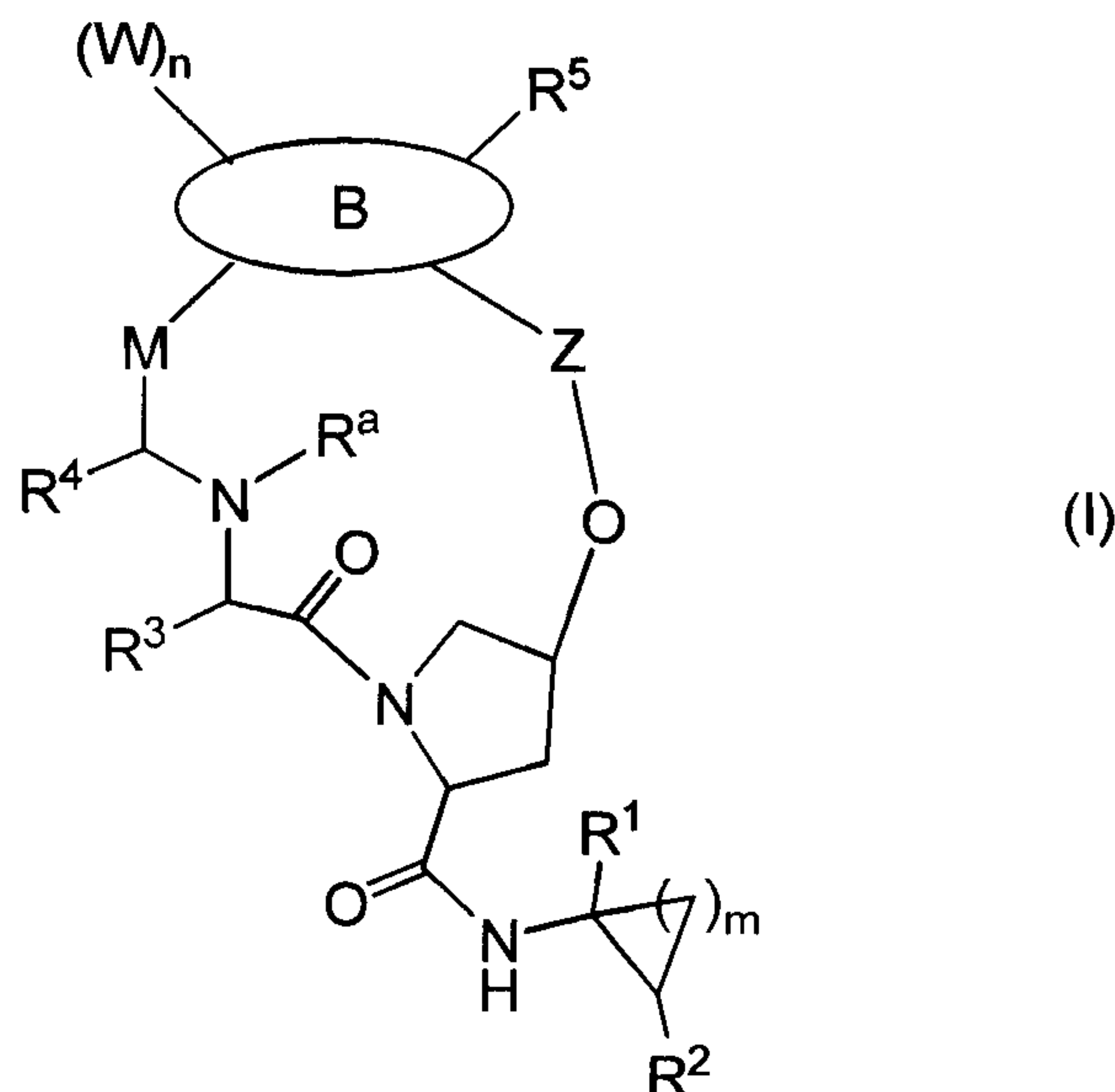
139	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i>)-7-cyclohexyl-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2 <i>H</i> -16,18-etheno-2,5-methanopyrido[3,4- <i>r</i>][1,5,8]oxadiazacyclononadecine-4-carboxamide		812	18
140	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i> ,15 <i>E</i>)-7-cyclohexyl-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-24-methoxy-6-oxo-21-phenyl-3,4,7,8,9,10,11,12,13,14-decahydro-2 <i>H</i> ,6 <i>H</i> -17,19-etheno-2,5-methanopyrido[3,4- <i>s</i>][1,5,8]oxadiazacycloicosine-4-carboxamide		824	18
141	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i>)-7-cyclohexyl-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-24-methoxy-6-oxo-21-phenyl-3,4,7,8,9,10,11,12,13,14,15,16-dodecahydro-2 <i>H</i> ,6 <i>H</i> -17,19-etheno-2,5-methanopyrido[3,4- <i>s</i>][1,5,8]oxadiazacycloicosine-4-carboxamide		826	18
142	(9 <i>R</i> ,11 <i>S</i> ,14 <i>S</i>)-14-tert-butyl-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1 ^{2,6} .1 ^{9,12}]octacos-1(26),2(28),3,5,22,24-hexaene-11-carboxamide		705	16
143	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i> ,14 <i>Z</i>)-7-cyclohexyl-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6-oxo-3,4,6,7,8,9,10,11,12,13-decahydro-2 <i>H</i> -16,18-(ethanediylidene)-2,5-methanopyrido[3,2- <i>r</i>][1,5,8]oxadiazacyclononadecine-4-carboxamide		733	19
144	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i> ,14 <i>E</i>)-7-cyclohexyl-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6-oxo-3,4,6,7,8,9,10,11,12,13-decahydro-2 <i>H</i> -16,18-(ethanediylidene)-2,5-methanopyrido[3,2- <i>r</i>][1,5,8]oxadiazacyclo		733	19

	nonadecine-4-carboxamide			
145	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i>)-7-cyclohexyl-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6-oxo-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2 <i>H</i> -16,18-(ethanediylidene)-2,5-methanopyrido[3,2- <i>r</i>][1,5,8]oxadiazacyclononadecine-4-carboxamide		735	19
146	(9 <i>R</i> ,11 <i>S</i> ,14 <i>S</i> ,20 <i>E</i>)-14-cyclohexyl-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1 ^{2,6} .1 ^{9,12}]octacosan-1(26),2(28),3,5,20,22,24-heptaene-11-carboxamide		729	17
147	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i> ,14 <i>E</i>)-7-cyclohexyl-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13-decahydro-2 <i>H</i> -16,18-etheno-2,5-methanopyrido[3,4- <i>r</i>][1,5,8]oxadiazacyclononadecine-4-carboxamide		838	18
148	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i>)-7-cyclohexyl-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2 <i>H</i> -16,18-etheno-2,5-methanopyrido[3,4- <i>r</i>][1,5,8]oxadiazacyclononadecine-4-carboxamide		840	18
149	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i> ,14 <i>Z</i>)-7-cyclohexyl-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13-decahydro-2 <i>H</i> -16,18-etheno-2,5-methanopyrido[3,4- <i>r</i>][1,5,8]oxadiazacyclononadecine-4-carboxamide		838	18

150	(2 <i>R</i> ,4 <i>S</i> ,7 <i>S</i> ,14 <i>E</i>)-7-cyclohexyl-N-((1 <i>R</i> ,2 <i>S</i>)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6-oxo-3,4,6,7,8,9,10,11,12,13-decahydro-2 <i>H</i> -16,18-(ethanediylidene)-2,5-methanopyrido[3,2- <i>r</i>][1,5,8]oxadiazacyclononadecine-4-carboxamide		761	19
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Claims

1. A compound of formula (I):



- 5 or a pharmaceutically acceptable salt thereof,
wherein:

m is 1, 2, 3 or 4;

n is 0, 1 or 2;

$$R^1 \text{ is } CO_2R^6, CONR^6SO_2R^6 \text{ or } CONR^6SO_2N(R^6)_2;$$

- 10 R^2 is H, C₁₋₆alkyl, C₂₋₆alkenyl or C₃₋₈cycloalkyl, wherein said alkyl, alkenyl or cycloalkyl is optionally substituted with 1 to 3 halo;

R^3 is C_{1-6} alkyl, $(CH_2)_{0-3}C_{3-8}$ cycloalkyl, $(CH_2)_{0-3}$ aryl or $(CH_2)_{0-3}$ Het, optionally substituted by halo, OR^6 , SR^6 , $N(R^6)_2$, C_{1-6} alkyl, NO_2 , CN , CF_3 , $NR^6SO_2R^6$, $SO_2N(R^6)_2$, $NHCO_2R^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^6 , $C(O)R^6$ or $CON(R^6)_2$; wherein Het as a group or part of a group means a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1 to 4 heteroatoms selected from N, O and S;

R⁴ is hydrogen, halo, hydroxy, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, (CH₂)₀₋₃C₃₋₈cycloalkyl, (CH₂)₀₋₃aryl or C₁₋₆alkoxy, optionally substituted by halo, OR⁶, SR⁶, N(R⁶)₂, C₁₋₆alkyl, NO₂, CN, CF₃, NR⁶SO₂R⁶, SO₂N(R⁶)₂, NHCO₂R⁶, NHCOR⁶, NHCONHR⁶, CO₂R⁶, C(O)R⁶ or CON(R⁶)₂;

- 20 R⁵ is hydrogen, halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, CN, NO₂, C₃₋₈cycloalkyl, N(R⁶)₂, aryl or heteroaryl, optionally substituted by 1 to 8 halo, C₁₋₄alkyl or N(R⁶)₂;

each R⁶ is independently hydrogen, C₁₋₆alkyl or C₃₋₈cycloalkyl;

R^a is hydrogen or C₁₋₄alkyl;

or R^a and R³ are joined to form a 5- to 7-membered heterocycle containing 1, 2 or 3 N

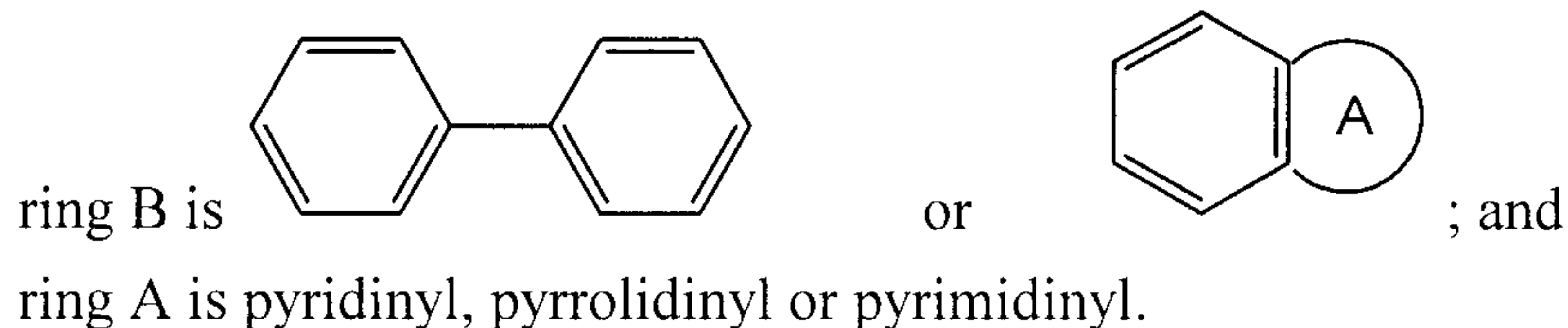
- 25 atoms, which heterocycle is optionally substituted by C₁₋₄alkyl;

each W is independently halo, OR⁶, C₁₋₆alkyl, CN, NO₂, CF₃, OCF₃, OCHF₂, CO₂R⁶, CON(R⁶)₂, COR⁶, NR⁶C(O)R⁶, aryl or heteroaryl;

Z is a bond, -CH₂- or C=O;

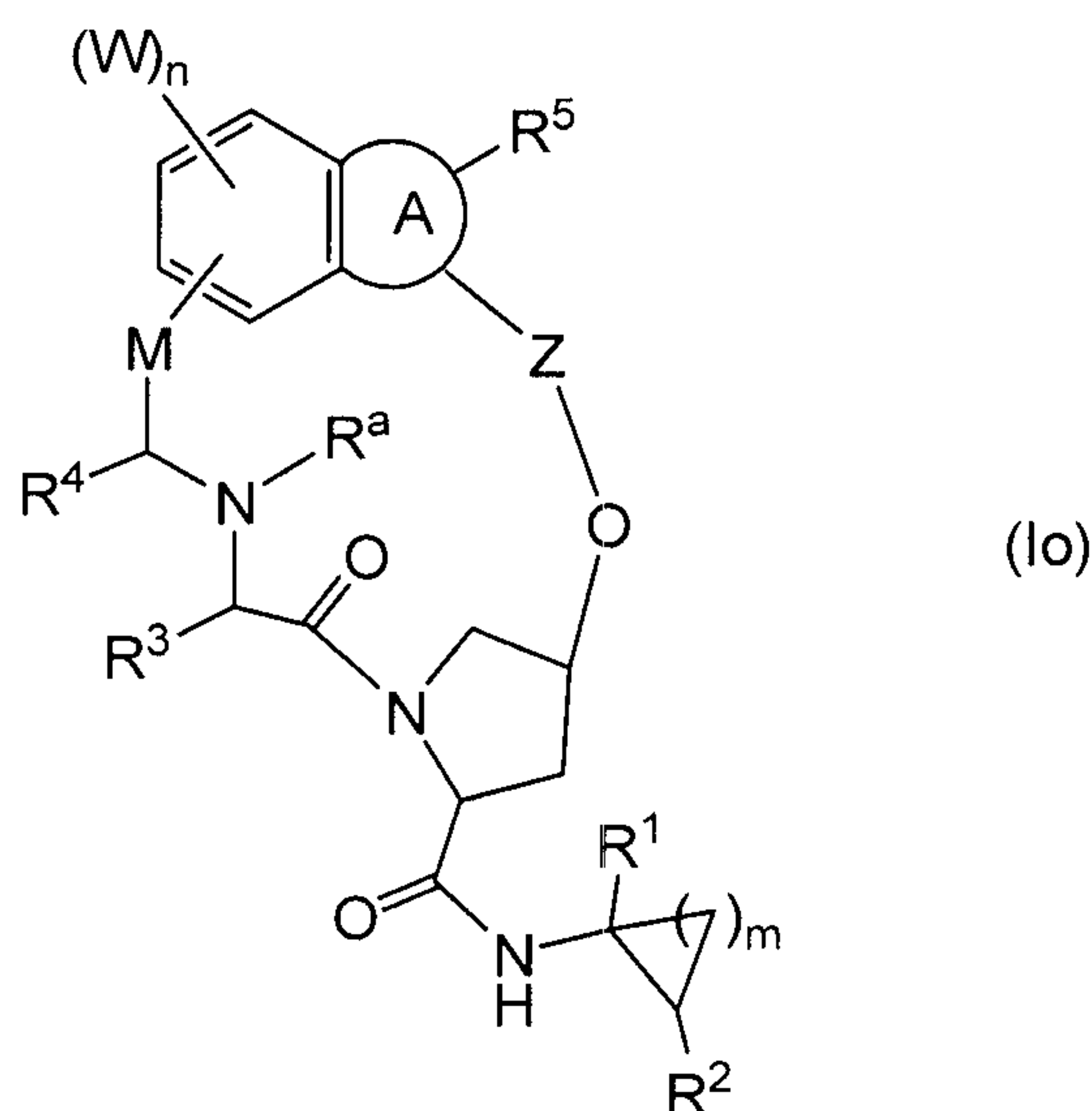
- 74 -

M is C₂₋₁₂alkylene or C₂₋₁₂alkenylene, optionally substituted by halo, C₁₋₆alkyl, (CH₂)₀₋₃C₃₋₈cycloalkyl or (CH₂)₀₋₃aryl, and optionally containing O, NR⁶, S, SO or SO₂; and



5

2. A compound as claimed in Claim 1 of formula (Io):



or a pharmaceutically acceptable salt thereof,
wherein:

10 m is 1, 2, 3 or 4;

n is 0, 1 or 2;

R¹ is CO₂R⁶, CONR⁶SO₂R⁶ or CONR⁶SO₂N(R⁶)₂;

R² is H, C₁₋₆alkyl, C₂₋₆alkenyl or C₃₋₈cycloalkyl, wherein said alkyl, alkenyl or cycloalkyl is optionally substituted with 1 to 3 halo;

15 R³ is C₁₋₆alkyl, (CH₂)₀₋₃C₃₋₈cycloalkyl, (CH₂)₀₋₃aryl or (CH₂)₀₋₃Het, optionally substituted by halo, OR⁶, SR⁶, N(R⁶)₂, C₁₋₆alkyl, NO₂, CN, CF₃, NR⁶SO₂R⁶, SO₂N(R⁶)₂, NHCO₂R⁶, NHCOR⁶, NHCONHR⁶, CO₂R⁶, C(O)R⁶ or CON(R⁶)₂; wherein Het as a group or part of a group means a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1 to 4 heteroatoms selected from N, O and S;

20 R⁴ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, (CH₂)₀₋₃C₃₋₈cycloalkyl, (CH₂)₀₋₃aryl or C₁₋₆alkoxy, optionally substituted by halo, OR⁶, SR⁶, N(R⁶)₂, C₁₋₆alkyl, NO₂, CN, CF₃, NR⁶SO₂R⁶, SO₂N(R⁶)₂, NHCO₂R⁶, NHCOR⁶, NHCONHR⁶, CO₂R⁶, C(O)R⁶ or CON(R⁶)₂;

R⁵ is hydrogen, halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, CN, NO₂, C₃₋₈cycloalkyl, N(R⁶)₂, aryl or heteroaryl, optionally substituted by 1 to 8 halo, C₁₋₄alkyl or N(R⁶)₂;

25 each R⁶ is independently hydrogen, C₁₋₆alkyl or C₃₋₈cycloalkyl;

R^a is hydrogen or C₁₋₄alkyl;

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or R^a and R³ are joined to form a 5- to 7-membered heterocycle containing 1, 2 or 3 N atoms, which heterocycle is optionally substituted by C₁₋₄alkyl;

each W is independently halo, OR⁶, C₁₋₆alkyl, CN, NO₂, CF₃, OCF₃, OCHF₂, CO₂R⁶, CON(R⁶)₂, COR⁶, NR⁶C(O)R⁶, aryl or heteroaryl;

5 Z is a bond or C=O;

M is C₂₋₁₂alkylene or C₂₋₁₂alkenylene, optionally substituted by halo, C₁₋₆alkyl, (CH₂)₀₋₃C₃₋₈cycloalkyl or (CH₂)₀₋₃aryl, and optionally containing O, NR⁶, S, SO or SO₂; and ring A is pyridinyl, pyrrolidinyl or pyrimidinyl.

10 3. A compound as claimed in Claim 1 or Claim 2 wherein m is 1 or 2.

4. A compound as claimed in any one of Claims 1 to 3 wherein n is 0 or 1.

5. A compound as claimed in any one of Claims 1 to 4 wherein R¹ is CO₂R⁶, CONR⁶SO²R⁶ or CONR⁶SO₂N(R⁶)₂ where R⁶ is as defined in Claim 1.

6. A compound as claimed in any one of Claims 1 to 5 wherein R² is C₁₋₆alkyl or C₂₋₆alkenyl.

7. A compound as claimed in any one of Claims 1 to 6 wherein R³ is C₁₋₆alkyl, or (CH₂)₀₋₃C₃₋₈cycloalkyl, optionally substituted by halo, OR⁶ or C₁₋₆alkyl, where R⁶ is as defined in Claim 1.

8. A compound as claimed in any one of Claims 1 to 7 wherein R^a is hydrogen or C₁₋₂alkyl.

9. A compound as claimed in any one of Claims 1 to 6 wherein R^a and R³ are joined to form a 5- or 6- membered heterocycle containing 1 or 2 N atoms, which heterocycle is optionally substituted by C₁₋₄alkyl.

10. A compound as claimed in any one of Claims 1 to 9 wherein R⁴ is hydrogen, C₁₋₆alkyl, (CH₂)₀₋₃C₃₋₈cycloalkyl, (CH₂)₀₋₃phenyl or C₁₋₆alkoxy, optionally substituted by halo, OR⁶, SR⁶, N(R⁶)₂, C₁₋₆alkyl, NO₂ or CN, where R⁶ is as defined in Claim 1.

11. A compound as claimed in any one of Claims 1 to 10 wherein R⁵ is hydrogen, halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, C₃₋₈cycloalkyl, aryl or heteroaryl, optionally substituted by N(R⁶)₂, where R⁶ is as defined in Claim 1.

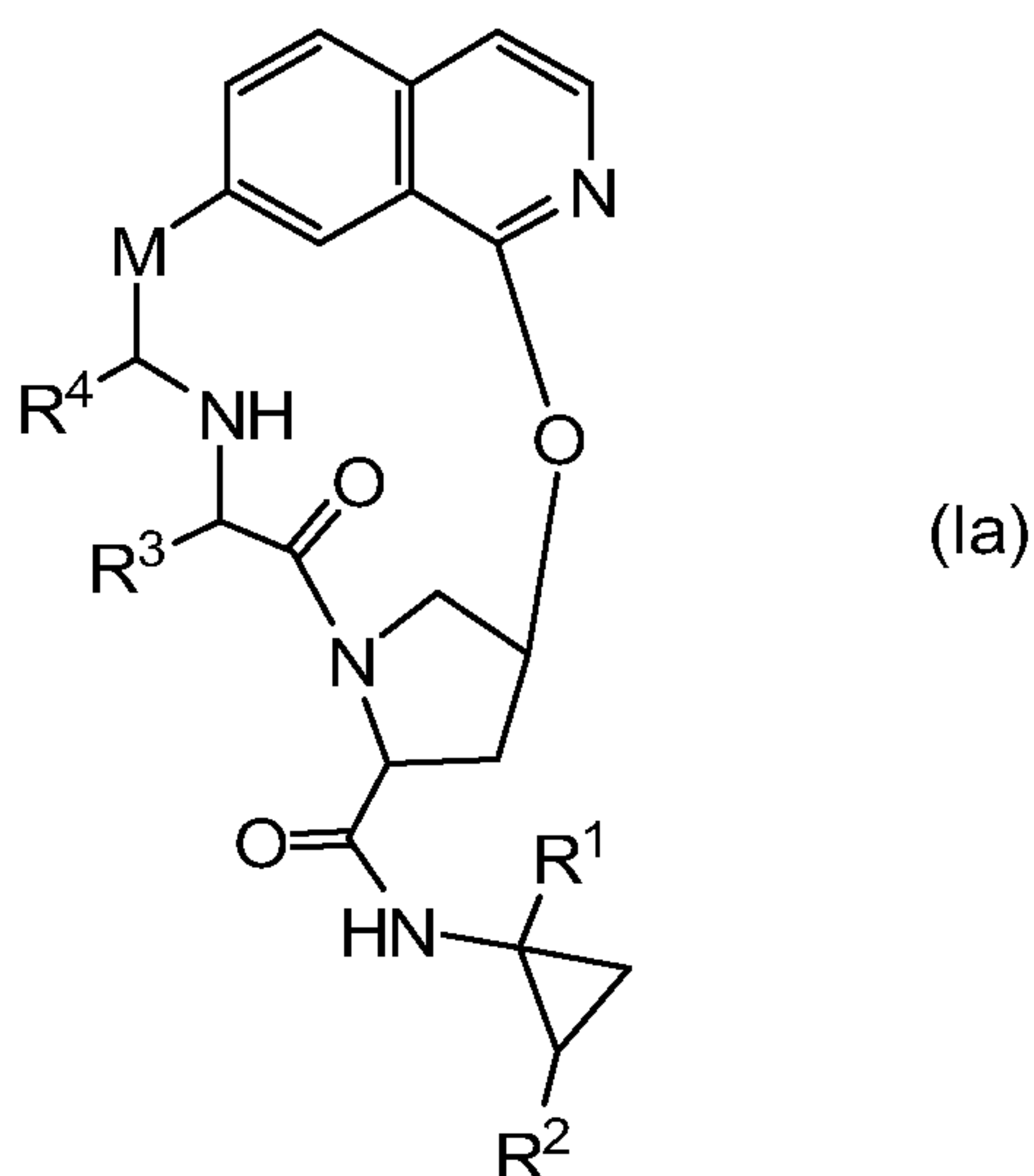
12. A compound as claimed in any one of Claims 1 to 11 wherein each W is independently halo, OR⁶, C₁₋₆alkyl, CF₃, CO₂R⁶, CON(R⁶)₂, COR⁶ or NR⁶C(O)R⁶, where R⁶ is as defined in Claim 1.

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13. A compound as claimed in any one of Claims 1 to 12 wherein M is C₂₋₈alkylene or C₂₋₈alkenylene, optionally substituted by halo, C₁₋₄alkyl or C₃₋₆cycloalkyl, and optionally containing O.

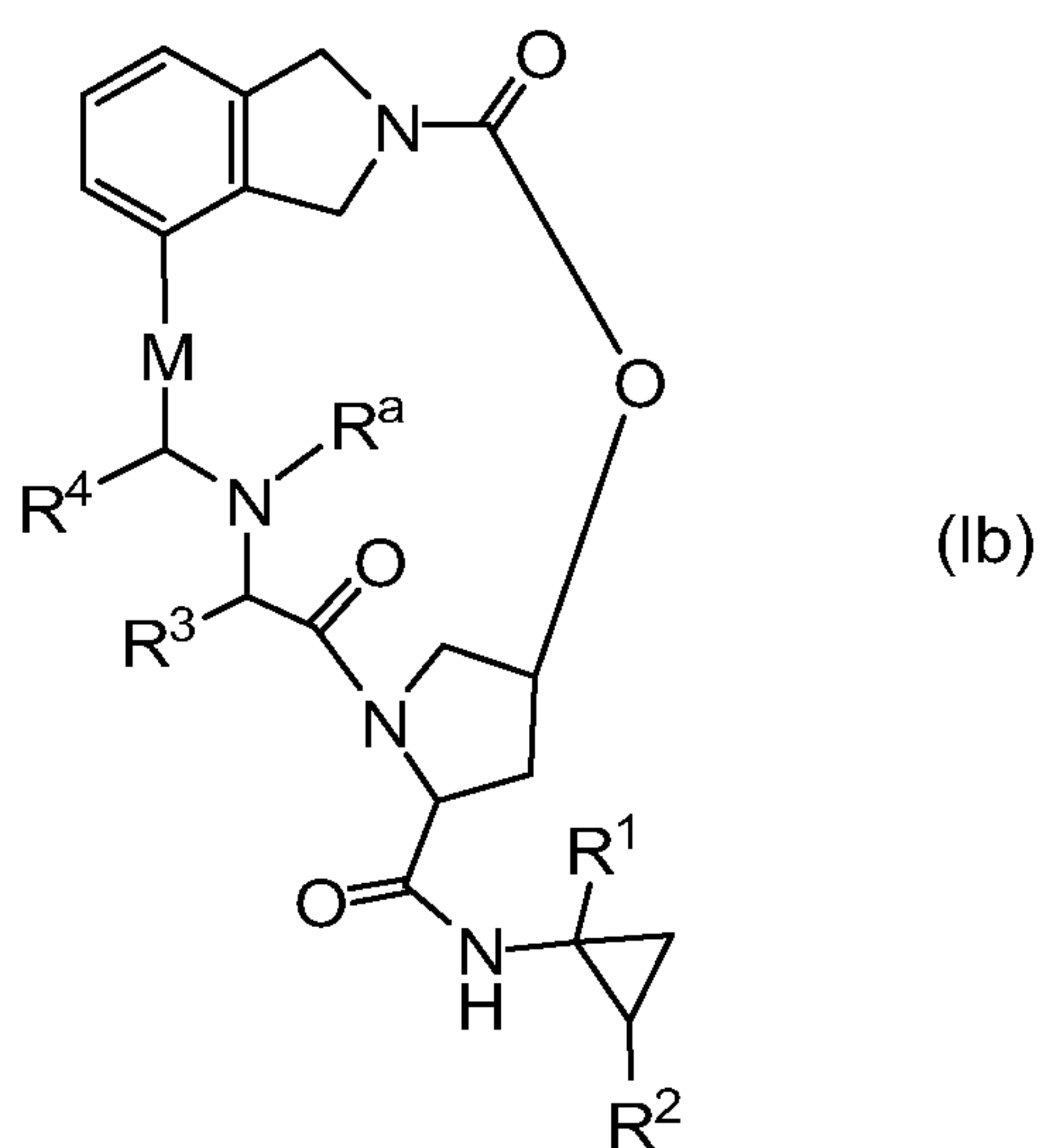
14. A compound as claimed in any one of Claims 2 to 13 wherein ring A is pyridinyl or pyrrolidinyl.

15. A compound as claimed in Claim 1 of formula (Ia):



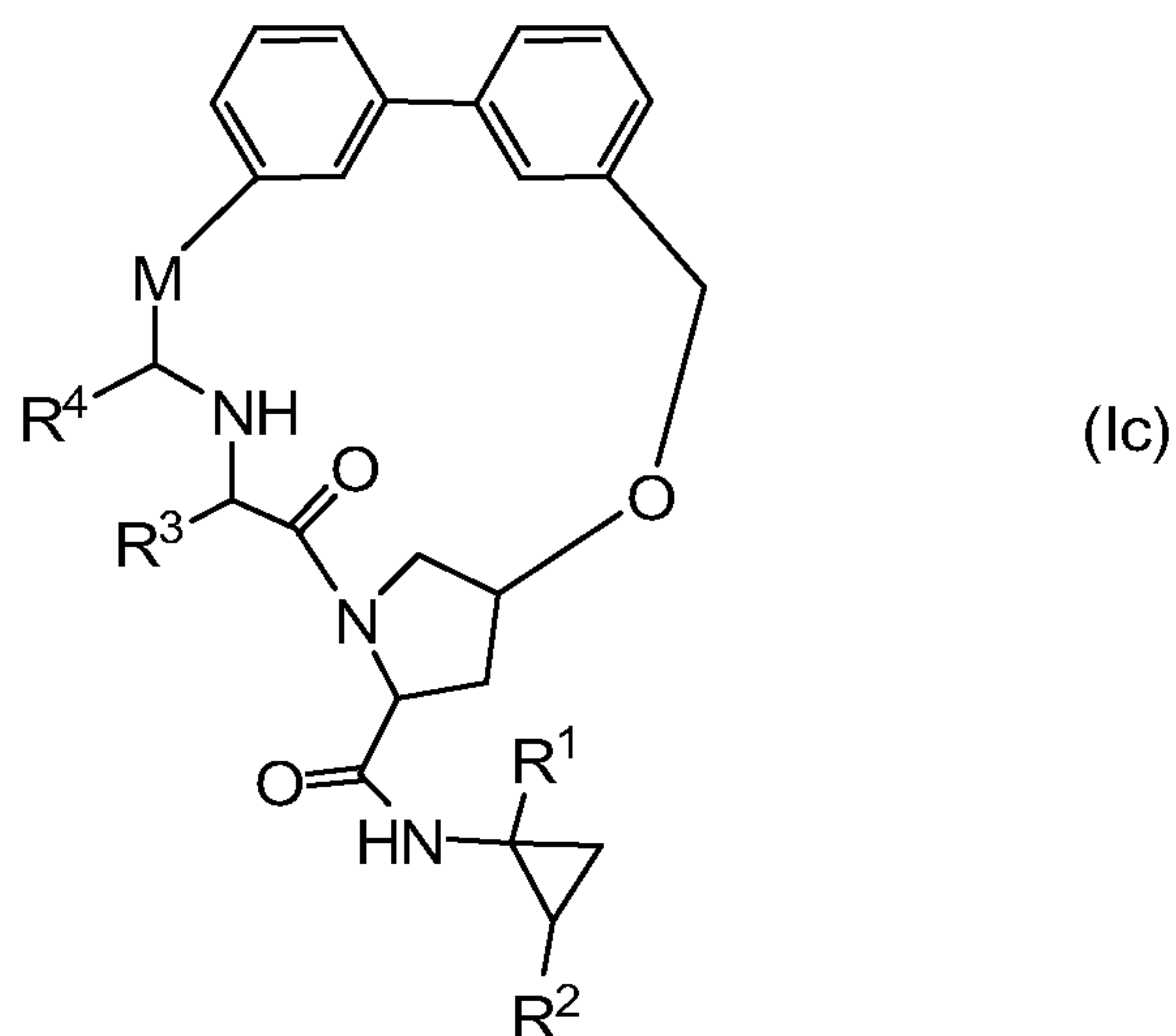
10 or a pharmaceutically acceptable salt thereof,
wherein R¹, R², R³, R⁴ and M are as defined in Claim 1.

16. A compound as claimed in Claim 1 of formula (Ib):



15 or a pharmaceutically acceptable salt thereof,
wherein R¹, R², R³, R⁴ and M are as defined in Claim 1.

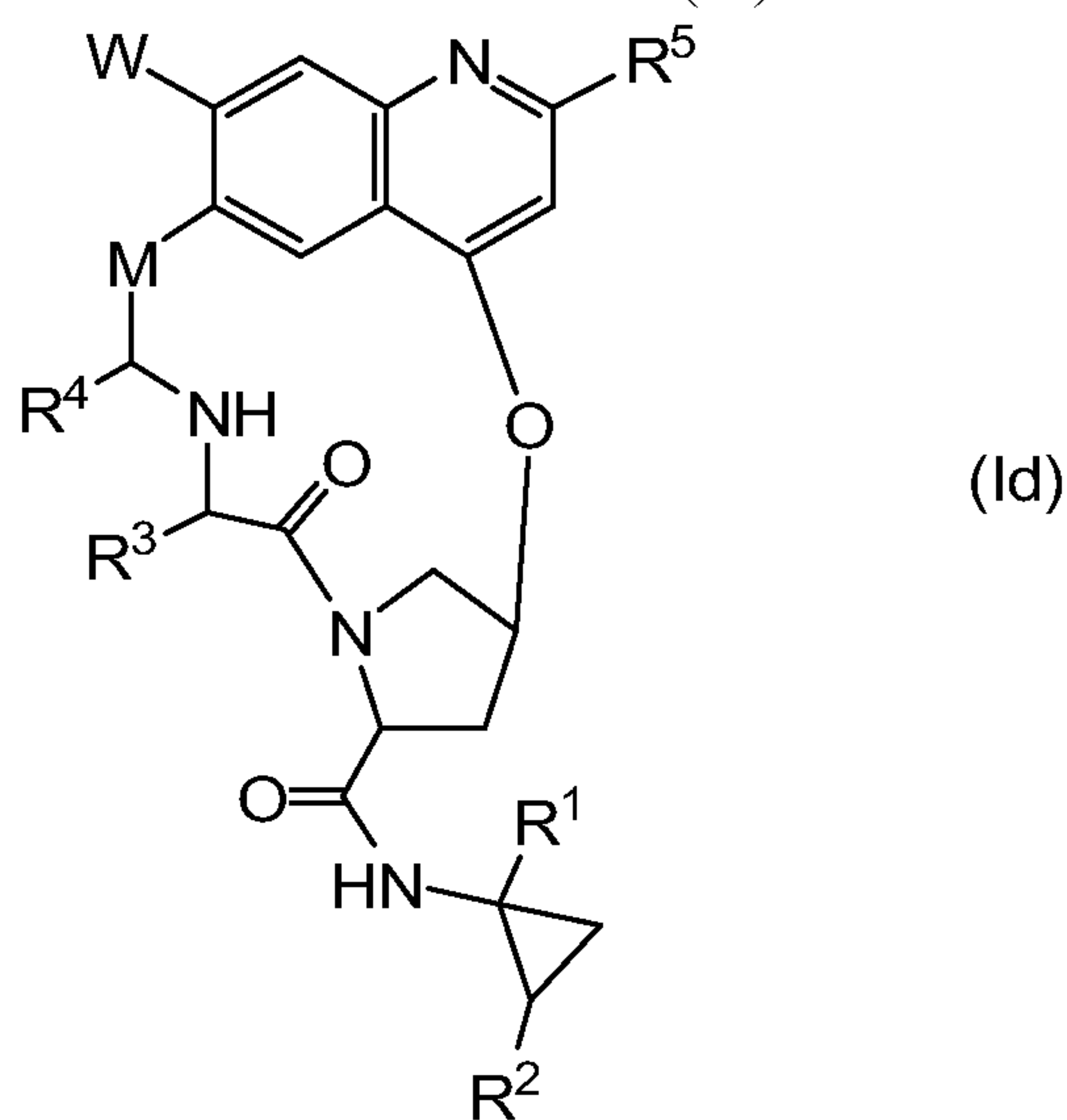
17. A compound as claimed in Claim 1 of formula (Ic):



or a pharmaceutically acceptable salt thereof,
wherein R^1 , R^2 , R^3 , R^4 and M are defined in Claim 1.

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18. A compound as claimed in Claim 1 of formula (Id):



or a pharmaceutically acceptable salt thereof,
wherein R^1 , R^2 , R^3 , R^4 , R^5 , M and W are defined in Claim 1.

10

19. A compound as claimed in Claim 1 selected from:

(5*R*,7*S*,10*S*,12*R* or *S*)-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-isopropyl-3,9-dioxo-12-(trifluoromethyl)-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,
(2*R*,4*S*,7*S*,9*R* or *S*)-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-isopropyl-6-oxo-9-(trifluoromethyl)-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide,

- (5*R*,7*S*,10*R*,17*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,9-dioxo-10-(trifluoromethyl)-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriaza cycl icosine-7-carboxamide,
- (5*R*,7*S*,10*S*,12*R* or *S*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-isopropyl-3,9-dioxo-12-(trifluoromethyl)-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,
- (5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,9-dioxo-12-(trifluoromethyl)-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,
- (5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclohexyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3,9-dioxo-12-(trifluoromethyl)-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide
- (5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,9-dioxo-12-(trifluoromethyl)-1,6,7,9,10,11,12,13,14,15,16,17-dodecahydro-5*H*-2,21:5,8-dimethano-4,2,8,11-benzoxatriazacyclononadecine-7-carboxamide,
- (2*R*,4*S*,7*R*,14*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6-oxo-7-(trifluoromethyl)-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide,
- (2*R*,4*S*,7*R*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6-oxo-7-(trifluoromethyl)-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide,
- (5*R*,7*S*,10*S*,12*R* or *S*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-isopropyl-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,
- (5*R*,7*S*,10*S*,12*R* or *S*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-isopropyl-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,
- (5*R*,7*S*,10*S*,17*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,
- (5*R*,7*S*,10*S*,17*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-13,13-difluoro-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacyclo icosine-7-carboxamide,
- (5*R*,7*S*,10*S*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-13,13-difluoro-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide,
- (5*R*,7*S*,10*S*,12*R* or *S*,17*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-isopropyl-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-

1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,
 (5*R*,7*S*,10*S*,12*R* or *S*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-isopropyl-3,9-dioxo-12-(pentafluoroethyl)-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide,
 (5*R*,7*S*,10*S*,12*R* or *S*)-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-10-isopropyl-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,
 (5*R*,7*S*,10*S*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,
 (5*R*,7*S*,10*S*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,
 (5*R*,7*S*,10*S*,17*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-isopropyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,
 (5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide,
 (2*R*,4*S*,7*S*,9*R* or *S*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-isopropyl-9-methyl-6-oxo-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide,
 (2*R*,4*S*,7*S*,9*S* or *R*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-isopropyl-9-methyl-6-oxo-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide,
 (5*R*,7*S*,10*S*,12*R* or *S*,7*E*)-10-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,
 (5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxa triazacycloicosine-7-carboxamide,
 (5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-11,12-dimethyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,
 (5*R*,7*S*,10*S*,12*R* or *S*,17*E*)-10-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,
 (5*R*,7*S*,10*S*,12*R* or *S*,17*E*)-10-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]

carbonyl}-2-vinylcyclopropyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,

(5*R*,7*S*,10*S*,12*R* or *S*)-10-cyclopentyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriaza cycloicosine-7-carboxamide,

(1*R*,2*S*)-1-({[(5*R*,7*S*,10*S*,12*R* or *S*,17*E*)-10-cyclohexyl-12-methyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16-decahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosin-7-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid,

(5*R*,7*S*,10*S*,12*R* or *S*)-N-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-12-methyl-10-[(1*S*)-1-methylpropyl]-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,

(2*R*,4*S*,7*S*,14*E*)-7-cyclopentyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6-oxo-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide,

(2*R*,4*S*,7*S*)-7-cyclopentyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6-oxo-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide,

(3*S*,3*aR*,6*S*,8*R*)-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3-methyl-4,10-dioxo-2,3,3*a*,4,7,8,12,17,18,19,20,21,22,23-tetradecahydro-1*H*,6*H*-5,8:11,13-dimethanopyrrolo[2,1-*j*][4,2,8,11]benzoxatriazacycloicosine-6-carboxamide,

(5*R*,7*S*,10*S*)-10-cyclopentyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-11-methyl-3,9-dioxo-6,7,10,11,12,13,15,16,17,18-decahydro-1*H*,5*H*,9*H*-2,22:5,8-dimethano-4,14,2,8,11-benzodioxatriazacycloicosine-7-carboxamide,

(5*R*,7*S*,10*S*)-10-cyclopentyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-13,13-dimethyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxa triazacycloicosine-7-carboxamide,

(5*R*,7*S*,10*S*)-10-cyclopentyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-11,13,13-trimethyl-3,9-dioxo-6,7,9,10,11,12,13,14,15,16,17,18-dodecahydro-1*H*,5*H*-2,22:5,8-dimethano-4,2,8,11-benzoxatriazacycloicosine-7-carboxamide,

(2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,4-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide,

(2*R*,4*S*,7*S*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,4-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide,

(2*R*,4*S*,7*S*,15*E*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-24-methoxy-6-oxo-21-phenyl-3,4,7,8,9,10,11,12,13,14-decahydro-2*H*,6*H*-17,19-etheno-2,5-methanopyrido[3,4-*s*][1,5,8]oxadiazacycloicosine-4-carboxamide,

(2*R*,4*S*,7*S*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-24-methoxy-6-oxo-21-phenyl-3,4,7,8,9,10,11,12,13,14,15,16-dodecahydro-2*H*,6*H*-17,19-etheno-2,5-methanopyrido[3,4-*s*][1,5,8]oxadiazacycloicosine-4-carboxamide,

(9*R*,11*S*,14*S*)-14-tert-butyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-1(26),2(28),3,5,22,24-hexaene-11-carboxamide,

(2*R*,4*S*,7*S*,14*Z*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6-oxo-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide,

(2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6-oxo-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide,

(2*R*,4*S*,7*S*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6-oxo-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide, (9*R*,11*S*,14*S*,20*E*)-14-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-13-oxo-8-oxa-12,15-diazatetracyclo[20.3.1.1^{2,6}.1^{9,12}]octacos-1(26),2(28),3,5,20,22,24-heptaene-11-carboxamide,

(2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,4-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide,

(2*R*,4*S*,7*S*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,4-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide,

(2*R*,4*S*,7*S*,14*Z*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6-oxo-20-phenyl-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,4-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide, and

(2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-N-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6-oxo-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-*r*][1,5,8]oxadiazacyclononadecine-4-carboxamide, or a pharmaceutically acceptable salt thereof.

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20. A compound as claimed in any one of Claims 1 to 19 or a pharmaceutically acceptable salt thereof for use in treatment or prevention of infection by hepatitis C virus.

21. A compound as claimed in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treatment or prevention of infection by hepatitis C virus in a human or animal.

22. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

23. The pharmaceutical composition as claimed in Claim 22, further comprising one or more other agents for the treatment of viral infections.

24. The pharmaceutical composition as claimed in Claim 23, wherein said one or more other agents is an antiviral agent, or an immunomodulatory agent.

25. The pharmaceutical composition as claimed in Claim 24, wherein said immunomodulatory agent is α -, β - or γ -interferon.

26. A pharmaceutical composition for use in inhibiting hepatitis C virus protease and/or treating or preventing an illness due to hepatitis C virus comprising a compound as claimed in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.