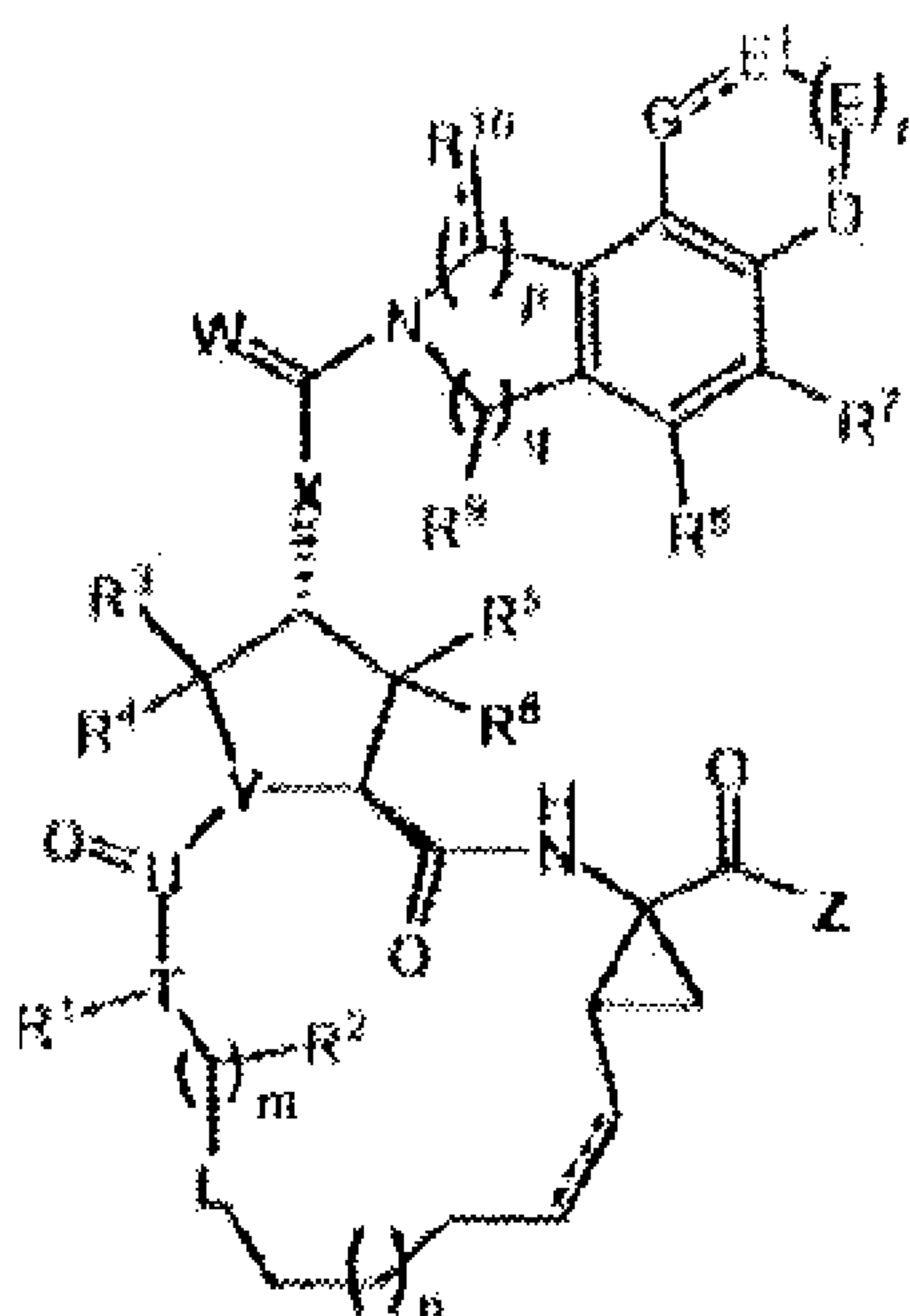




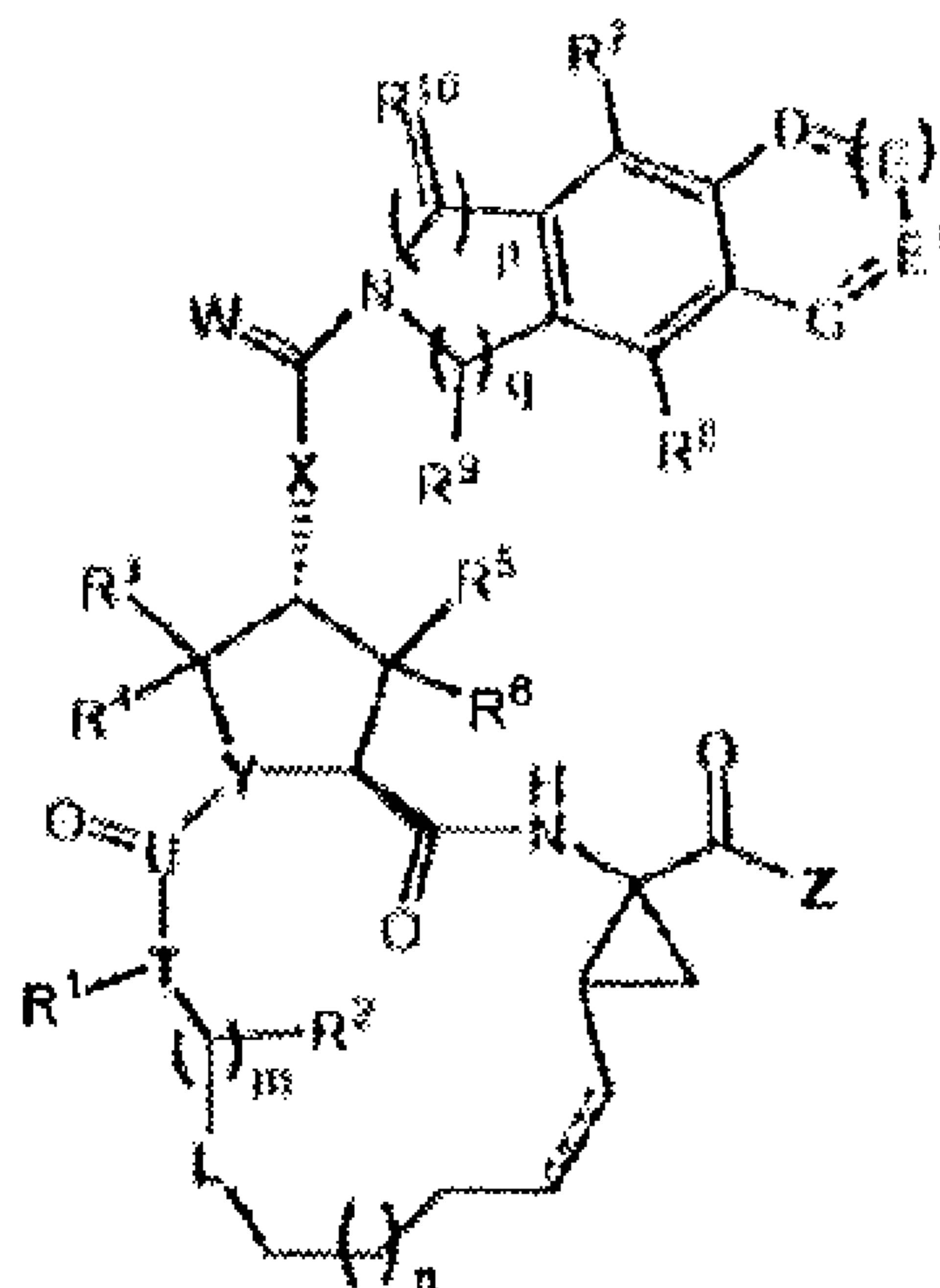
(86) **Date de dépôt PCT/PCT Filing Date:** 2011/01/27
(87) **Date publication PCT/PCT Publication Date:** 2011/08/04
(45) **Date de délivrance/Issue Date:** 2018/04/24
(85) **Entrée phase nationale/National Entry:** 2012/07/26
(86) **N° demande PCT/PCT Application No.:** CN 2011/070702
(87) **N° publication PCT/PCT Publication No.:** 2011/091757
(30) **Priorité/Priority:** 2010/01/27 (CN201010101403.7)

(51) **Cl.Int./Int.Cl.** **C07D 491/056** (2006.01),
A61K 31/403 (2006.01), **A61P 1/16** (2006.01),
A61P 31/14 (2006.01)
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(54) **Titre : COMPOSES POLYHETEROCYCLIQUES HAUTEMENT PUISSANTS EN TANT QU'INHIBITEURS DU VHC**
(54) **Title: POLYHETEROCYCLIC COMPOUNDS HIGHLY POTENT AS HCV INHIBITORS**



Ia



Ib

(57) **Abrégé/Abstract:**

The present invention discloses novel polyheterocyclic based compounds having general formula Ia-Ib and IIa-IIb, and preparation methods and uses thereof. These compounds are highly effective for inhibition of hepatitis C virus (HCV). The present invention is also related to treatment of HCV infection by the polyheterocyclic based HCV inhibitory compounds and compositions thereof, and to therapeutic methods thereof.

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

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
4 August 2011 (04.08.2011)

PCT

(10) International Publication Number
WO 2011/091757 A1

(51) International Patent Classification:

C07D 491/056 (2006.01) A61P 1/16 (2006.01)
A61K 31/403 (2006.01) A61P 31/14 (2006.01)

(21) International Application Number:

PCT/CN2011/070702

(22) International Filing Date:

27 January 2011 (27.01.2011)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

201010101403.7 27 January 2010 (27.01.2010) CN

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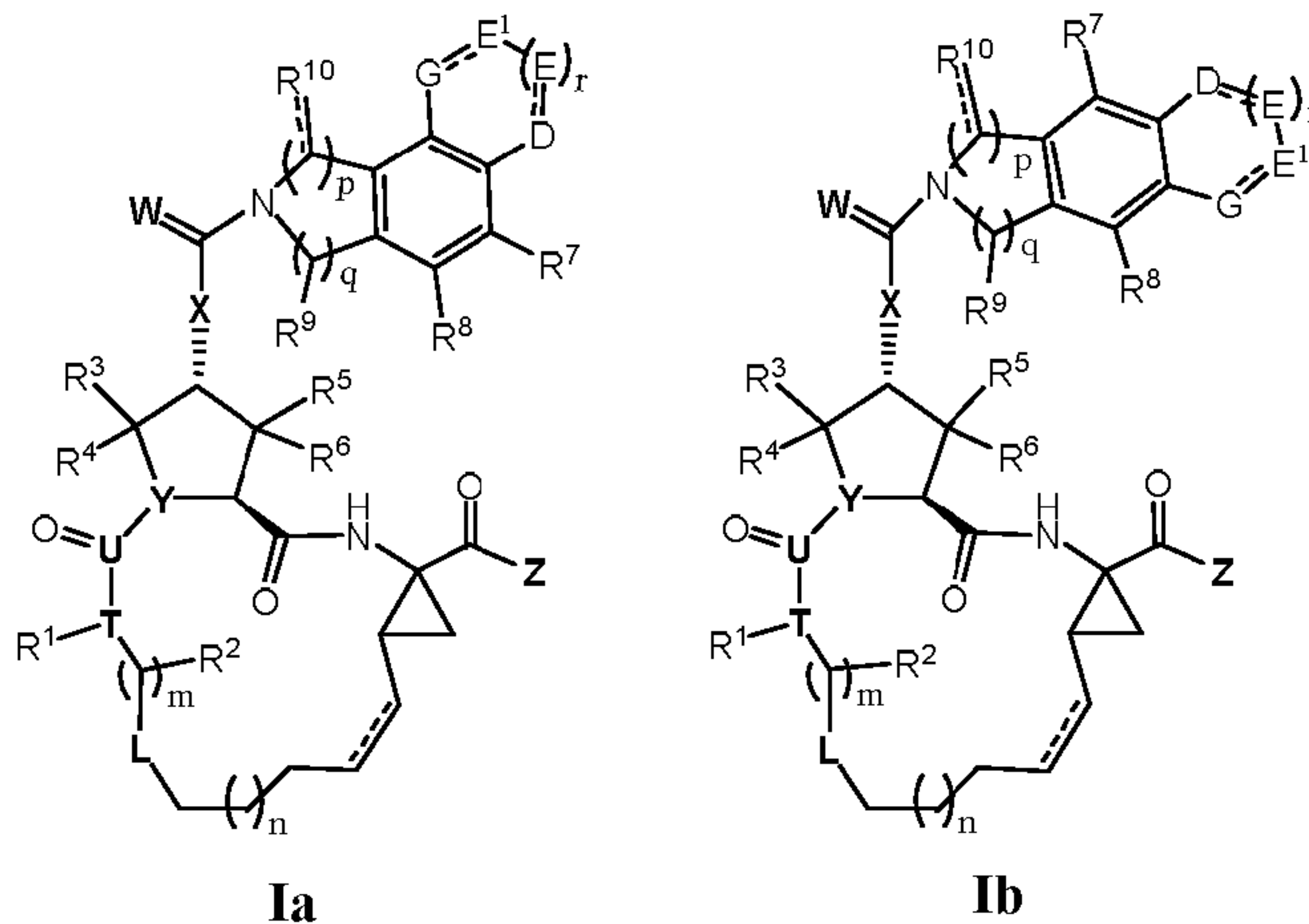
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,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

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

Published:

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

(54) Title: POLYHETEROCYCLIC COMPOUNDS HIGHLY POTENT AS HCV INHIBITORS



(57) Abstract: The present invention discloses novel polyheterocyclic based compounds having general formula Ia-Ib and IIa-IIb, and preparation methods and uses thereof. These compounds are highly effective for inhibition of hepatitis C virus (HCV). The present invention is also related to treatment of HCV infection by the polyheterocyclic based HCV inhibitory compounds and compositions thereof, and to therapeutic methods thereof.

POLYHETEROCYCLIC COMPOUNDS HIGHLY POTENT AS HCV INHIBITORS**FIELD OF THE INVENTION**

The present invention relates to novel polyheterocyclic based compounds with both
5 macrocyclic and linear structure, especially with tri-heterocyclic functional groups, which is highly
potent and effective to inhibit the NS3 protease replication of hepatitis C virus (HCV). The present
invention also relates to preparation and the pharmaceutical uses thereof as HCV inhibitors.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) is the major causative agent for most cases of non-A, non-B hepatitis,
10 and it is a single-stranded positive RNA virus in the Flaviviridae family. It includes a nucleocapsid
protein (C), envelope proteins (E1 and E2), and several non-structural proteins (NS1, NS2, NS3,
NS4a, NS5a, and NS5b). The NS3 protein possesses serine protease activity and is considered
essential for viral replication and infectivity, and the essentiality of the NS3 protease was inferred
from the fact that mutations in the yellow fever virus NS3 protease decreased viral infectivity
15 [reference: Chamber et al, *Proc. Natl. Acad. Sci. USA* 87, 8898-8902 (1990)].

So far, HCV infection is one of major human health problems since HCV infection leads to
chronic liver disease such as cirrhosis and hepatocellular carcinoma. Due to the fact that the
number of HCV infected individuals is estimated 2-15 % of the world's population while no any
effective vaccines or therapeutic agents are available to control or cure HCV [reference: WO
20 89/04669; Lavanchy, *J. Viral Hepatitis*, 6, 35-47 (1999); Alter, *J. Hepatology*, 31 (Suppl. 1), 88-91
(1999); and Alberti et al, *J. Hepatology*, 31 (Suppl. 1), 17-24 (1999)].

It has been demonstrated that mutations at the active site of the HCV NS3 protease completely
inhibited the HCV infection in chimpanzee model [reference: Rice et al, *J. Virol.* 74 (4) 2046-51
(2000)]. Furthermore, the HCV NS3 serine protease has been found to facilitate proteolysis at the
25 NS3/NS4a, NS4a/NS4b, NS4b/NS5a, NS5a/NS5b junctions and is thus responsible for generating
four viral proteins during viral replication [reference: US 2003/0207861]. Consequently, the HCV
NS3 serine protease enzyme is an attractive and effective target to develop new inhibitors for HCV
infection. So far, there are different kinds of potential NS3 HCV protease inhibitors reported by
global research institutes and pharmaceuticals, such as WO2010033466, WO2010075127,
30 US20100003214, US20100022578, US20100029715, US20100041889, WO2009134624,

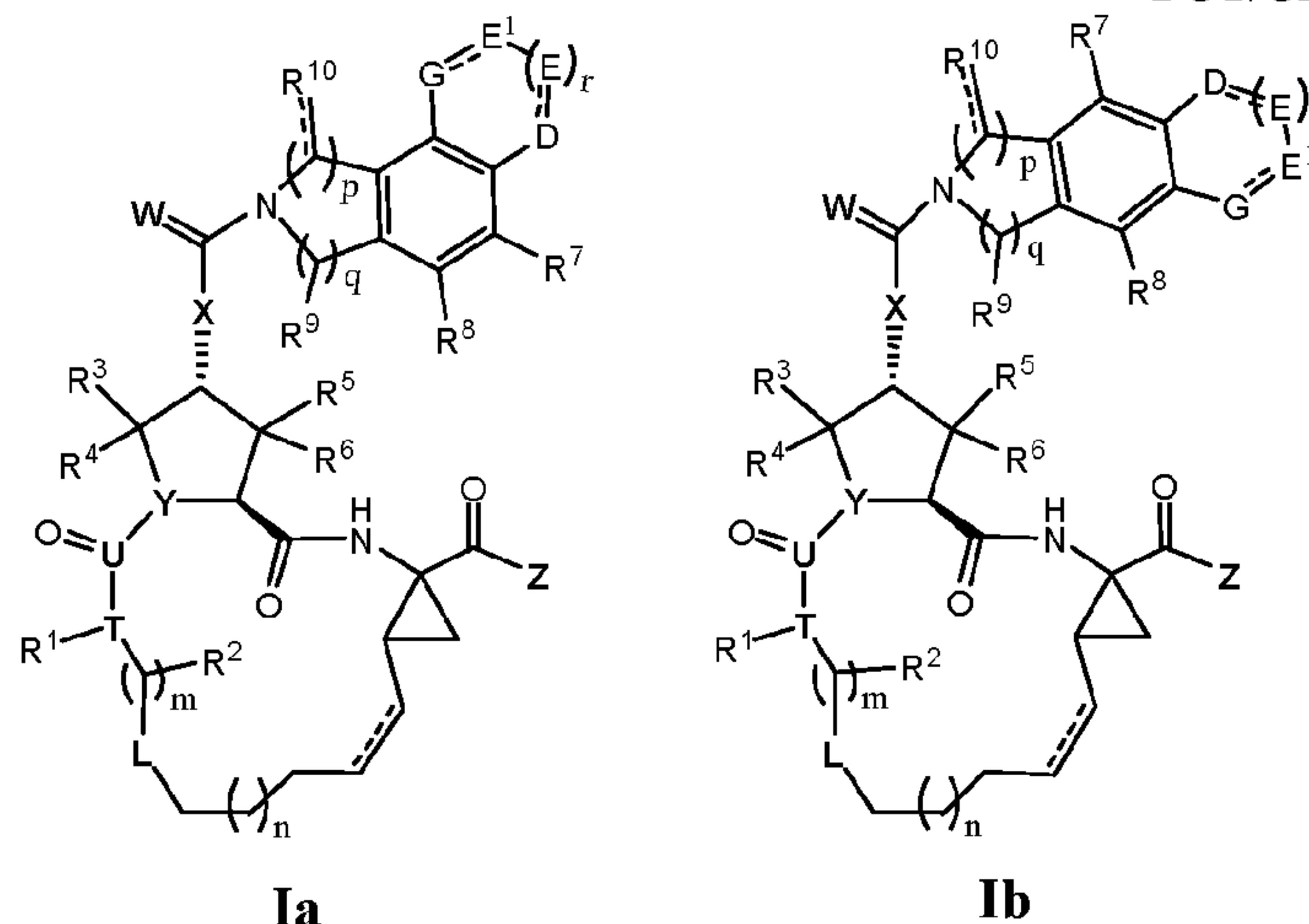
WO2009010804, US20090269305, WO2008057209, WO2008057208, WO2007015787,
 WO2005037214, WO200218369, WO200009558, WO200009543, WO199964442,
 WO199907733, WO199907734, WO199950230, WO199846630, WO199817679, US5,990,276,
 Dunsdon et al, *Biorg. Med. Chem. Lett.* 10, 1571-1579 (2000); Llinas-Brunet et al, *Biorg. Med.*
 5 *Chem. Lett.* 10, 2267-2270 (2000); and S. LaPlante et al., *Biorg. Med. Chem. Lett.* 10, 2271-
 2274 (2000).

Currently, due to lack of immunity or remission associated with HCV infection, hepatitis
 caused by HCV infection is more difficult to treat comparing to other forms of hepatitis. Now,
 the only available anti-HCV therapies are interferon-a, interferon-a/ribavirin combination, and
 10 pegylated interferon-a. However, sustained response rates for interferon-a or interferon-
 a/ribavirin combination were found to be <50% and patients suffer greatly from side effects of
 these therapeutic agents [reference: Walker, *DDT*, 4, 518-529 (1999); Weiland, *FEMS*
Microbial. Rev., 14, 279-288 (1994); and WO 02/18369]. Based on the significant importance
 for controlling HCV infection, the aim of the present invention is to develop more effective and
 15 better-tolerated therapeutic drugs for inhibiting HCV NS3 protease replication.

SUMMARY OF THE DISCLOSURE

The present disclosure relates to two classes of novel polyheterocyclic based compounds
 of the following formulas **Ia-Ib** with macrocyclic structure and **IIa-IIb** with linear structure,
 20 especially with tri-heterocyclic functional groups, which has been evaluated to be highly potent
 and effective for inhibiting the NS3 protease replication of hepatitis C virus (HCV). This
 disclosure further relates to pharmaceutical compositions comprising one or more of new
 developed compounds (in a pure form or a mixture of stereoisomers, solvates, hydrates,
 tautomers, prodrugs, or pharmaceutically acceptable salts thereof), and optionally other agent(s)
 25 developed as therapeutic drugs for HCV treatment.

In the first aspect, the present disclosure provides novel polyheterocyclic based
 compounds represented by the formula **Ia** or **Ib**:



wherein:

$$m = 0, 1 \text{ or } 2;$$
$$n = 0, 1 \text{ or } 2;$$

5 $p = 0, 1$ or 2 ;

 $q = 0, 1 \text{ or } 2;$
$$r = 0, 1, 2 \text{ or } 3;$$

the dashed line “” is single bond or double bond, respectively;

wherein when “ ” is single bond, D, E, E¹ and G are each independently selected from the group consisting of oxygen, sulfur, amino, or -C(Ra)(Rb)- group, respectively; and R¹⁰ is hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C₁-C₂₀ alkyl, C₁-C₂₀ alkoxy, C₁-C₂₀ alkylthio, C₁-C₂₀ alkoxycarbonyl, C₁-C₂₀ aminocarbonyl, C₁-C₂₀ carbonylamino, C₆-C₂₀ aryl, C₆-C₂₀ aryloxy, C₆-C₂₀ aryloxy carbonyl, or C₂-C₂₀ heterocyclic group.

wherein when “ ” is double bond, D, E, E¹ and G each is independently selected from the
15 group consisting of nitrogen N or -C(Rc)- group; and R¹⁰ is oxygen or sulfur.

20 Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C₁-C₂₀ alkyl, C₃-C₂₀ cycloalkyl, C₆-C₂₀ aryl, C₁-C₂₀ alkoxy, C₁-C₂₀ alkylthio, C₁-C₂₀ alkoxycarbonyl, C₆-C₂₀ aryloxy, C₆-C₂₀ aryloxycarbonyl, C₂-C₂₀ heterocyclic alkoxycarbonyl, C₂-C₂₀ heterocyclic aryl, C₁-C₂₀ alkylamino, C₂-C₂₀ heterocyclic amino, C₆-C₂₀ aryl amino, C₁-C₂₀ aminocarbonyl, C₁-C₂₀ amido, C₁-C₂₀ amidocarbonyl, C₁-C₂₀ carbonylamino, C₁-C₂₀ alkylsulfonamido, C₂-C₂₀ heterocyclic sulfonamido, C₆-C₂₀ arylsulfonamido, or C₁-C₂₀ aminosulfonamido group, respectively;

wherein when $r = 0$, E is nothing, and D is directly linked to E^1 ;

L is oxygen, sulfur, -S(O)-, -S(O)₂-, carbonyl, or -C(Rb)(Rc)-, C₁-C₂₀ alkenyl, C₁-C₂₀ alkoxy, C₂-C₂₀ heterocyclyl, C₂-C₂₀ heterocyclic alkoxy, C₁-C₂₀ amino, C₁-C₂₀ aminocarbonyl, C₁-C₂₀ alkoxycarbonyl, C₆-C₂₀ aryl, C₆-C₂₀ aryloxy, or C₆-C₂₀ aryloxycarbonyl group;

T is nitrogen, oxygen or CH;

5 U is carbon, sulfur, -S(O)-, phosphorus or phosphate;

W is oxygen or sulfur;

X is oxygen, sulfur or -NRa-; Ra is defined as in D, E, E¹, and G above;

Y is nitrogen or CH group;

10 Z is hydroxyl, C₁-C₂₀ alkyl, C₃-C₂₀ cycloalkyl, C₁-C₂₀ alkoxy, C₃-C₂₀ cycloalkoxy, C₁-C₂₀ alkylamino, C₃-C₂₀ cycloalkylamino, C₂-C₂₀ heterocyclic amino, C₆-C₂₀ aryl, C₆-C₂₀ arylamino, C₄-C₂₀ heteroaryl amino, C₁-C₂₀ alkyl sulfonamido, C₃-C₂₀ cycloalkylsulfonamido, C₆-C₂₀ arylsulfonamido, C₁-C₂₀ alkoxy sulfonamido, C₃-C₂₀ cycloalkoxy sulfonamido, C₁-C₂₀ alkylamino sulfonamido, C₃-C₂₀ cycloalkylamino sulfonamido, C₆-C₂₀ arylamino sulfonamido, C₁-C₂₀ uramido, C₁-C₂₀ thioureido, C₁-C₂₀ phosphate, or C₁-C₂₀ borate;

15 R¹ and R² are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C₁-C₂ alkyl, C₃-C₂₀ cycloalkyl, C₁-C₂₀ alkoxy, C₃-C₂₀ cycloalkoxy, C₁-C₂₀ alkoxycarbonyl, C₁-C₂₀ alkylamino, C₃-C₂₀ cycloalkylamino, C₂-C₂₀ heterocyclic amino, C₆-C₂₀ arylamino, C₁-C₂₀ alkoxycarbonylamino, C₆-C₂₀ aryloxycarbonylamino, C₁-C₂₀ alkylsulfonamido, C₃-C₂₀ cycloalkylsulfonamido, C₂-C₂₀ heterocyclic sulfonamido, C₆-C₂₀ arylsulfonamido, and C₁-C₂₀ aminosulfonamido group;

R³, R⁴, R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, nitro, C₁-C₂₀ alkyl, C₃-C₂₀ cycloalkyl, C₁-C₂₀ alkoxy, C₁-C₂₀ alkylamino, C₂-C₂₀ heterocyclic amino, C₆-C₂₀ aryl, C₆-C₂₀ arylamino, C₁-C₂₀ alkylsulfonamido, C₂-C₂₀ heterocyclic sulfonamido, and C₆-C₂₀ arylsulfonamido group; and

25 R⁷, R⁸ and R⁹ are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C₁-C₂₀ alkyl, C₁-C₂₀ alkoxy, C₁-C₂₀ alkylthio, C₁-C₂₀ alkoxycarbonyl, C₁-C₂₀ aminocarbonyl, C₁-C₂₀ carbonylamino, C₆-C₂₀ aryl, C₆-C₂₀ aryloxy, C₆-C₂₀ aryloxycarbonyl, and C₂-C₂₀ heterocyclic group.

In one preferred embodiment of the compounds of formula **Ia-Ib**:
 $m = 0, 1$ or 2 ;

n = 0, 1 or 2;

p = 0, 1 or 2;

q = 0, 1 or 2;

r = 0, 1, 2 or 3;

5 the dashed line “ ” is single bond or double bond, respectively;

wherein when “ ” is single bond, D, E, E¹ and G are each independently selected from the group consisting of oxygen, sulfur, amino, or -C(Ra)(Rb)- group, respectively; and R¹⁰ is hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C₁-C₁₅ alkyl, C₁-C₁₅ alkoxy, C₁-C₁₅ alkylthio, C₁-C₁₅ alkoxycarbonyl, C₁-C₁₅ aminocarbonyl, C₁-C₁₅ carbonylamino, C₆-C₁₅ aryl, C₆-C₁₅ aryloxy, 10 C₆-C₁₅ aryloxycarbonyl, or C₂-C₁₅ heterocyclic group.

wherein when “ ” is double bond, D, E, E¹ and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R¹⁰ is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₆-C₁₅ aryl, C₁-C₁₅ alkoxy, C₁-C₁₅ 15 alkylthio, C₁-C₁₅ alkoxycarbonyl, C₆-C₁₅ aryloxy, C₆-C₁₅ aryloxycarbonyl, C₂-C₁₅ heterocyclic alkoxycarbonyl, C₂-C₁₅ heterocyclic aryl, C₁-C₁₅ alkylamino, C₂-C₁₅ heterocyclic amino, C₆-C₁₅ aryl amino, C₁-C₁₅ aminocarbonyl, C₁-C₁₅ amido, C₁-C₁₅ amidocarbonyl, C₁-C₁₅ carbonylamino, C₁-C₁₅ alkylsulfonamido, C₂-C₁₅ heterocyclic sulfonamido, C₆-C₁₅ arylsulfonamido, or C₁-C₁₅ aminosulfonamido group, respectively;

20 wherein when r = 0, E is nothing, and D is directly linked to E¹;

L is oxygen, sulfur, -S(O)-, -S(O)₂-, carbonyl, or -C(Rb)(Rc)-, C₁-C₁₅ alkenyl, C₁-C₁₅ alkoxy, C₂-C₁₅ heterocyclyl, C₂-C₁₅ heterocyclic alkoxy, C₁-C₁₅ amino, C₁-C₁₅ aminocarbonyl, C₁-C₁₅ alkoxycarbonyl, C₆-C₁₅ aryl, C₆-C₁₅ aryloxy, or C₆-C₁₅ aryloxycarbonyl group;

T is nitrogen, oxygen or CH;

25 U is carbon, sulfur, -S(O)-, phosphorus or phosphate;

W is oxygen or sulfur;

X is oxygen, sulfur or -NRa-; Ra is defined as in D, E, E¹, and G above;

Y is nitrogen or CH group;

30 Z is hydroxyl, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₁-C₁₅ alkoxy, C₃-C₁₅ cycloalkoxy, C₁-C₁₅ alkylamino, C₃-C₁₅ cycloalkylamino, C₂-C₁₅ heterocyclic amino, C₆-C₁₅ aryl, C₆-C₁₅ arylamino, C₄-C₁₅ heteroaryl amino, C₁-C₁₅ alkyl sulfonamido, C₃-C₁₅ cycloalkylsulfonamido, C₆-C₁₅

arylsulfonamido, C₁-C₁₅ alkoxy sulfonamido, C₃-C₁₅ cycloalkoxy sulfonamido, C₁-C₁₅ alkylamino sulfonamido, C₃-C₁₅ cycloalkylamino sulfonamido, C₆-C₁₅ arylamino sulfonamido, C₁-C₁₅ uramido, C₁-C₁₅ thioureido, C₁-C₁₅ phosphate, or C₁-C₁₅ borate;

R¹ and R² are each independently selected from the group consisting of hydrogen,
 5 hydroxyl, amino, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₁-C₁₅ alkoxy, C₃-C₁₅ cycloalkoxy, C₁-C₁₅ alkoxycarbonyl, C₁-C₁₅ alkylamino, C₃-C₁₅ cycloalkylamino, C₂-C₁₅ heterocyclic amino, C₆-C₁₅ arylamino, C₁-C₁₅ alkoxycarbonylamino, C₆-C₁₅ aryloxy carbonylamino, C₁-C₁₅ alkylsulfonamido, C₃-C₁₅ cycloalkylsulfonamido, C₂-C₁₅ heterocyclic sulfonamido, C₆-C₁₅ arylsulfonamido, and C₁-C₁₅ aminosulfonamido group;

10 R³, R⁴, R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, nitro, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₁-C₁₅ alkoxy, C₁-C₁₅ alkylamino, C₂-C₁₅ heterocyclicamino, C₆-C₁₅ aryl, C₆-C₁₅ arylamino, C₁-C₁₅ alkylsulfonamido, C₂-C₁₅ heterocyclic sulfonamido, and C₆-C₁₅ arylsulfonamido group; and

R⁷, R⁸ and R⁹ are each independently selected from the group consisting of hydrogen,
 15 cyano, nitro, trifluoromethyl, C₁-C₁₅ alkyl, C₁-C₁₅ alkoxy, C₁-C₁₅ alkylthio, C₁-C₁₅ alkoxycarbonyl, C₁-C₁₅ aminocarbonyl, C₁-C₁₅ carbonylamino, C₆-C₁₅ aryl, C₆-C₁₅ aryloxy, C₆-C₁₅ aryloxy carbonyl, and C₂-C₁₅ heterocyclic group.

In a more preferred embodiment of the compounds of formula **Ia-Ib**:

m = 0, 1 or 2;

20 n = 0, 1 or 2;

p = 0, 1 or 2;

q = 0, 1 or 2;

r = 0, 1, 2 or 3;

the dashed line “ ” is single bond or double bond, respectively;

25 wherein when “ ” is single bond, D, E, E¹ and G are each independently selected from the group consisting of oxygen, sulfur, amino, or -C(Ra)(Rb)- group, respectively; and R¹⁰ is hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, C₁-C₈ alkoxycarbonyl, C₁-C₈ aminocarbonyl, C₁-C₈ carbonylamino, C₆-C₁₂ aryl, C₆-

C₁₂ aryloxy, C₆-C₁₂ aryloxycarbonyl, or C₂-C₁₂ heterocyclic group.

wherein when “ ” is double bond, D, E, E¹ and G each is independently selected from the

group consisting of nitrogen N or -C(Rc)- group; and R¹⁰ is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₆-C₁₂ aryl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, C₁-C₈ alkoxycarbonyl, C₆-C₁₂ aryloxy, C₆-C₁₂ aryloxycarbonyl, C₂-C₈ heterocyclic alkoxy, C₂-C₁₂ heterocyclic aryl, C₁-C₈ alkylamino, C₂-C₈ heterocyclic amino, C₆-C₁₂ aryl amino, C₁-C₈ aminocarbonyl, C₁-C₈ amido, C₁-C₈ amidocarbonyl, C₁-C₈ carbonylamino, C₁-C₈ alkylsulfonamido, C₂-C₈ heterocyclic sulfonamido, C₆-C₁₂ arylsulfonamido, or C₁-C₈ aminosulfonamido group, respectively;

wherein when r = 0, E is nothing, and D is directly linked to E¹;

L is oxygen, sulfur, -S(O)-, -S(O)₂-, carbonyl, or -C(Rb)(Rc)-, C₁-C₈ alkenyl, C₁-C₈ alkoxy, C₂-C₈ heterocyclyl, C₂-C₈ heterocyclic alkoxy, C₁-C₈ amino, C₁-C₈ aminocarbonyl, C₁-C₈ alkoxycarbonyl, C₆-C₁₂ aryl, C₆-C₁₂ aryloxy, or C₆-C₁₂ aryloxycarbonyl group;

T is nitrogen, oxygen or CH;

U is carbon, sulfur, -S(O)-, phosphorus or phosphate;

W is oxygen or sulfur;

X is oxygen, sulfur or -NRa-; Ra is defined as in D, E, E¹, and G above;

Y is nitrogen or CH group;

Z is hydroxyl, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₁-C₈ alkoxy, C₃-C₈ cycloalkoxy, C₁-C₈ alkylamino, C₃-C₈ cycloalkylamino, C₂-C₈ heterocyclic amino, C₆-C₁₂ aryl, C₆-C₁₂ arylamino, C₄-C₁₂ heteroaryl amino, C₁-C₈ alkyl sulfonamido, C₃-C₈ cycloalkylsulfonamido, C₆-C₁₂ arylsulfonamido, C₁-C₈ alkoxy sulfonamido, C₃-C₈ cycloalkoxy sulfonamido, C₁-C₈ alkylamino sulfonamido, C₃-C₈ cycloalkylamino sulfonamido, C₆-C₁₂ arylamino sulfonamido, C₁-C₈ uramido, C₁-C₈ thioureido, C₁-C₈ phosphate, or C₁-C₈ borate;

R¹ and R² are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₁-C₈ alkoxy, C₃-C₈ cycloalkoxy, C₁-C₈ alkoxycarbonyl, C₁-C₈ alkylamino, C₃-C₈ cycloalkylamino, C₂-C₈ heterocyclic amino, C₆-C₁₂ arylamino, C₁-C₈ alkoxycarbonylamino, C₆-C₁₂ aryloxycarbonylamino, C₁-C₈ alkylsulfonamido, C₃-C₈ cycloalkylsulfonamido, C₂-C₈ heterocyclic sulfonamido, C₆-C₁₂ arylsulfonamido, and C₁-C₈ aminosulfonamido group;

R³, R⁴, R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, nitro, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₁-C₈ alkoxy, C₁-C₈ alkylamino,

C₂-C₈ heterocyclicamino, C₆-C₁₂ aryl, C₆-C₁₂ arylamino, C₁-C₈ alkylsulfonamido, C₂-C₈ heterocyclic sulfonamido, and C₆-C₁₂ arylsulfonamido group; and

R⁷, R⁸ and R⁹ are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, C₁-C₈ alkoxycarbonyl, C₁-C₈ aminocarbonyl, C₁-C₈ carbonylamino, C₆-C₁₂ aryl, C₆-C₁₂ aryloxy, C₆-C₁₂ aryloxycarbonyl, and C₂-C₈ heterocyclic group.

In one most preferred embodiment of the compounds of the formula **Ia-Ib**:

m = 1 or 2;

n = 1 or 2;

10 p = 1;

q = 1;

r = 0, 1 or 2;

the dashed line “-----” is a single bond or double bond;

15 the dashed line “-----” linked to the cyclopropylaminocarbonyl group inside of the macrocyclic ring is a double bond;

the dashed line “-----” linked to R¹⁰ is a single bond, and R¹⁰ is H;

the dashed line “-----” is a single bond in the tricyclic ring consisting of D, E, E¹, G and other cyclic groups; D and G are each oxygen; E and E¹ are each -CH₂-, respectively;

wherein when r = 0, E is nothing, and D is directly linked to E¹;

20 L is -CH₂-;

T is N or CH;

U is carbon;

W and X are each oxygen;

Y is N or CH;

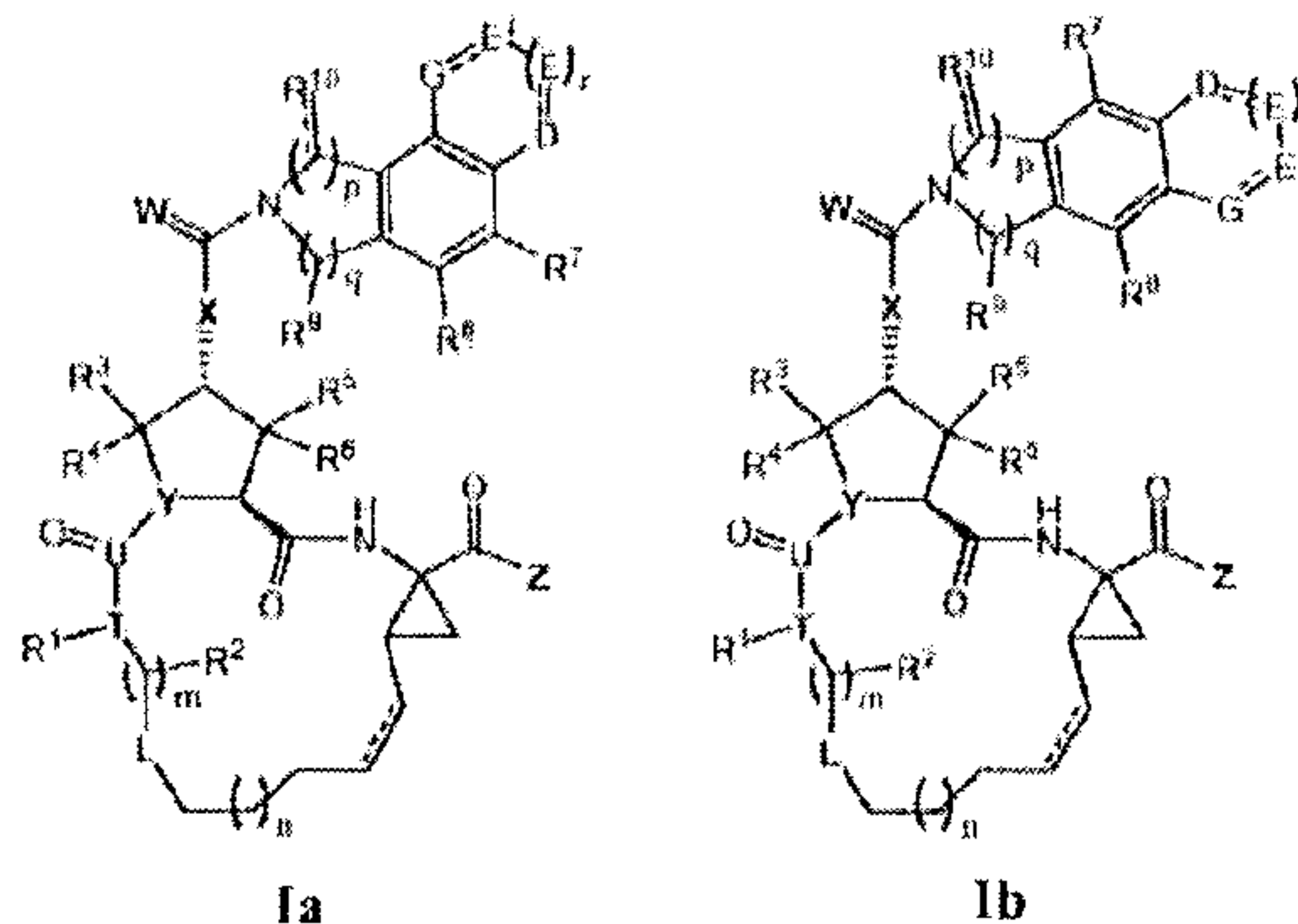
25 Z is hydroxyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfonamido, C₃-C₆ cycloalkylsulfonamido or C₆-C₁₀ arylsulfonamido group;

R¹ is hydrogen, C₆-C₁₀ arylamino, C₁-C₆ alkoxycarbonylamino, C₂-C₆ heterocyclic amino, C₁-C₆ alkylsulfonamido, or C₆-C₁₀ arylsulfonamido; and

R², R³, R⁴, R⁵ and R⁶ are each H;

R^7 , R^8 and R^9 are each H.

In one aspect, the invention provides a compound represented by the formula **1a** or **1b**,



stereoisomers, solvates, hydrates, tautomers, pharmaceutically acceptable salt, or mixtures

5 thereof,

wherein:

$m = 0, 1$ or 2 ;

$n = 0, 1$ or 2 ;

$p = 0, 1$ or 2 ;

10 $q = 0, 1$ or 2 ;

$r = 0, 1, 2$ or 3 ;

the dashed line " $\cdots$ " is single bond or double bond;

wherein " $\cdots$ " linked to the cyclopropyl formyl inside of the macrocyclic ring is a double bond; and " $\cdots$ " is a single bond in the ring consisting of D, E, E^1 and G, where D and G are

15 each oxygen, E and E^1 are each $C(Ra)(Rb)$;

R^{10} is hydrogen;

Ra, Rb and Rc are each hydrogen;

wherein when $r = 0$, E is nothing, and D is directly linked to E^1 ;

L is $-C(Rb)(Rc)-$;

20 T is nitrogen or CH;

U is carbon;

W is oxygen;

q = 0, 1 or 2;

r = 0, 1, 2 or 3;

the dashed line “-----” is single bond or double bond, respectively;

wherein when “-----” is single bond, D, E, E¹ and G are each independently selected from
 5 the group consisting of oxygen, sulfur, amino, or -C(Ra)(Rb)- group, respectively; and R¹⁰ is
 hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C₁-C₂₀ alkyl, C₁-C₂₀ alkoxy, C₁-C₂₀
 alkylthio, C₁-C₂₀ alkoxycarbonyl, C₁-C₂₀ aminocarbonyl, C₁-C₂₀ carbonylamino, C₆-C₂₀ aryl, C₆-
 C₂₀ aryloxy, C₆-C₂₀ aryloxycarbonyl, or C₂-C₂₀ heterocyclic group.

wherein when “-----” is double bond, D, E, E¹ and G each is independently selected from
 10 the group consisting of nitrogen N or -C(Rc)- group; and R¹⁰ is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen,
 halogen atom, cyano, nitro, C₁-C₂₀ alkyl, C₃-C₂₀ cycloalkyl, C₆-C₂₀ aryl, C₁-C₂₀ alkoxy, C₁-C₂₀
 alkylthio, C₁-C₂₀ alkoxycarbonyl, C₆-C₂₀ aryloxy, C₆-C₂₀ aryloxycarbonyl, C₂-C₂₀ heterocyclic
 15 alkoxycarbonyl, C₂-C₂₀ heterocyclic aryl, C₁-C₂₀ alkylamino, C₂-C₂₀ heterocyclic amino, C₆-C₂₀
 aryl amino, C₁-C₂₀ aminocarbonyl, C₁-C₂₀ amido, C₁-C₂₀ amidocarbonyl, C₁-C₂₀ carbonylamino,
 C₁-C₂₀ alkylsulfonamido, C₂-C₂₀ heterocyclic sulfonamido, C₆-C₂₀ arylsulfonamido, or C₁-C₂₀
 aminosulfonamido group, respectively;

wherein when r = 0, E is nothing, and D is directly linked to E¹;

W is oxygen or sulfur;

20 X is oxygen, sulfur or -NRa-; Ra is defined as in D, E, E¹, and G above;

Y is nitrogen or CH group;

Z is hydroxyl, C₁-C₂₀ alkyl, C₃-C₂₀ cycloalkyl, C₁-C₂₀ alkoxy, C₃-C₂₀ cycloalkoxy, C₁-C₂₀
 alkylamino, C₃-C₂₀ cycloalkylamino, C₂-C₂₀ heterocyclic amino, C₆-C₂₀ aryl, C₆-C₂₀ arylamino,
 C₄-C₂₀ heteroaryl amino, C₁-C₂₀ alkyl sulfonamido, C₃-C₂₀ cycloalkylsulfonamido, C₆-C₂₀
 25 arylsulfonamido, C₁-C₂₀ alkoxy sulfonamido, C₃-C₂₀ cycloalkoxy sulfonamido, C₁-C₂₀
 alkylamino sulfonamido, C₃-C₂₀ cycloalkylamino sulfonamido, C₆-C₂₀ arylamino sulfonamido,
 C₁-C₂₀ uramido, C₁-C₂₀ thioureido, C₁-C₂₀ phosphate, or C₁-C₂₀ borate;

R³, R⁴, R⁵ and R⁶ are each independently selected from the group consisting of hydrogen,
 halogen, hydroxyl, cyano, nitro, C₁-C₂₀ alkyl, C₃-C₂₀ cycloalkyl, C₁-C₂₀ alkoxy,

C₁-C₂₀ alkylamino, C₂-C₂₀ heterocyclicamino, C₆-C₂₀ aryl, C₆-C₂₀ arylamino, C₁-C₂₀ alkylsulfonamido, C₂-C₂₀ heterocyclic sulfonamido, and C₆-C₂₀ arylsulfonamido group; and

R⁷, R⁸ and R⁹ are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C₁-C₂₀ alkyl, C₁-C₂₀ alkoxy, C₁-C₂₀ alkylthio, C₁-C₂₀ alkoxycarbonyl, C₁-C₂₀ aminocarbonyl, C₁-C₂₀ carbonylamino, C₆-C₂₀ aryl, C₆-C₂₀ aryloxy, C₆-C₂₀ aryloxycarbonyl, and C₂-C₂₀ heterocyclic group.

R¹¹ is H, C₁-C₂₀ alkyl, C₃-C₂₀ cycloalkyl, C₆-C₂₀ aryl, C₄-C₂₀ heteroaryl, C₁-C₂₀ alkylcarbonyl, C₁-C₂₀ alkoxycarbonyl, C₆-C₂₀ aryloxycarbonyl, C₁-C₂₀ alkylaminocarbonyl, C₆-C₂₀ arylsulfonyl, C₁-C₂₀ alkylaminosulfonyl, C₃-C₂₀ cycloalkylaminosulfonyl, C₆-C₂₀ arylaminosulfonyl, C₃-C₂₀ heterocyclicaminosulfonyl group.

In a preferred embodiment of the compounds of formula IIa or IIb:

p = 0, 1 or 2;

q = 0, 1 or 2;

r = 0, 1, 2 or 3;

the dashed line “ ” is single bond or double bond, respectively;

wherein when “ ” is single bond, D, E, E¹ and G are each independently selected from the group consisting of oxygen, sulfur, amino, or -C(Ra)(Rb)- group, respectively; and R¹⁰ is hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C₁-C₁₅ alkyl, C₁-C₁₅ alkoxy, C₁-C₁₅ alkylthio, C₁-C₁₅ alkoxycarbonyl, C₁-C₁₅ aminocarbonyl, C₁-C₁₅ carbonylamino, C₆-C₁₅ aryl, C₆-C₁₅ aryloxy,

C₆-C₁₅ aryloxy carbonyl, or C₂-C₁₅ heterocyclic group.

wherein when “~~.....~~” is double bond, D, E, E¹ and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R¹⁰ is oxygen or sulfur.

5 Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₆-C₁₅ aryl, C₁-C₁₅ alkoxy, C₁-C₁₅ alkylthio, C₁-C₁₅ alkoxycarbonyl, C₆-C₁₅ aryloxy, C₆-C₁₅ aryloxy carbonyl, C₂-C₁₅ heterocyclic
10 alkoxycarbonyl, C₂-C₁₅ heterocyclic aryl, C₁-C₁₅ alkylamino, C₂-C₁₅ heterocyclic amino, C₆-C₁₅ aryl amino, C₁-C₁₅ aminocarbonyl, C₁-C₁₅ amido, C₁-C₁₅ amidocarbonyl, C₁-C₁₅ carbonylamino, C₁-C₁₅ alkylsulfonamido, C₂-C₁₅ heterocyclic sulfonamido, C₆-C₁₅ arylsulfonamido, or C₁-C₁₅ aminosulfonamido group, respectively;

wherein when r = 0, E is nothing, and D is directly linked to E¹;

W is oxygen or sulfur;

X is oxygen, sulfur or -NRa-; Ra is defined as in D, E, E¹, and G above;

Y is nitrogen or CH group;

15 Z is hydroxyl, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₁-C₁₅ alkoxy, C₃-C₁₅ cycloalkoxy, C₁-C₁₅ alkylamino, C₃-C₁₅ cycloalkylamino, C₂-C₁₅ heterocyclic amino, C₆-C₁₅ aryl, C₆-C₁₅ arylamino, C₄-C₁₅ heteroaryl amino, C₁-C₁₅ alkyl sulfonamido, C₃-C₁₅ cycloalkylsulfonamido, C₆-C₁₅ arylsulfonamido, C₁-C₁₅ alkoxy sulfonamido, C₃-C₁₅ cycloalkoxy sulfonamido, C₁-C₁₅ alkylamino sulfonamido, C₃-C₁₅ cycloalkylamino sulfonamido, C₆-C₁₅ arylamino sulfonamido, C₁-C₁₅ uramido,
20 C₁-C₁₅ thioureido, C₁-C₁₅ phosphate, or C₁-C₁₅ borate;

R³, R⁴, R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, nitro, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₁-C₁₅ alkoxy, C₁-C₁₅ alkylamino, C₂-C₁₅ heterocyclic amino, C₆-C₁₅ aryl, C₆-C₁₅ arylamino, C₁-C₁₅ alkylsulfonamido, C₂-C₁₅ heterocyclic sulfonamido, and C₆-C₁₅ arylsulfonamido group; and

25 R⁷, R⁸ and R⁹ are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C₁-C₁₅ alkyl, C₁-C₁₅ alkoxy, C₁-C₁₅ alkylthio, C₁-C₁₅ alkoxycarbonyl, C₁-C₁₅ aminocarbonyl, C₁-C₁₅ carbonylamino, C₆-C₁₅ aryl, C₆-C₁₅ aryloxy, C₆-C₁₅ aryloxy carbonyl, and C₂-C₁₅ heterocyclic group.

R¹¹ is H, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₆-C₁₅ aryl, C₄-C₁₅ heteroaryl, C₁-C₁₅ alkylcarbonyl, C₁-C₁₅ alkoxycarbonyl, C₆-C₁₅ aryloxy carbonyl, C₁-C₁₅ alkylaminocarbonyl, C₆-C₁₅ arylsulfonyl, C₁-C₁₅ alkylaminosulfonyl, C₃-C₁₅ cycloalkylaminosulfonyl, C₆-C₁₅ arylaminosulfonyl, C₃-C₁₅

heterocyclicaminosulfonyl group.

In one more preferred embodiment of the formula **IIa** or **IIb**:

$p = 0, 1 \text{ or } 2$;

$q = 0, 1 \text{ or } 2$;

5 $r = 0, 1, 2 \text{ or } 3$;

the dashed line “ $\cdots$ ” is single bond or double bond, respectively;

wherein when “ $\cdots$ ” is single bond, D, E, E¹ and G are each independently selected from the group consisting of oxygen, sulfur, amino, or -C(Ra)(Rb)- group, respectively; and R¹⁰ is hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, C₁-C₈ alkoxycarbonyl, C₁-C₈ aminocarbonyl, C₁-C₈ carbonylamino, C₆-C₁₂ aryl, C₆-C₁₂ aryloxy, C₆-C₁₂ aryloxycarbonyl, or C₂-C₁₂ heterocyclic group.

wherein when “ $\cdots$ ” is double bond, D, E, E¹ and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R¹⁰ is oxygen or sulfur.

15 Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₆-C₁₂ aryl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, C₁-C₈ alkoxycarbonyl, C₆-C₁₂ aryloxy, C₆-C₁₂ aryloxycarbonyl, C₂-C₈ heterocyclic alkoxycarbonyl, C₂-C₁₂ heterocyclic aryl, C₁-C₈ alkylamino, C₂-C₈ heterocyclic amino, C₆-C₁₂ aryl amino, C₁-C₈ aminocarbonyl, C₁-C₈ amido, C₁-C₈ amidocarbonyl, C₁-C₈ carbonylamino, C₁-C₈ alkylsulfonamido, C₂-C₈ heterocyclic sulfonamido, C₆-C₁₂ arylsulfonamido, or C₁-C₈ aminosulfonamido group, respectively;

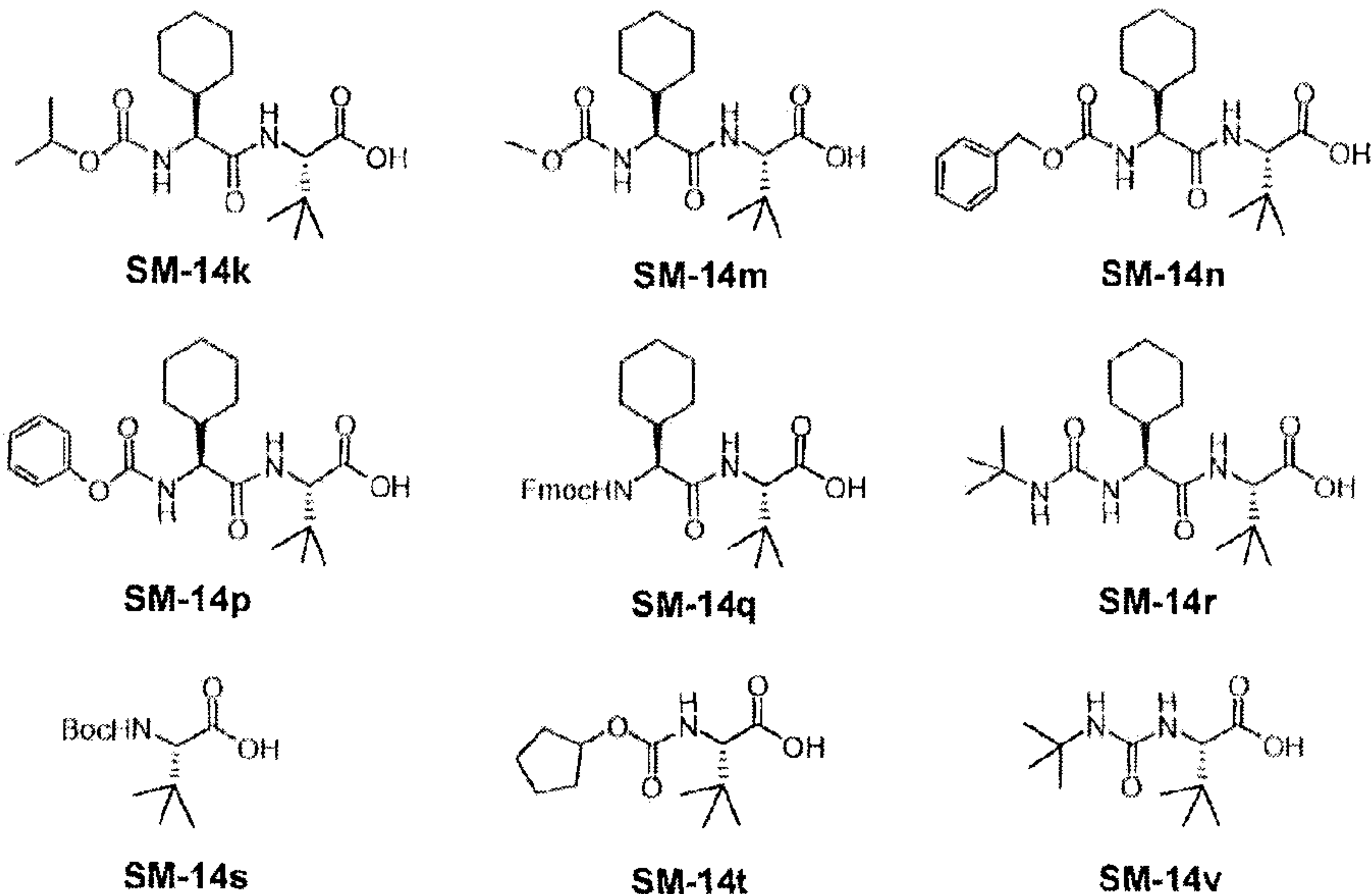
wherein when $r = 0$, E is nothing, and D is directly linked to E¹;

W is oxygen or sulfur ;

X is oxygen, sulfur or -NRa-; Ra is defined as in D, E, E¹, and G above;

25 Y is nitrogen or CH group;

Z is hydroxyl, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₁-C₈ alkoxy, C₃-C₈ cycloalkoxy, C₁-C₈ alkylamino, C₃-C₈ cycloalkylamino, C₂-C₈ heterocyclic amino, C₆-C₁₂ aryl, C₆-C₁₂ arylamino, C₄-C₁₂ heteroaryl amino, C₁-C₈ alkyl sulfonamido, C₃-C₈ cycloalkylsulfonamido, C₆-C₁₂ arylsulfonamido, C₁-C₈ alkoxy sulfonamido, C₃-C₈ cycloalkoxy sulfonamido, C₁-C₈ alkylamino sulfonamido, C₃-C₈ cycloalkylamino sulfonamido, C₆-C₁₂ arylamino sulfonamido, C₁-C₈ uramido, C₁-C₈ thioureido, C₁-C₈ phosphate, or C₁-C₈ borate;



In one most preferred embodiment of the formula **IIa** or **IIb**:

$p = 1$;

$q = 1$;

5 $r = 0, 1 \text{ or } 2$;

the dashed line “-----” is a single bond or double bond;

the dashed line “-----” linked to the cyclopropylaminocarbonyl group is a double bond;

the dashed line “-----” linked to R^{10} is a single bond, and R^{10} is H;

10 the dashed line “-----” is a single bond in the tricyclic ring consisting of D, E, E^1 , G and other cyclic groups; D and G are each oxygen; E and E^1 are each $-\text{CH}_2-$, respectively;

wherein when $r = 0$, E is nothing, and D is directly linked to E^1 ;

W and X are each oxygen;

Y is N or CH;

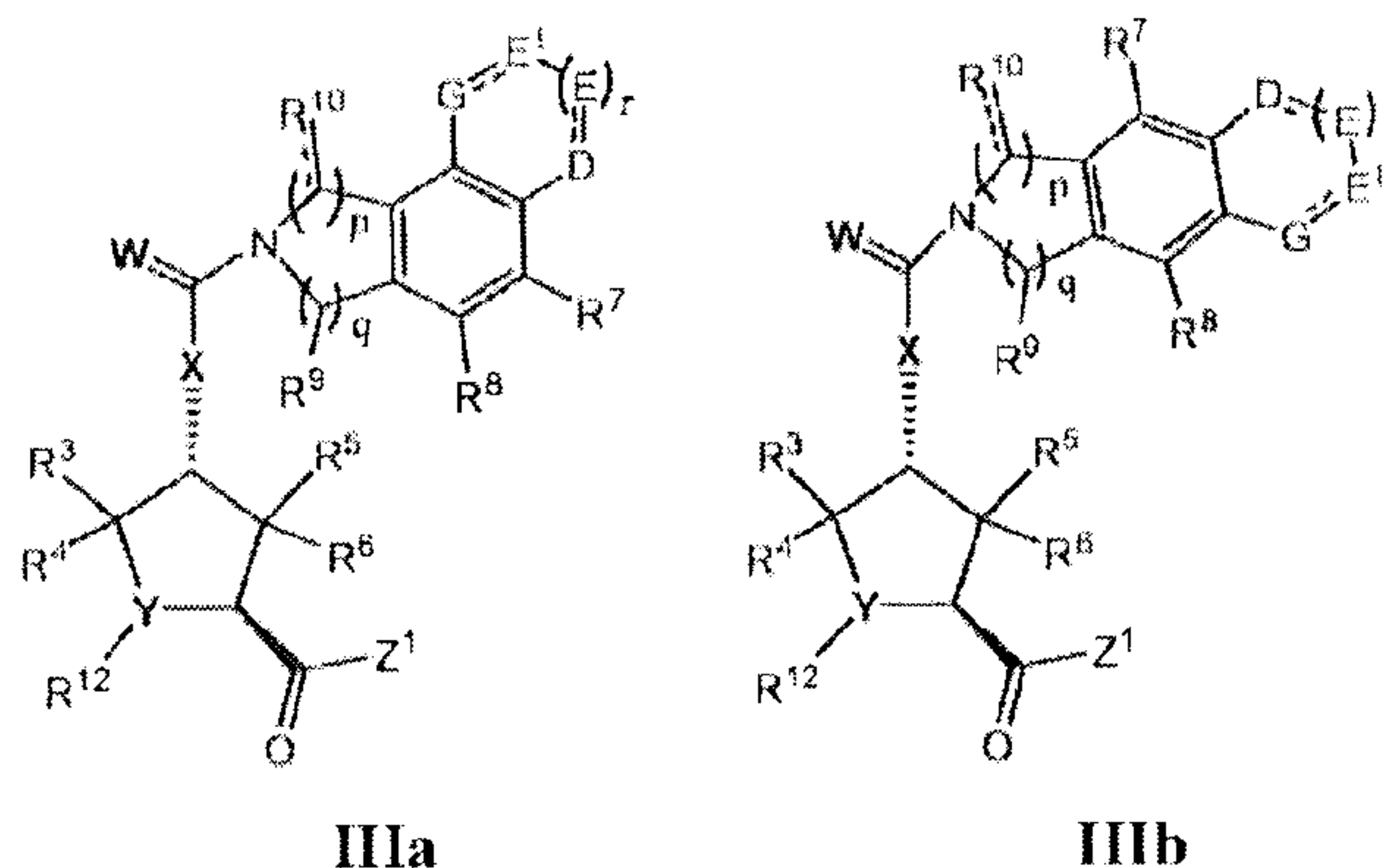
15 Z is hydroxyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylsulfonamido, C_3 - C_6 cycloalkylsulfonamido or C_6 - C_{10} arylsulfonamido group;

R^3 , R^4 , R^5 and R^6 are each H;

R^7 , R^8 and R^9 are each H.

R^{11} is H, C_1 - C_6 alkyl, C_1 - C_6 alkylcarbonyl, C_1 - C_6 alkoxy carbonyl, or preferably a group having the structure selected from **SM-14a** to **SM-14v** as defined above.

The third aspect of the present disclosure provides polyheterocyclic based compounds represented by the formula **IIIa** or **IIIb**:



Wherein:

- 5 $p = 0, 1 \text{ or } 2$;
 $q = 0, 1 \text{ or } 2$;
 $r = 0, 1, 2 \text{ or } 3$;

the dashed line “-----” is single bond or double bond, respectively;

- wherein when “-----” is single bond, D, E, E¹ and G are each independently selected from
 10 the group consisting of oxygen, sulfur, amino, or -C(Ra)(Rb)- group, respectively; and R¹⁰ is
 hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C₁-C₂₀ alkyl, C₁-C₂₀ alkoxy, C₁-C₂₀
 alkylthio, C₁-C₂₀ alkoxy carbonyl, C₁-C₂₀ aminocarbonyl, C₁-C₂₀ carbonylamino, C₆-C₂₀ aryl, C₆-
 C₂₀ aryloxy, C₆-C₂₀ aryloxy carbonyl, or C₂-C₂₀ heterocyclic group.

- wherein when “-----” is double bond, D, E, E¹ and G each is independently selected from
 15 the group consisting of nitrogen N or -C(Rc)- group; and R¹⁰ is oxygen or sulfur.

- Ra, Rb and Rc are each independently selected from the group consisting of hydrogen,
 halogen atom, cyano, nitro, C₁-C₂₀ alkyl, C₃-C₂₀ cycloalkyl, C₆-C₂₀ aryl, C₁-C₂₀ alkoxy, C₁-C₂₀
 alkylthio, C₁-C₂₀ alkoxy carbonyl, C₆-C₂₀ aryloxy, C₆-C₂₀ aryloxy carbonyl, C₂-C₂₀ heterocyclic
 alkoxy carbonyl, C₂-C₂₀ heterocyclic aryl, C₁-C₂₀ alkylamino, C₂-C₂₀ heterocyclic amino, C₆-C₂₀
 20 aryl amino, C₁-C₂₀ aminocarbonyl, C₁-C₂₀ amido, C₁-C₂₀ amidocarbonyl, C₁-C₂₀ carbonylamino,
 C₁-C₂₀ alkylsulfonamido, C₂-C₂₀ heterocyclic sulfonamido, C₆-C₂₀ arylsulfonamido, or C₁-C₂₀
 aminosulfonamido group, respectively;

wherein when $r = 0$, E is nothing, and D is directly linked to E^1 ;

W is oxygen or sulfur ;

X is oxygen, sulfur or -NRa-; Ra is defined as in D, E, E^1 , and G above;

Y is nitrogen or CH group;

5

Z^1 is hydroxyl, C_1 - C_{20} alkyl, C_3 - C_{20} cycloalkyl, C_1 - C_{20} alkoxy, C_3 - C_{20} cycloalkoxy, C_1 - C_{20} alkylamino, C_3 - C_{20} cycloalkylamino, C_2 - C_{20} heterocyclic amino, C_6 - C_{20} aryl, C_6 - C_{20} arylamino, C_4 - C_{20} heteroaryl amino, C_1 - C_{20} alkyl sulfonamido, C_3 - C_{20} cycloalkylsulfonamido, C_6 - C_{20} arylsulfonamido, C_1 - C_{20} alkoxy sulfonamido, C_3 - C_{20} cycloalkoxy sulfonamido, C_1 - C_{20} alkylamino sulfonamido, C_3 - C_{20} cycloalkylamino sulfonamido, C_6 - C_{20} arylamino sulfonamido, C_1 - C_{20} uramido, C_1 - C_{20} thioureido, C_1 - C_{20} phosphate, or C_1 - C_{20} borate;

10

R^3 , R^4 , R^5 and R^6 are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, nitro, C_1 - C_{20} alkyl, C_3 - C_{20} cycloalkyl, C_1 - C_{20} alkoxy, C_1 - C_{20} alkylamino, C_2 - C_{20} heterocyclic amino, C_6 - C_{20} aryl, C_6 - C_{20} arylamino, C_1 - C_{20} alkylsulfonamido, C_2 - C_{20} heterocyclic sulfonamido, and C_6 - C_{20} arylsulfonamido group; and

15

R^7 , R^8 and R^9 are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C_1 - C_{20} alkyl, C_1 - C_{20} alkoxy, C_1 - C_{20} alkylthio, C_1 - C_{20} alkoxycarbonyl, C_1 - C_{20} aminocarbonyl, C_1 - C_{20} carbonylamino, C_6 - C_{20} aryl, C_6 - C_{20} aryloxy, C_6 - C_{20} aryloxycarbonyl, and C_2 - C_{20} heterocyclic group.

20

R^{12} is H, C_1 - C_{20} alkyl, C_3 - C_{20} cycloalkyl, C_6 - C_{20} aryl, C_4 - C_{20} heteroaryl, C_1 - C_{20} alkylcarbonyl, C_1 - C_{20} alkoxycarbonyl, C_6 - C_{20} aryloxycarbonyl, C_1 - C_{20} alkylaminocarbonyl, C_6 - C_{20} arylsulfonyl, C_1 - C_{20} alkylaminosulfonyl, C_3 - C_{20} cycloalkylaminosulfonyl, C_6 - C_{20} arylaminosulfonyl, C_3 - C_{20} heterocyclicaminosulfonyl group.

In one preferred embodiment of the formula **IIIa-IIIb**:

$p = 0, 1$ or 2 ;

25

$q = 0, 1$ or 2 ;

$r = 0, 1, 2$ or 3 ;

the dashed line “ $\cdots$ ” is single bond or double bond, respectively;

wherein when “ $\cdots$ ” is single bond, D, E, E^1 and G are each independently selected from the group consisting of oxygen, sulfur, amino, or -C(Ra)(Rb)- group, respectively; and R^{10} is

30

hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C_1 - C_{15} alkyl, C_1 - C_{15} alkoxy, C_1 - C_{15}

alkylthio, C₁-C₁₅ alkoxy carbonyl, C₁-C₁₅ aminocarbonyl, C₁-C₁₅ carbonylamino, C₆-C₁₅ aryl, C₆-C₁₅ aryloxy, C₆-C₁₅ aryloxy carbonyl, or C₂-C₁₅ heterocyclic group.

wherein when “ ” is double bond, D, E, E¹ and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R¹⁰ is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₆-C₁₅ aryl, C₁-C₁₅ alkoxy, C₁-C₁₅ alkylthio, C₁-C₁₅ alkoxy carbonyl, C₆-C₁₅ aryloxy, C₆-C₁₅ aryloxy carbonyl, C₂-C₁₅ heterocyclic alkoxy carbonyl, C₂-C₁₅ heterocyclic aryl, C₁-C₁₅ alkylamino, C₂-C₁₅ heterocyclic amino, C₆-C₁₅ aryl amino, C₁-C₁₅ aminocarbonyl, C₁-C₁₅ amido, C₁-C₁₅ amidocarbonyl, C₁-C₁₅ carbonylamino, C₁-C₁₅ alkylsulfonamido, C₂-C₁₅ heterocyclic sulfonamido, C₆-C₁₅ arylsulfonamido, or C₁-C₁₅ aminosulfonamido group, respectively;

wherein when r = 0, E is nothing, and D is directly linked to E¹;

W is oxygen or sulfur ;

X is oxygen, sulfur or -NRa-; Ra is defined as in D, E, E¹, and G above;

Y is nitrogen or CH group;

Z¹ is hydroxyl, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₁-C₁₅ alkoxy, C₃-C₁₅ cycloalkoxy, C₁-C₁₅ alkylamino, C₃-C₁₅ cycloalkylamino, C₂-C₁₅ heterocyclic amino, C₆-C₁₅ aryl, C₆-C₁₅ arylamino, C₄-C₁₅ heteroaryl amino, C₁-C₁₅ alkyl sulfonamido, C₃-C₁₅ cycloalkylsulfonamido, C₆-C₁₅ arylsulfonamido, C₁-C₁₅ alkoxy sulfonamido, C₃-C₁₅ cycloalkoxy sulfonamido, C₁-C₁₅ alkylamino sulfonamido, C₃-C₁₅ cycloalkylamino sulfonamido, C₆-C₁₅ arylamino sulfonamido, C₁-C₁₅ uramido, C₁-C₁₅ thioureido, C₁-C₁₅ phosphate, or C₁-C₁₅ borate;

R³, R⁴, R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, nitro, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₁-C₁₅ alkoxy, C₁-C₁₅ alkylamino, C₂-C₁₅ heterocyclic amino, C₆-C₁₅ aryl, C₆-C₁₅ arylamino, C₁-C₁₅ alkylsulfonamido, C₂-C₁₅ heterocyclic sulfonamido, and C₆-C₁₅ arylsulfonamido group; and

R⁷, R⁸ and R⁹ are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C₁-C₁₅ alkyl, C₁-C₁₅ alkoxy, C₁-C₁₅ alkylthio, C₁-C₁₅ alkoxy carbonyl, C₁-C₁₅ aminocarbonyl, C₁-C₁₅ carbonylamino, C₆-C₁₅ aryl, C₆-C₁₅ aryloxy, C₆-C₁₅ aryloxy carbonyl, and C₂-C₁₅ heterocyclic group.

R¹² is H, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₆-C₁₅ aryl, C₄-C₁₅ heteroaryl, C₁-C₁₅ alkylcarbonyl, C₁-C₁₅ alkoxy carbonyl, C₆-C₁₅ aryloxy carbonyl, C₁-C₁₅ alkylaminocarbonyl, C₆-

C₁₅ arylsulfonyl, C₁-C₁₅ alkylaminosulfonyl, C₃-C₁₅ cycloalkylaminosulfonyl, C₆-C₁₅ arylaminosulfonyl, C₃-C₁₅ heterocyclicaminosulfonyl group.

In one more preferred embodiment of the formula **IIIa-IIIb**:

p = 0, 1 or 2 ;

5 q = 0, 1 or 2 ;

r = 0, 1, 2 or 3 ;

the dashed line “-----” is single bond or double bond, respectively;

wherein when “-----” is single bond, D, E, E¹ and G are each independently selected from the group consisting of oxygen, sulfur, amino, or -C(Ra)(Rb)- group, respectively; and R¹⁰ is
 10 hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, C₁-C₈ alkoxycarbonyl, C₁-C₈ aminocarbonyl, C₁-C₈ carbonylamino, C₆-C₁₂ aryl, C₆-C₁₂ aryloxy, C₆-C₁₂ aryloxycarbonyl, or C₂-C₁₂ heterocyclic group.

wherein when “-----” is double bond, D, E, E¹ and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R¹⁰ is oxygen or sulfur.
 15

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₆-C₁₂ aryl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, C₁-C₈ alkoxycarbonyl, C₆-C₁₂ aryloxy, C₆-C₁₂ aryloxycarbonyl, C₂-C₈ heterocyclic alkoxycarbonyl, C₂-C₁₂ heterocyclic aryl, C₁-C₈ alkylamino, C₂-C₈ heterocyclic amino, C₆-C₁₂ aryl amino, C₁-C₈ aminocarbonyl, C₁-C₈ amido, C₁-C₈ amidocarbonyl, C₁-C₈ carbonylamino,
 20 C₁-C₈ alkylsulfonamido, C₂-C₈ heterocyclic sulfonamido, C₆-C₁₂ arylsulfonamido, or C₁-C₈ aminosulfonamido group, respectively;

wherein when r = 0, E is nothing, and D is directly linked to E¹;

W is oxygen or sulfur ;

X is oxygen, sulfur or -NRa-; Ra is defined as in D, E, E¹, and G above;

25 Y is nitrogen or CH group;

Z¹ is hydroxyl, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₁-C₈ alkoxy, C₃-C₈ cycloalkoxy, C₁-C₈ alkylamino, C₃-C₈ cycloalkylamino, C₂-C₈ heterocyclic amino, C₆-C₁₂ aryl, C₆-C₁₂ arylamino, C₄-C₁₂ heteroaryl amino, C₁-C₈ alkyl sulfonamido, C₃-C₈ cycloalkylsulfonamido, C₆-C₁₂ arylsulfonamido, C₁-C₈ alkoxy sulfonamido, C₃-C₈ cycloalkoxy sulfonamido, C₁-C₈ alkylamino

sulfonamido, C₃-C₈ cycloalkylamino sulfonamido, C₆-C₁₂ arylamino sulfonamido, C₁-C₈ uramido, C₁-C₈ thioureido, C₁-C₈ phosphate, or C₁-C₈ borate;

R¹ and R² are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₁-C₈ alkoxy, C₃-C₈ cycloalkoxy, C₁-C₈ alkoxy carbonyl, C₁-C₈ alkylamino, C₃-C₈ cycloalkylamino, C₂-C₈ heterocyclic amino, C₆-C₁₂ arylamino, C₁-C₈ alkoxy carbonylamino, C₆-C₁₂ aryloxy carbonylamino, C₁-C₈ alkylsulfonamido, C₃-C₈ cycloalkylsulfonamido, C₂-C₈ heterocyclic sulfonamido, C₆-C₁₂ arylsulfonamido, and C₁-C₈ aminosulfonamido group;

R³, R⁴, R⁵ and R⁶ are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, nitro, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₁-C₈ alkoxy, C₁-C₈ alkylamino, C₂-C₈ heterocyclic amino, C₆-C₁₂ aryl, C₆-C₁₂ arylamino, C₁-C₈ alkylsulfonamido, C₂-C₈ heterocyclic sulfonamido, and C₆-C₁₂ arylsulfonamido group; and

R⁷, R⁸ and R⁹ are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio, C₁-C₈ alkoxy carbonyl, C₁-C₈ aminocarbonyl, C₁-C₈ carbonylamino, C₆-C₁₂ aryl, C₆-C₁₂ aryloxy, C₆-C₁₂ aryloxy carbonyl, and C₂-C₈ heterocyclic group.

R¹² is H, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₆-C₁₂ aryl, C₄-C₁₂ heteroaryl, C₁-C₈ alkyl carbonyl, C₁-C₈ alkoxy carbonyl, C₆-C₁₂ aryloxy carbonyl, C₁-C₈ alkylaminocarbonyl, C₆-C₁₂ arylsulfonyl, C₁-C₈ alkylaminosulfonyl, C₃-C₈ cycloalkylaminosulfonyl, C₆-C₁₂ arylaminosulfonyl, C₃-C₈ heterocyclicaminosulfonyl group.

In one most preferred embodiment of the formula **III-IIIb**:

p = 1 ;

q = 1 ;

r = 0, 1 or 2 ;

the dashed line “-----” is a single bond;

the dashed line “-----” linked to R¹⁰ is a single bond, and R¹⁰ is H;

the dashed line “-----” is a single bond in the tricyclic ring consisting of D, E, E¹, G and other cyclic groups; D and G are each oxygen; E and E¹ are each -CH₂-, respectively;

wherein when r = 0, E is nothing, and D is directly linked to E¹;

W and X are each oxygen;

Y is N or CH;

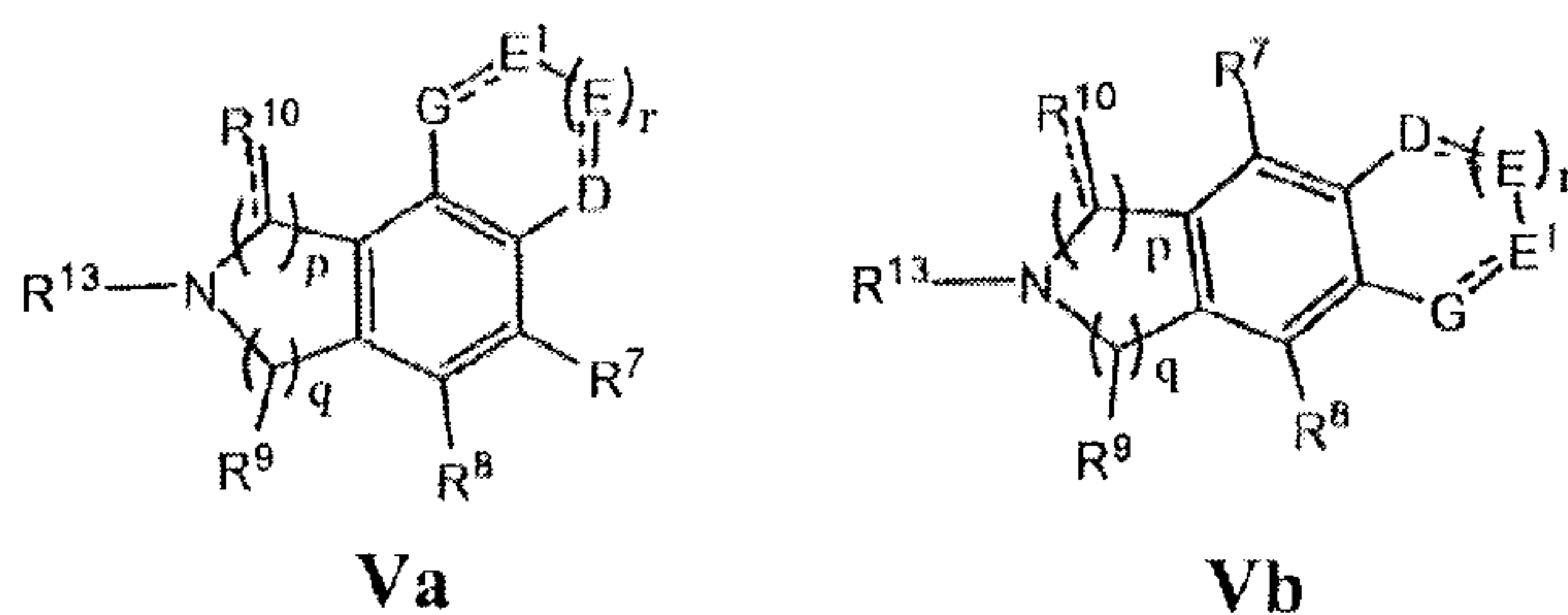
Z¹ is hydroxyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfonamido, C₃-C₆ cycloalkylsulfonamido or C₆-C₁₀ arylsulfonamido group;

R³, R⁴, R⁵ and R⁶ are each H;

5 R⁷, R⁸ and R⁹ are each H.

R¹² is H, C₁-C₈ alkyl, C₁-C₆ alkoxycarbonyl, C₆-C₁₀ aryloxycarbonyl, or C₆-C₁₀ arylsulfonyl group.

The fourth aspect of the present present disclosure provides polyheterocyclic based compounds represented by the formula **Va** and **Vb**:



wherein:

p = 0, 1 or 2 ;

q = 0, 1 or 2 ;

r = 0, 1, 2 or 3 ;

15 the dashed line “-----” is single bond or double bond, respectively;

wherein when “-----” is single bond, D, E, E¹ and G are each independently selected from the group consisting of oxygen, sulfur, amino, or -C(Ra)(Rb)- group, respectively; and R¹⁰ is hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C₁-C₂₀ alkyl, C₁-C₂₀ alkoxy, C₁-C₂₀ alkylthio, C₁-C₂₀ alkoxycarbonyl, C₁-C₂₀ aminocarbonyl, C₁-C₂₀ carbonylamino, C₆-C₂₀ aryl, C₆-C₂₀ aryloxy, C₆-C₂₀ aryloxycarbonyl, or C₂-C₂₀ heterocyclic group.

wherein when “-----” is double bond, D, E, E¹ and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R¹⁰ is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C₁-C₂₀ alkyl, C₃-C₂₀ cycloalkyl, C₆-C₂₀ aryl, C₁-C₂₀ alkoxy, C₁-C₂₀ alkylthio, C₁-C₂₀ alkoxycarbonyl, C₆-C₂₀ aryloxy, C₆-C₂₀ aryloxycarbonyl, C₂-C₂₀ heterocyclic

alkoxycarbonyl, C₂-C₂₀ heterocyclic aryl, C₁-C₂₀ alkylamino, C₂-C₂₀ heterocyclic amino, C₆-C₂₀ aryl amino, C₁-C₂₀ aminocarbonyl, C₁-C₂₀ amido, C₁-C₂₀ amidocarbonyl, C₁-C₂₀ carbonylamino, C₁-C₂₀ alkylsulfonamido, C₂-C₂₀ heterocyclic sulfonamido, C₆-C₂₀ arylsulfonamido, or C₁-C₂₀ aminosulfonamido group, respectively;

5 wherein when $r = 0$, E is nothing, and D is directly linked to E¹;

R⁷, R⁸ and R⁹ are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C₁-C₂₀ alkyl, C₁-C₂₀ alkoxy, C₁-C₂₀ alkylthio, C₁-C₂₀ alkoxycarbonyl, C₁-C₂₀ aminocarbonyl, C₁-C₂₀ carbonylamino, C₆-C₂₀ aryl, C₆-C₂₀ aryloxy, C₆-C₂₀ aryloxycarbonyl, and C₂-C₂₀ heterocyclic group.

10 R¹³ is H, C₁-C₂₀ alkyl, C₃-C₂₀ cycloalkyl, C₆-C₂₀ aryl, C₄-C₂₀ heteroaryl, C₁-C₂₀ alkylcarbonyl, C₁-C₂₀ alkoxycarbonyl, C₆-C₂₀ aryloxycarbonyl, C₁-C₂₀ alkylaminocarbonyl, C₁-C₂₀ alkoxysulfonyl, C₆-C₂₀ aryloxysulfonyl, C₆-C₂₀ arylsulfonyl and C₂-C₂₀ heterocyclic group,

In one preferred embodiment of the formula **Va-Vb**:

$p = 0, 1 \text{ or } 2$;

15 $q = 0, 1 \text{ or } 2$;

$r = 0, 1, 2 \text{ or } 3$;

the dashed line “-----” is single bond or double bond, respectively;

wherein when “-----” is single bond, D, E, E¹ and G are each independently selected from the group consisting of oxygen, sulfur, amino, or -C(Ra)(Rb)- group, respectively; and R¹⁰ is
20 hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C₁-C₁₅ alkyl, C₁-C₁₅ alkoxy, C₁-C₁₅ alkylthio, C₁-C₁₅ alkoxycarbonyl, C₁-C₁₅ aminocarbonyl, C₁-C₁₅ carbonylamino, C₆-C₁₅ aryl, C₆-C₁₅ aryloxy, C₆-C₁₅ aryloxycarbonyl, or C₂-C₁₅ heterocyclic group.

wherein when “-----” is double bond, D, E, E¹ and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R¹⁰ is oxygen or sulfur.

25 Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₆-C₁₅ aryl, C₁-C₁₅ alkoxy, C₁-C₁₅ alkylthio, C₁-C₁₅ alkoxycarbonyl, C₆-C₁₅ aryloxy, C₆-C₁₅ aryloxycarbonyl, C₂-C₁₅ heterocyclic alkoxycarbonyl, C₂-C₁₅ heterocyclic aryl, C₁-C₁₅ alkylamino, C₂-C₁₅ heterocyclic amino, C₆-C₁₅ aryl amino, C₁-C₁₅ aminocarbonyl, C₁-C₁₅ amido, C₁-C₁₅ amidocarbonyl, C₁-C₁₅ carbonylamino,

C₁-C₁₅ alkylsulfonamido, C₂-C₁₅ heterocyclic sulfonamido, C₆-C₁₅ arylsulfonamido, or C₁-C₁₅ aminosulfonamido group, respectively;

wherein when $r = 0$, E is nothing, and D is directly linked to E¹;

R⁷, R⁸ and R⁹ are each independently selected from the group consisting of hydrogen,
 5 cyano, nitro, trifluoromethyl, C₁-C₁₅ alkyl, C₁-C₁₅ alkoxy, C₁-C₁₅ alkylthio, C₁-C₁₅
 alkoxycarbonyl, C₁-C₁₅ aminocarbonyl, C₁-C₁₅ carbonylamino, C₆-C₁₅ aryl, C₆-C₁₅ aryloxy, C₆-
 C₁₅ aryloxycarbonyl, and C₂-C₁₅ heterocyclic group.

R¹³ is H, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₆-C₁₅ aryl, C₄-C₁₅ heteroaryl, C₁-C₁₅
 alkylcarbonyl, C₁-C₁₅ alkoxycarbonyl, C₆-C₁₅ aryloxycarbonyl, C₁-C₁₅ alkylaminocarbonyl, C₁-
 10 C₁₅ alkoxysulfonyl, C₆-C₁₅ aryloxysulfonyl, C₆-C₁₅ arylsulfonyl and C₂-C₁₅ heterocyclic group.

In one more preferred embodiment of the formula **Va-Vb**:

$p = 0, 1$ or 2 ;

$q = 0, 1$ or 2 ;

$r = 0, 1, 2$ or 3 ;

15 the dashed line “-----” is single bond or double bond, respectively;

wherein when “-----” is single bond, D, E, E¹ and G are each independently selected from
 the group consisting of oxygen, sulfur, amino, or -C(Ra)(Rh)- group, respectively; and R¹⁰ is
 hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈
 alkylthio, C₁-C₈ alkoxycarbonyl, C₁-C₈ aminocarbonyl, C₁-C₈ carbonylamino, C₆-C₁₂ aryl, C₆-
 20 C₁₂ aryloxy, C₆-C₁₂ aryloxycarbonyl, or C₂-C₁₂ heterocyclic group.

wherein when “-----” is double bond, D, E, E¹ and G each is independently selected from
 the group consisting of nitrogen N or -C(Rc)- group; and R¹⁰ is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen,
 25 halogen atom, cyano, nitro, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₆-C₁₂ aryl, C₁-C₈ alkoxy, C₁-C₈
 alkylthio, C₁-C₈ alkoxycarbonyl, C₆-C₁₂ aryloxy, C₆-C₁₂ aryloxycarbonyl, C₂-C₈ heterocyclic
 alkoxycarbonyl, C₂-C₁₂ heterocyclic aryl, C₁-C₈ alkylamino, C₂-C₈ heterocyclic amino, C₆-C₁₂
 aryl amino, C₁-C₈ aminocarbonyl, C₁-C₈ amido, C₁-C₈ amidocarbonyl, C₁-C₈ carbonylamino,
 C₁-C₈ alkylsulfonamido, C₂-C₈ heterocyclic sulfonamido, C₆-C₁₂ arylsulfonamido, or C₁-C₈
 aminosulfonamido group, respectively;

30 wherein when $r = 0$, E is nothing, and D is directly linked to E¹;

R^7 , R^8 and R^9 are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, C_1 - C_8 alkylthio, C_1 - C_8 alkoxycarbonyl, C_1 - C_8 aminocarbonyl, C_1 - C_8 carbonylamino, C_6 - C_{12} aryl, C_6 - C_{12} aryloxy, C_6 - C_{12} aryloxycarbonyl, and C_2 - C_8 heterocyclic group.

- 5 R^{13} is H, C_1 - C_8 alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{12} aryl, C_4 - C_{12} heteroaryl, C_1 - C_8 alkylcarbonyl, C_1 - C_8 alkoxycarbonyl, C_6 - C_{12} aryloxycarbonyl, C_1 - C_8 alkylaminocarbonyl, C_1 - C_8 alkoxysulfonyl, C_6 - C_{12} aryloxysulfonyl, C_6 - C_{12} arylsulfonyl and C_2 - C_8 heterocyclic group.

In one most preferred embodiment of the formula **Va-Vb**:

$p = 1$;

10 $q = 1$;

$r = 0, 1$ or 2 ;

the dashed line “-----” is a single bond;

the dashed line “-----” linked to R^{10} is a single bond, and R^{10} is H;

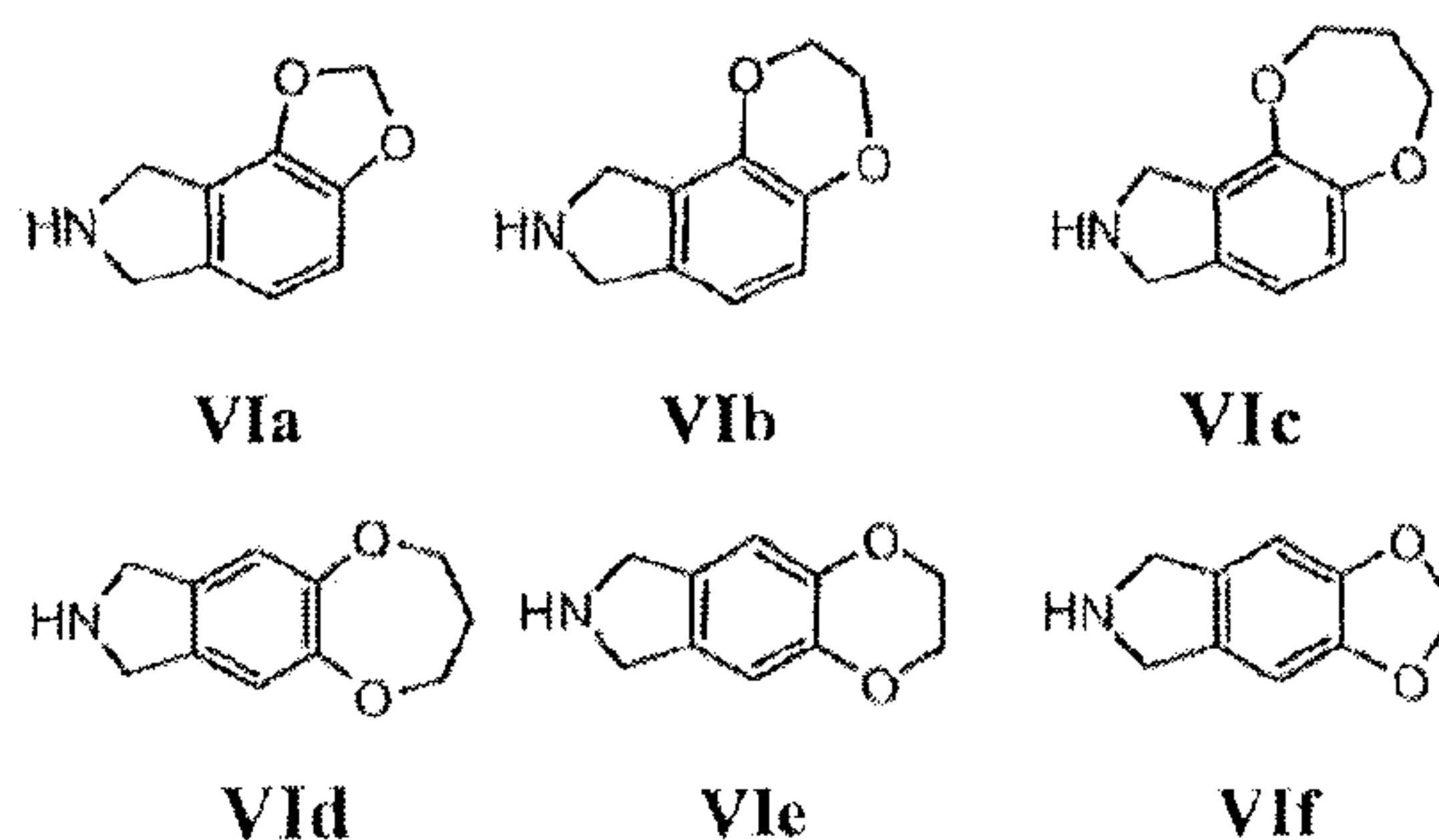
- 15 the dashed line “-----” is a single bond in the tricyclic ring consisting of D, E, E^1 , G and other cyclic groups; D and G are each oxygen; E and E^1 are each $-CH_2-$, respectively;

wherein when $r = 0$, E is nothing, and D is directly linked to E^1 ;

R^7 , R^8 and R^9 are each H. and

R^{13} is H, C_1 - C_8 alkyl, C_1 - C_8 alkylcarbonyl, C_1 - C_8 alkoxycarbonyl and C_6 - C_{10} arylsulfonyl group,

- 20 wherein when R^{13} is H, **Va** or **Vb** having the following formulas **Vla-VIf**:



The fifth aspect of the present disclosure provides new compounds of present invention, and/or stereoisomers, solvates, hydrates, tautomers, prodrugs and/or pharmaceutically acceptable salts, or mixtures thereof.

The sixth aspect of the present disclosure provides a pharmaceutical composition,
 5 including: one or more of compounds **Ia-Ib** or **IIa-IIb**, and/or their stereoisomers, tautomers, esterified prodrugs, pharmaceutically acceptable salts, and pharmaceutically acceptable excipients.

The seventh aspect of the present disclosure provides a method for inhibiting HCV by using one or more compounds of the present invention, or one or more of these compounds in
 10 combination with any of the following: (1) Immune modulators including but not limited to Interferons, pegulated-interferons, or interferon derivatives, (2) HCV protease inhibitors, (3) HCV polymerase inhibitors, (4) nucleosides and its derivatives, (5) Cyclophilin inhibitors, (6) Glucosidase I inhibitors, (7) IMPDH inhibitors, (8) Caspase inhibitors, (9) TLR agonists, (10) HIV inhibitors, (11) anti-inflammatory drugs, (12) Cancer drugs, or (13) other compounds not
 15 covered from above (1)-(12).

The present invention provides a pharmaceutical composition comprising one or more compounds of the invention and a pharmaceutically acceptable excipient.

The present invention provides a pharmaceutical combination of a compound of the invention and an HIV inhibitor. The present invention also provides a pharmaceutical
 20 combination of a compound of the invention and a hepatitis B virus (HBV) inhibitor.

The present invention further provides a use of one or more compounds of the invention in a therapeutically effective dose, for inhibiting hepatitis C virus (HCV), or in the preparation of a medicament for inhibiting hepatitis C virus (HCV).

The present invention further provides one or more compounds of the invention in a
 25 therapeutically effective dose, for use in inhibiting hepatitis C virus (HCV).

The present invention further provides a use of a combination of one or more compounds of the invention with one or more of the following agent: (1) immune modulator, (2) HCV protease inhibitor, (3) HCV polymerase inhibitor, (4) nucleoside and derivative thereof, (5) cyclophilin inhibitor, (6) glucosidase I inhibitor, (7) IMPDH inhibitor, (8) caspase inhibitor, (9)

TLR agonist, (10) HIV inhibitor, (11) anti-inflammatory drug, (12) cancer drug, or (13) hepatitis B virus (HBV) inhibitor, for inhibiting hepatitis C virus (HCV); or in the preparation of a medicament for inhibiting hepatitis C virus (HCV).

5 The present invention further provides a combination of one or more compounds of the invention with one or more of the following agent: (1) immune modulator, (2) HCV protease inhibitor, (3) HCV polymerase inhibitor, (4) nucleoside and derivative thereof, (5) cyclophilin inhibitor, (6) glucosidase I inhibitor, (7) IMPDH inhibitor, (8) caspase inhibitor, (9) TLR agonist, (10) HIV inhibitor, (11) anti-inflammatory drug, (12) cancer drug, or (13) hepatitis B virus (HBV) inhibitor, for use in inhibiting hepatitis C virus (HCV).

10 The present invention relates to two classes of novel polyheterocyclic based compounds highly potent as HCV inhibitors, e.g., which is highly effective to inhibit the NS3 protease replication of hepatitis C virus (HCV). The present invention also relates to preparation and the uses thereof as HCV inhibitors.

Currently, the present invention provides the following significant achievements:

15 1) The present invention provides several synthetic methods effectively to prepare various new polyheterocyclic building blocks and different kinds of novel polyheterocyclic based HCV inhibitor.

2) The present invention provides two classes of novel polyheterocyclic based macrocyclic and linear compounds that can be used to inhibit HCV effectively in vitro and in vivo.

20 3) The present invention explores the relationship between the structures of new polyheterocyclic compounds and efficacy of HCV inhibition, which provides valuable clue to develop an effective HCV inhibitors.

DEFINITION OF TERMS

25 As used herein, the term “alkyl” refers to any linear or branched chain alkyl group having a number of carbon atoms and/or “alkylene” in the specified range, wherein one or more hydrogens could be replaced by one or more halogens.

The term “alkoxy” refers to an “alkyl-O-” group.

The term “cycloalkyl” refers to any cyclic ring of an alkane or alkene having a number of carbon atoms and/or “alkylene” in the specified range, wherein one or more hydrogens could be replaced by one or more halogens.

The term “halogen” (or “halo”) refers to fluorine, chlorine, bromine and iodine atoms (or
5 referred as fluoro, chloro, bromo, and iodo).

The term “carbonyl” refers to an “-C(O)-” group.

The term “alkyl carbonyl” refers to an “alkyl-C(O)-” group.

The term “alkoxy carbonyl” refers to an “alkyl-O-C(O)-” group.

The term “alkylamino carbonyl” refers to an “alkyl-NH-C(O)-” or “dialkyl-N-C(O)-” group.

The term “alkyl sulfonamido” refers to an “alkyl-S(O)₂NH-” or “alkyl-S(O)₂N(R)-” group, wherein R is alkyl or alkylcarbonyl group.

5 The term “alkoxy sulfonamido” refers to an “alkyl-O-S(O)₂NH-” or “alkyl-O-S(O)₂N(R)-” group, wherein R is alkyl or alkylcarbonyl group.

The term “polyheterocyclic” refers to a tri-cyclic or tetra-cyclic functional group with 1-5 hetero atoms (e.g., O, N, S, and P) in one or more fused rings.

The term “sulfonamido” refers to an “-S(O)₂NH-” or “-S(O)₂N(R)-” group, wherein R is
10 alkyl or alkylcarbonyl group.

The term “administration” referred to a compound of the present invention means to provide the compound or a prodrug of the compound to the individual in need of treatment.

The term “composition” is intended to encompass a product comprising the specified ingredients, as well as any product which results, directly or indirectly, from combining the
15 specified ingredients.

The term “effective amount” means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term also includes herein the amount of active compound sufficient to inhibit HCV NS3 protease and
20 thereby elicit the response being sought (i.e., an “inhibition effective amount”). When the active compound (i.e., active ingredient) is administered as the salt, references to the amount of active ingredient are to the free acid or free base form of the compound.

The term “pharmaceutically acceptable” means that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

25 Details of the present invention are set forth in the following description for preparation and biological activity study of new HCV inhibitors **Ia-Ib** and **IIa-IIb**. The advantages of the present invention will be significantly observed from the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises two classes of novel polyheterocyclic based compounds
30 **Ia-Ib** and **IIa-IIb**, and pharmaceutically acceptable salts, and/or hydrates as HCV NS3 protease

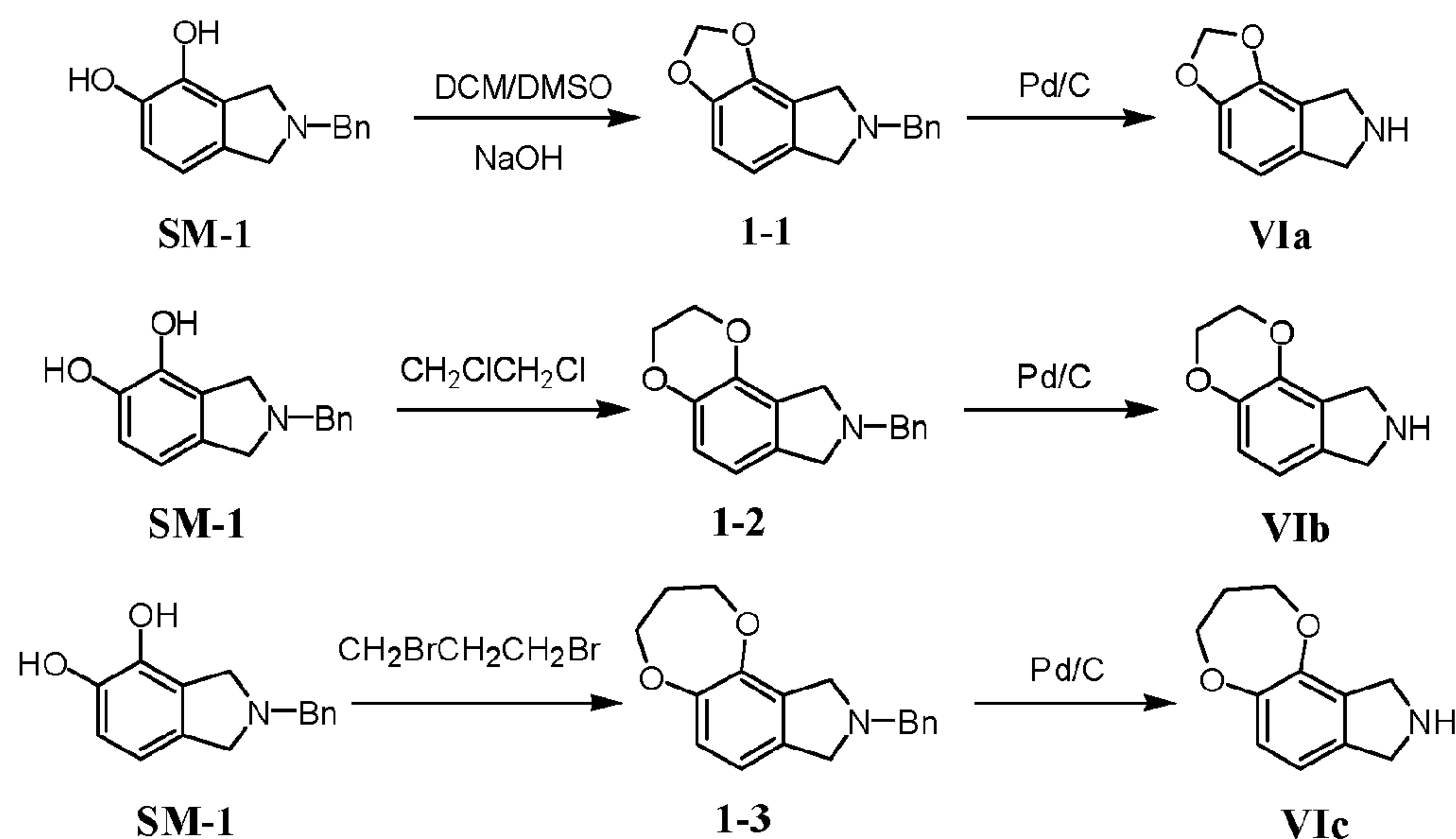
inhibitors with high potency. Moreover, toxicity study is determined to be non-toxic ($LD_{50} > 10,000$) for most of highly potent HCV inhibitors.

Synthesis of new polyheterocyclic based compounds with general structure Ia-Ib and IIa-IIb: According to previously reported references and our developed synthetic methods, different kinds of synthetic methods have been carried out effectively to prepare different compounds with the structure **Ia-Ib** and **IIa-IIb**.

Abbreviations of chemical reagents and solvents for the synthesis of all intermediates and products are listed in the example part at the end.

In the present invention, compounds **VIa-VIc** are prepared first as in the following Scheme 1:

Scheme 1:

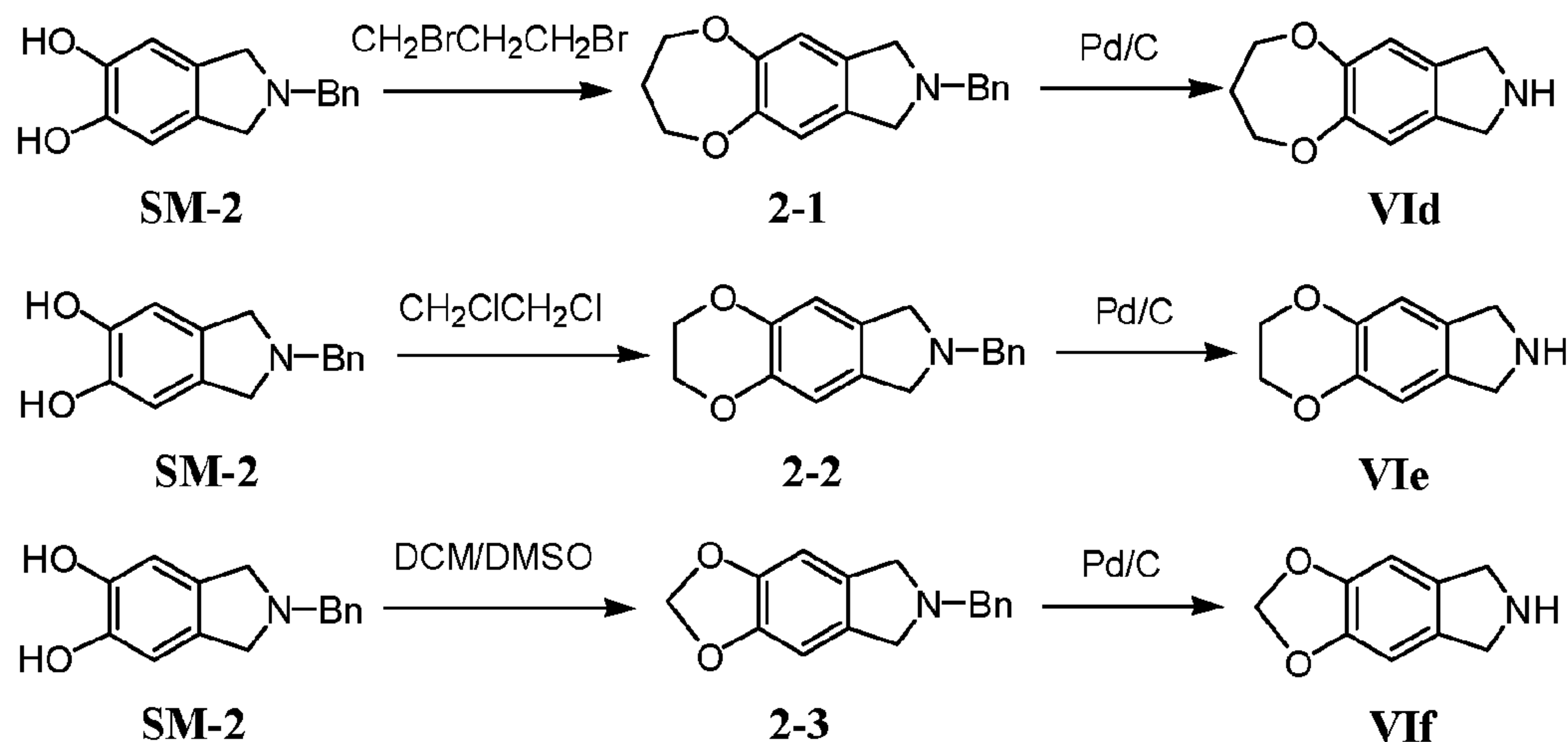


In Scheme 1, in the presence of inorganic base (e.g., sodium hydroxide, sodium methoxide, or sodium hydrogen), **SM-1** was dissolved in organic solvents (methanol, THF, DMF, or DMSO) and heated to 30-120°C, then reacted with ClCH_2Cl , $\text{ClCH}_2\text{CH}_2\text{Cl}$, or $\text{BrCH}_2\text{CH}_2\text{CH}_2\text{Br}$, respectively, to form five, six, or seven membered polyheterocyclic compound **1-1**, **1-2**, or **1-3**, followed by deprotection to obtain the key tri-heterocyclic compounds **VIa-VIc** by removing the protecting group (Bn: benzyl) with Pd/C catalyst and hydrogen in methanol or ethanol.

Scheme 2:

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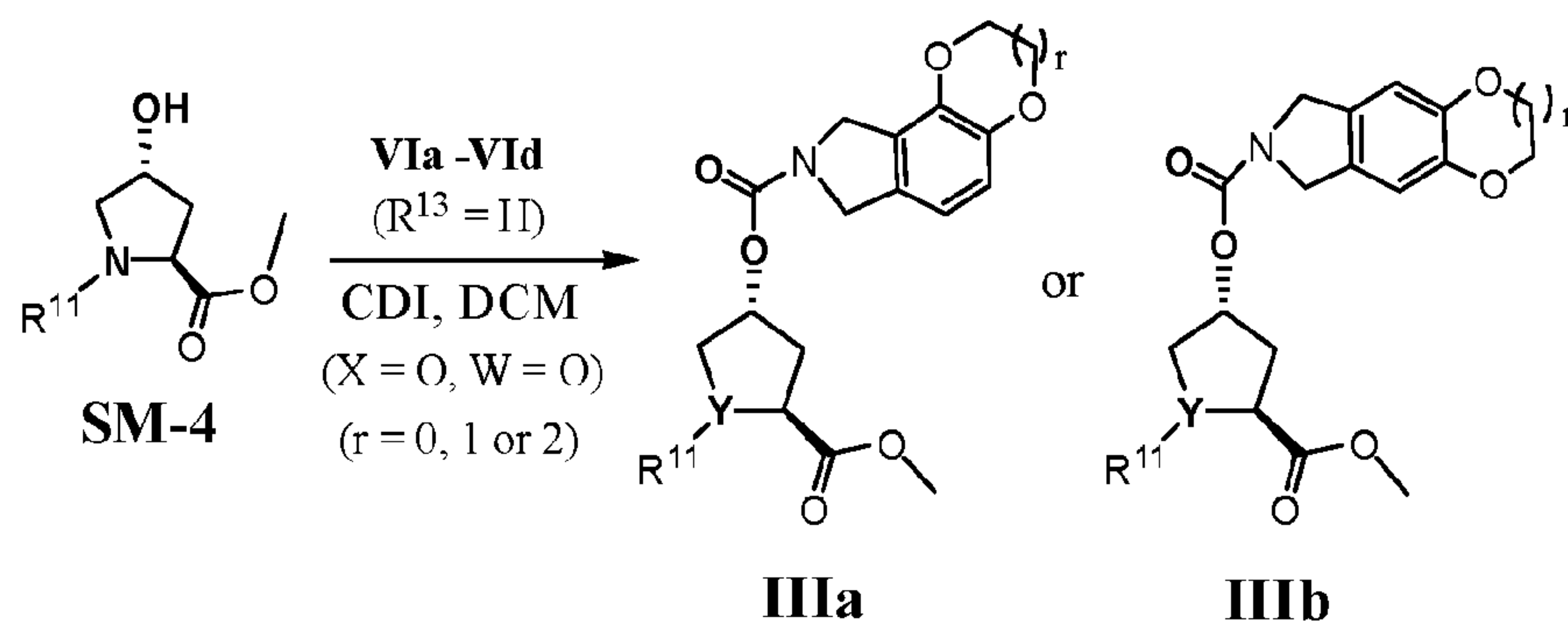


In Scheme 2, **SM-2** was dissolved in organic solvents (methanol, THF, DMF, or DMSO) and heated to 30-120°C, then reacted with $\text{BrCH}_2\text{CH}_2\text{CH}_2\text{Br}$, $\text{ClCH}_2\text{CH}_2\text{Cl}$ or ClCH_2Cl , respectively, to form seven, six or five membered polyheterocyclic compound **2-1**, **2-2**, or **2-3**, followed by deprotection to obtain the key tri-heterocyclic compounds **VId-VIf** by removing the protecting group (Bn: benzyl) with Pd/C catalyst and hydrogen in methanol or ethanol.

Preparation of the following specific compounds **IIIa-IIIb** has been carried out as follows in Scheme 3.

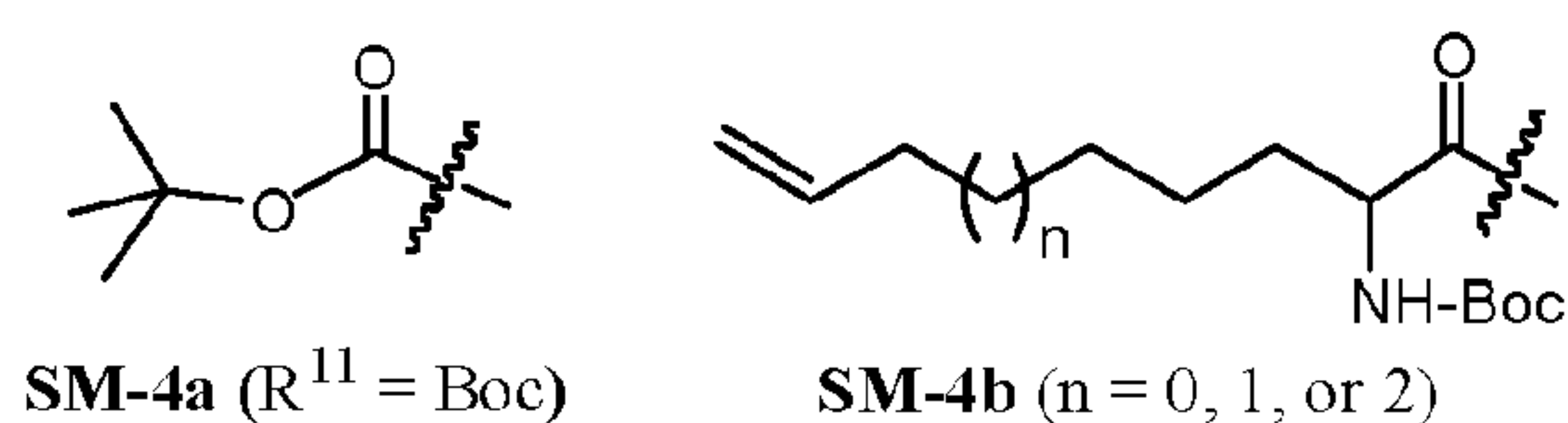
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Scheme 3:



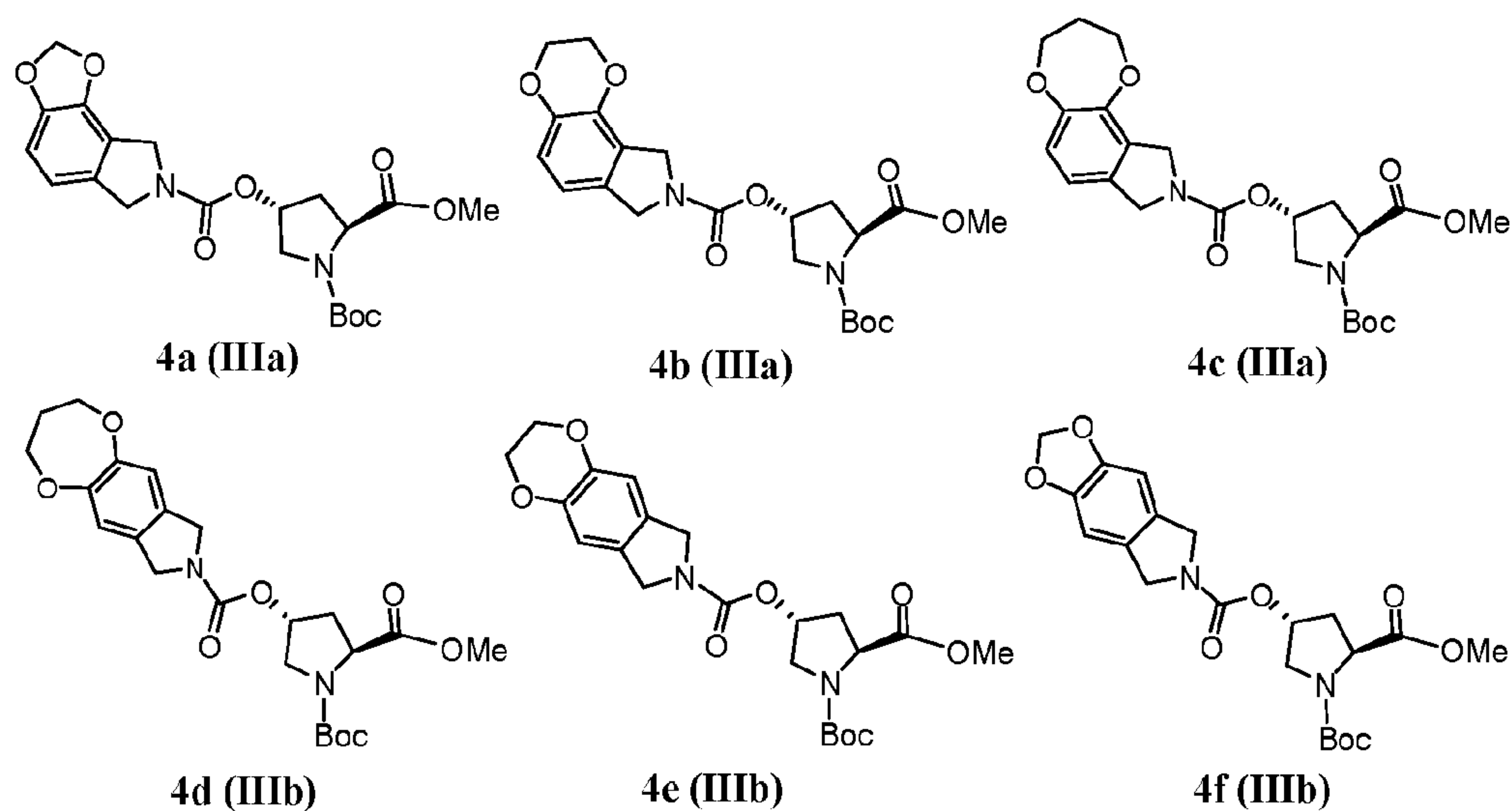
R^{11} is preferred to be selected from the following group: **SM-4a** (Boc) or **SM-4b**:

15



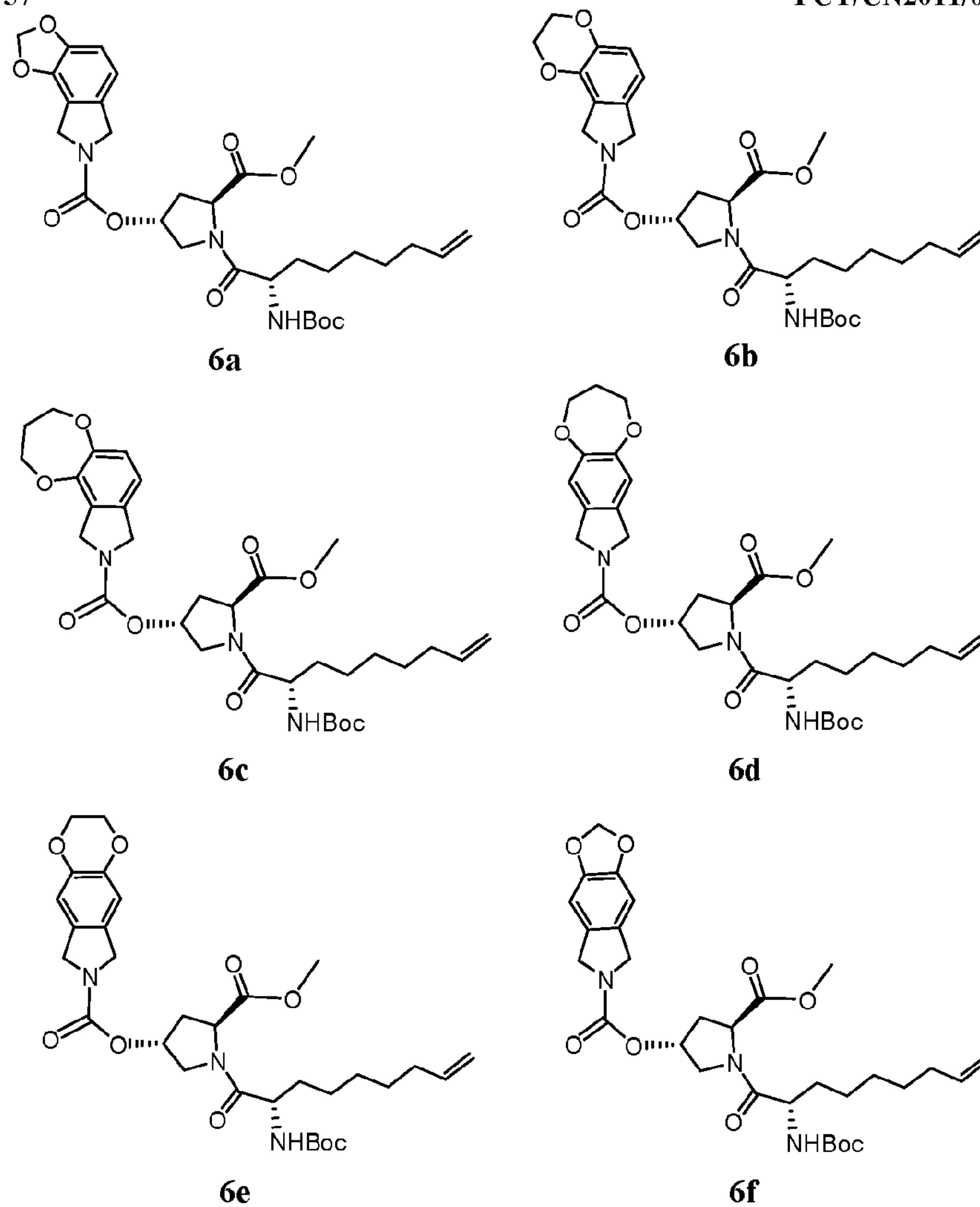
In the presence of coupling reagent CDI, starting material **SM-4** (e.g., **SM-4a** or **SM-4b**)

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was reacted with compounds **VIa-VIh**, respectively to obtain polyheterocyclic compounds **4a-4h**
and **6a-6d (IIIa-IIIb)** as shown in Figure 1-1 and Figure 1-2 by amidation reaction.



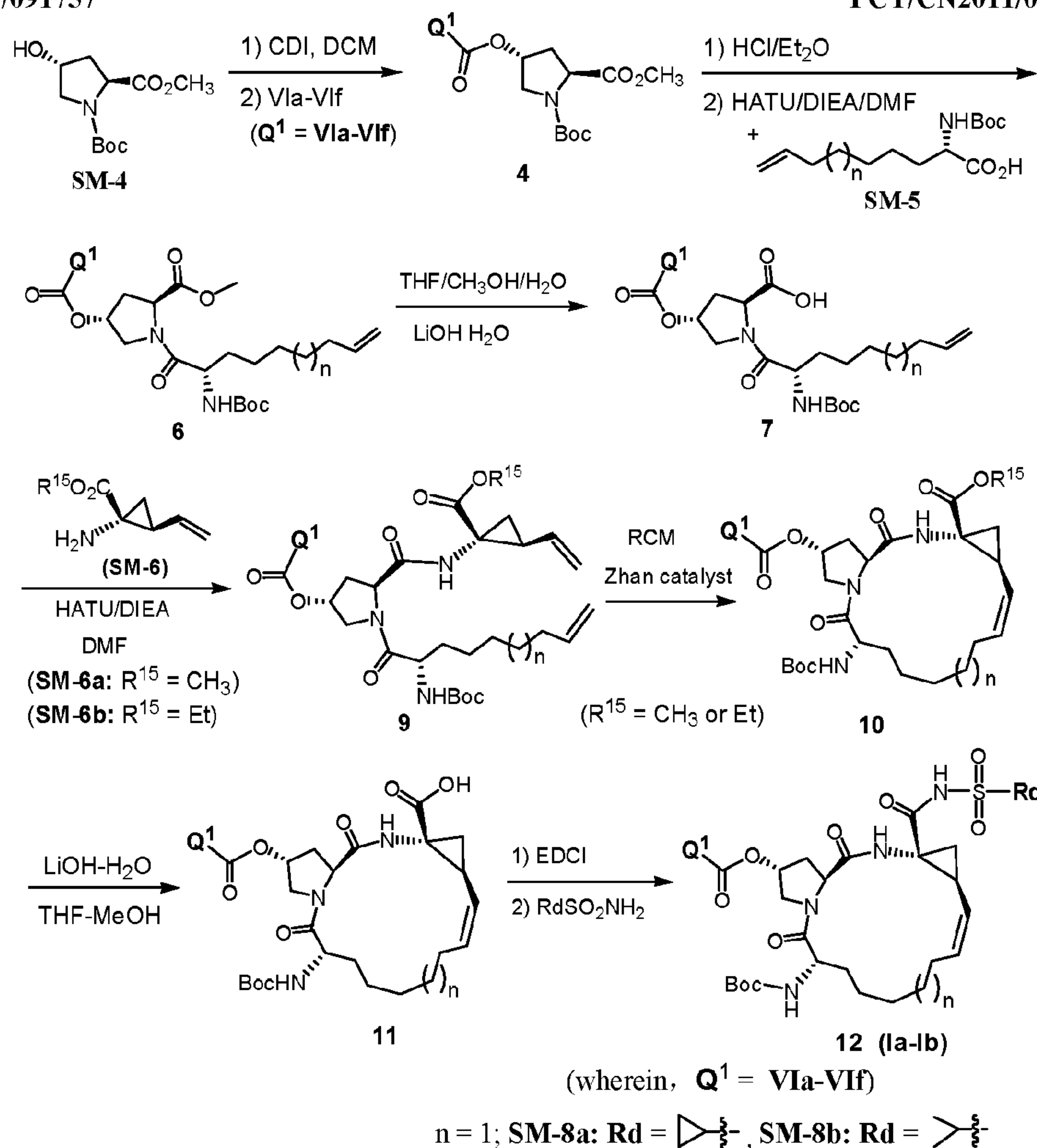
5

Figure 1-1: Structure of Compounds **4a-4f**

Figure 1-2: Structure of Compounds **6a-6f**

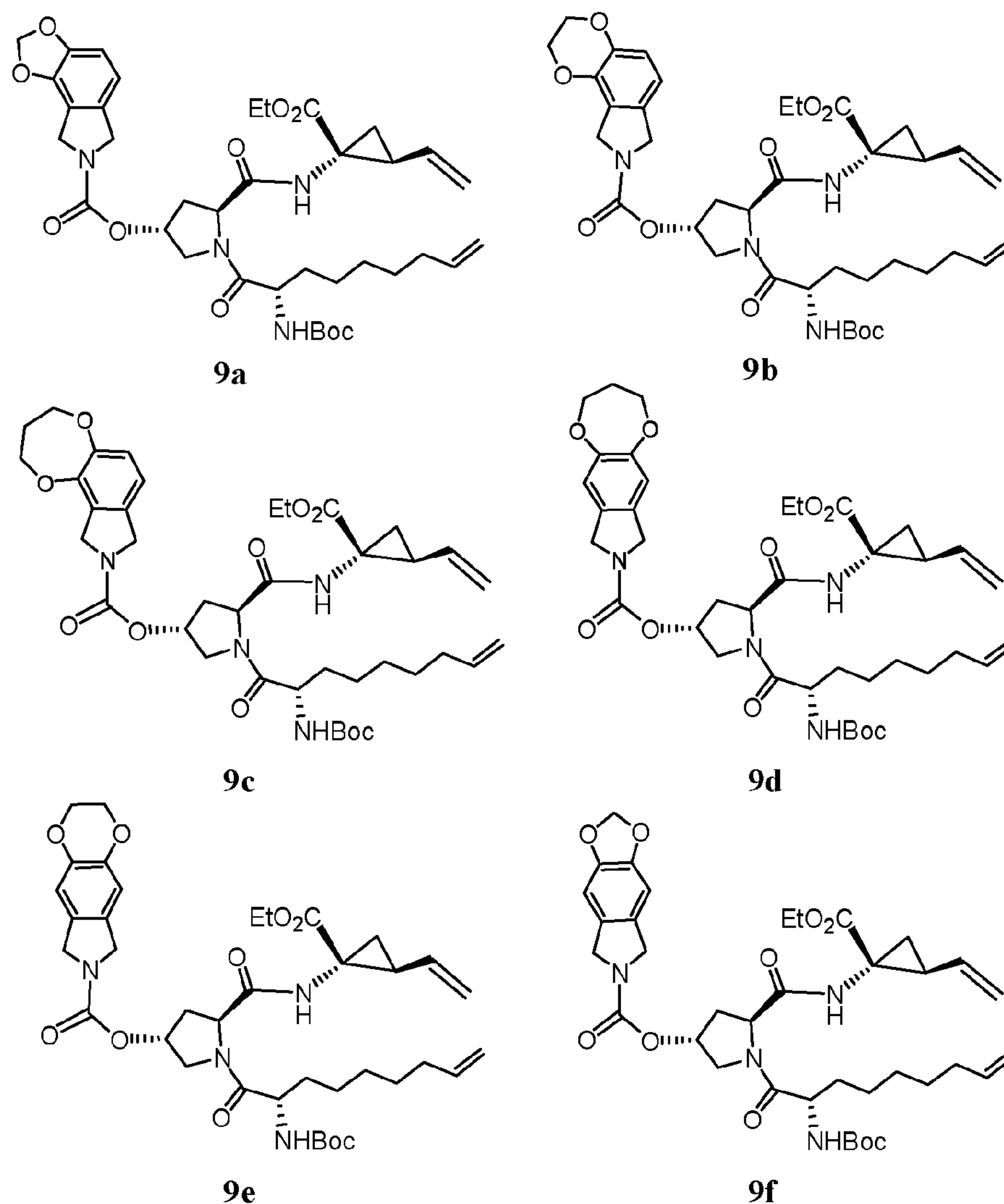
After the key intermediates **4a-4f** and **6a-6f** were prepared, there were several synthetic
5 methods developed as in Schemes 4-11 for preparation of different kinds of new HCV inhibitors.
The detail for each reaction condition and analytical results of products is listed in the detailed
examples.

Scheme 4:



In Scheme 4 above, the product 4 (e.g., compounds 4a-4f and 6a-6f) prepared as shown in Scheme 3 was deprotected to obtain an intermediate carboxylic acid (5) by removing HCl group, followed by amidation with an N-Boc protected amino acid SM-5 to form compound 6 in the presence of coupling reagent HATU. After hydrolysis of compound 6 in LiOH-Water/MeOH solution, another carboxylic acid (7) was obtained, and followed by amidation with another amino acid (methyl or ethyl ester) SM-6 in the presence of coupling reagent HATU to form product 9 (e.g., compounds 9a-9f in Figure 2-1). In anhydrous oxygen-free organic solvents (DCM, DCE, or toluene), Diene 9 intermediate was carried out an olefin ring-closing metathesis (RCM) reaction in the presence of metathesis catalyst (e.g., Zhan catalyst-1 or Zhan catalyst-1B used in this invention) at 20-80 °C to form 14-16 membered macrocyclic olefin-linked product 10, then the methyl/ethyl ester was hydrolyzed with LiOH in water-MeOH solution to offer a new carboxylic acid 11. Finally, in the presence of a coupling reagent such as EDCI or HATU, the carboxylic acid 11 reacted with different kinds of alkylsulfonamide, cycloalkylsulfonamide or arylsulfonamide

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 [RdS(O)₂NH₂], respectively, to form a series of novel polyheterocyclic based macrocyclic compounds **1a-1b**, such as **12a-12xx** shown in Figure 4).



5

Figure 2-1: Structure of Compounds **9a-9f**

The structure of Zhan catalysts (Zhan Catalyst-1 & 1B) used for RCM of diene intermediate **9** is shown in Figure 3:

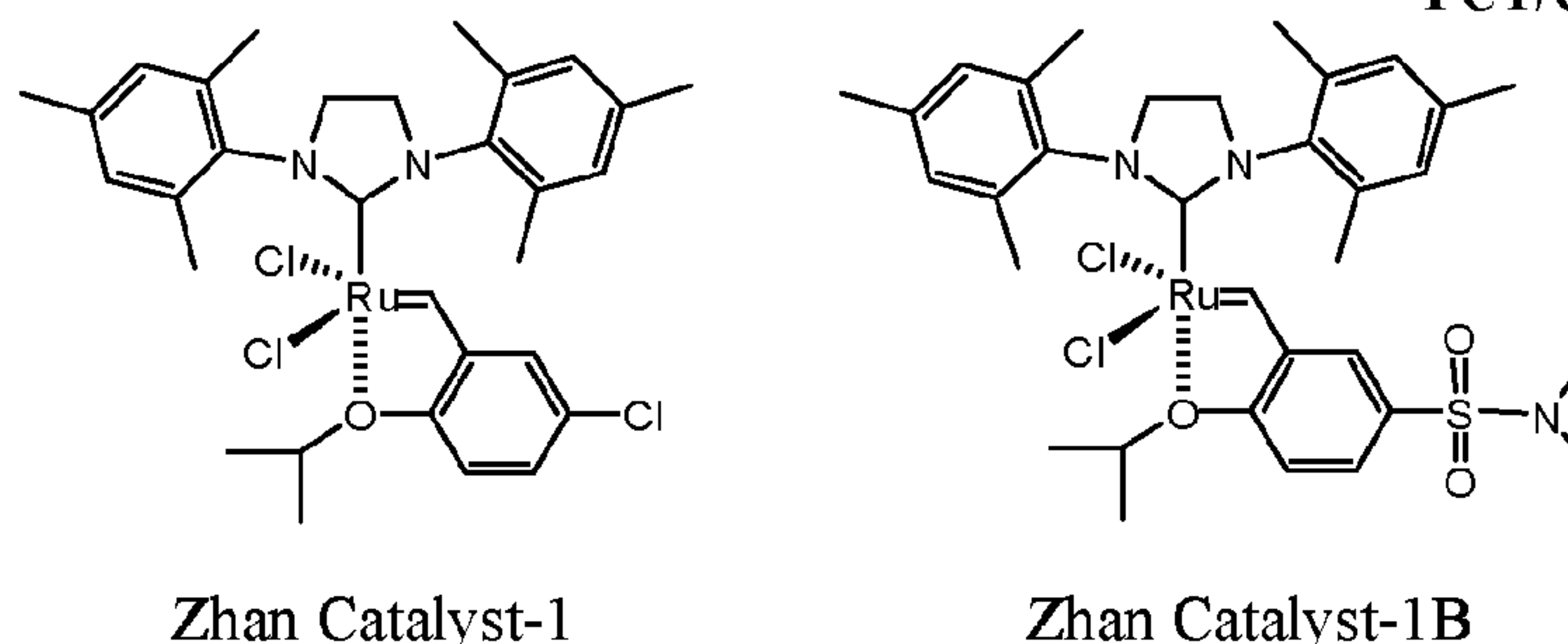
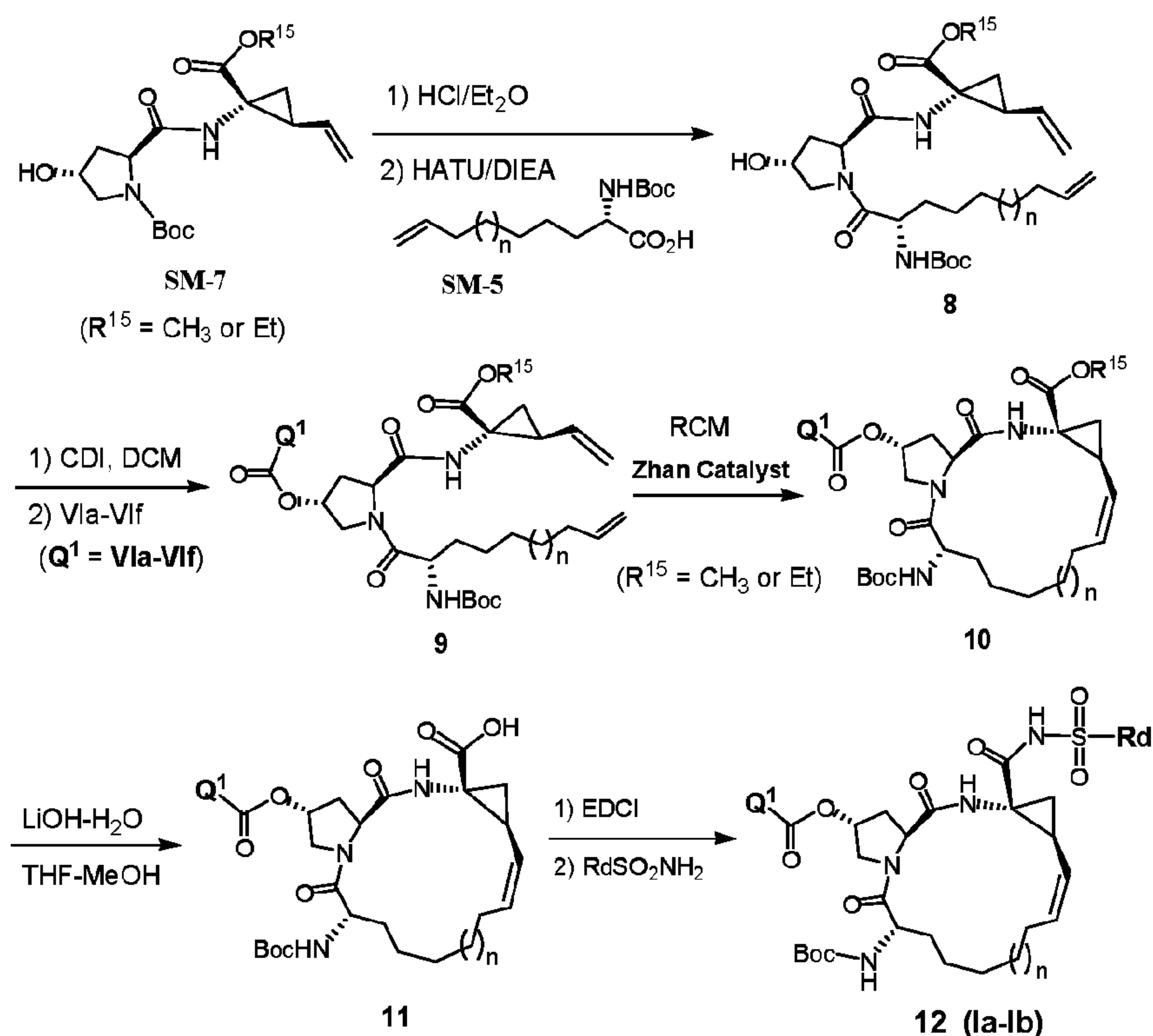


Figure 3: Structure of Zhan catalyst-1 and Zhan Catalyst-1B

In order to obtain more compounds efficiently for potency screening, there is another alternative synthetic route developed effectively for preparation of different new macrocyclic compounds **Ia-Ib** in Scheme 5.

Scheme 5:



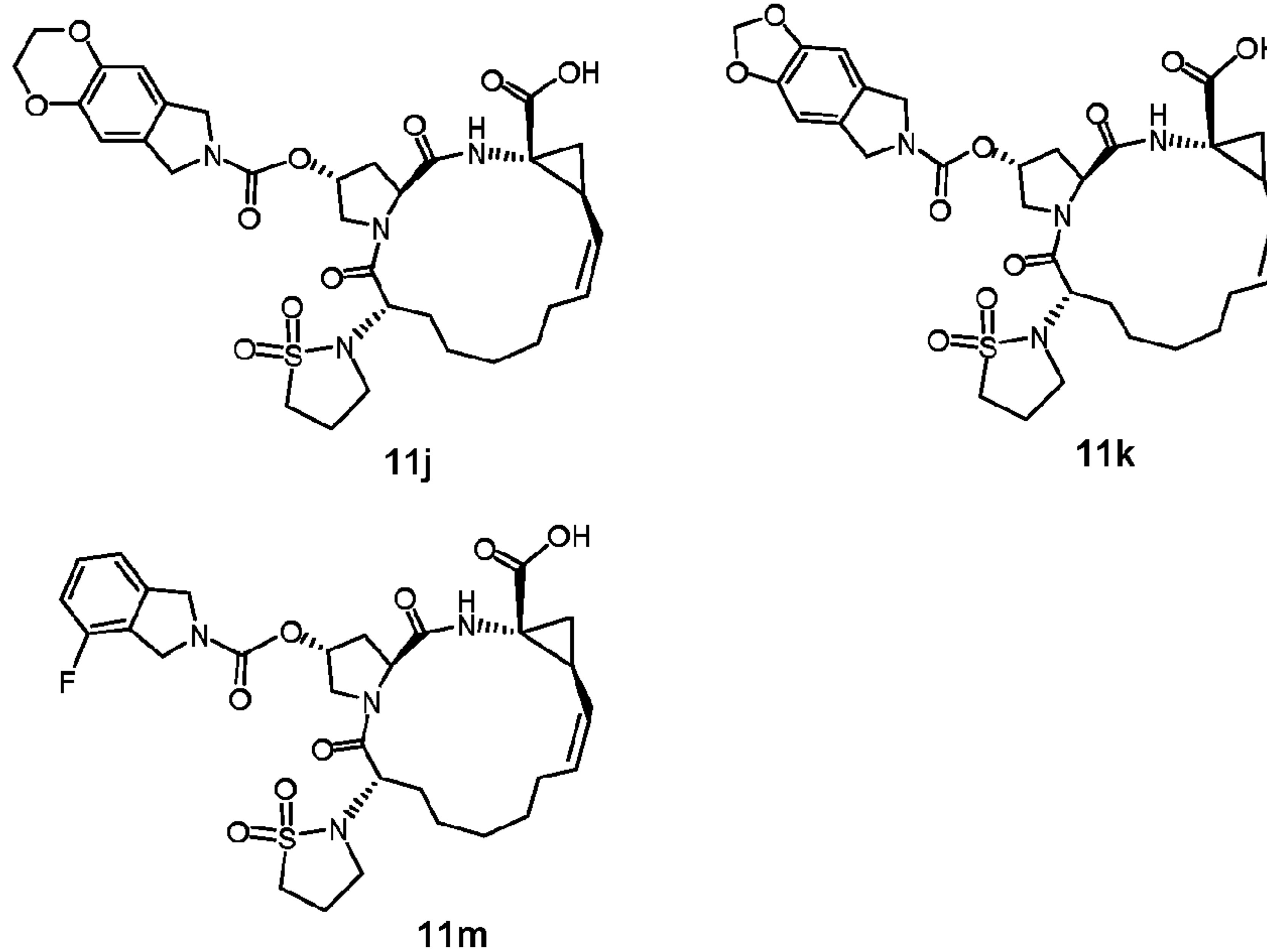
(wherein, $\text{Q}^1 = \text{VIa-VIf}$)

$n = 1$; SM-8a: $\text{Rd} = \text{cyclopropyl}$, SM-8b: $\text{Rd} = \text{isopropyl}$

In Scheme 5, first of all, the protecting group (Boc) in the starting material **SM-7** was removed by HCl acid, followed by amidation with an N-Boc protected amino acid **SM-5** to form compound **8** in the presence of coupling reagent HATU. In the presence of coupling reagent CDI,

5



Figure 4-1: Structure of Compounds **11a-11m**

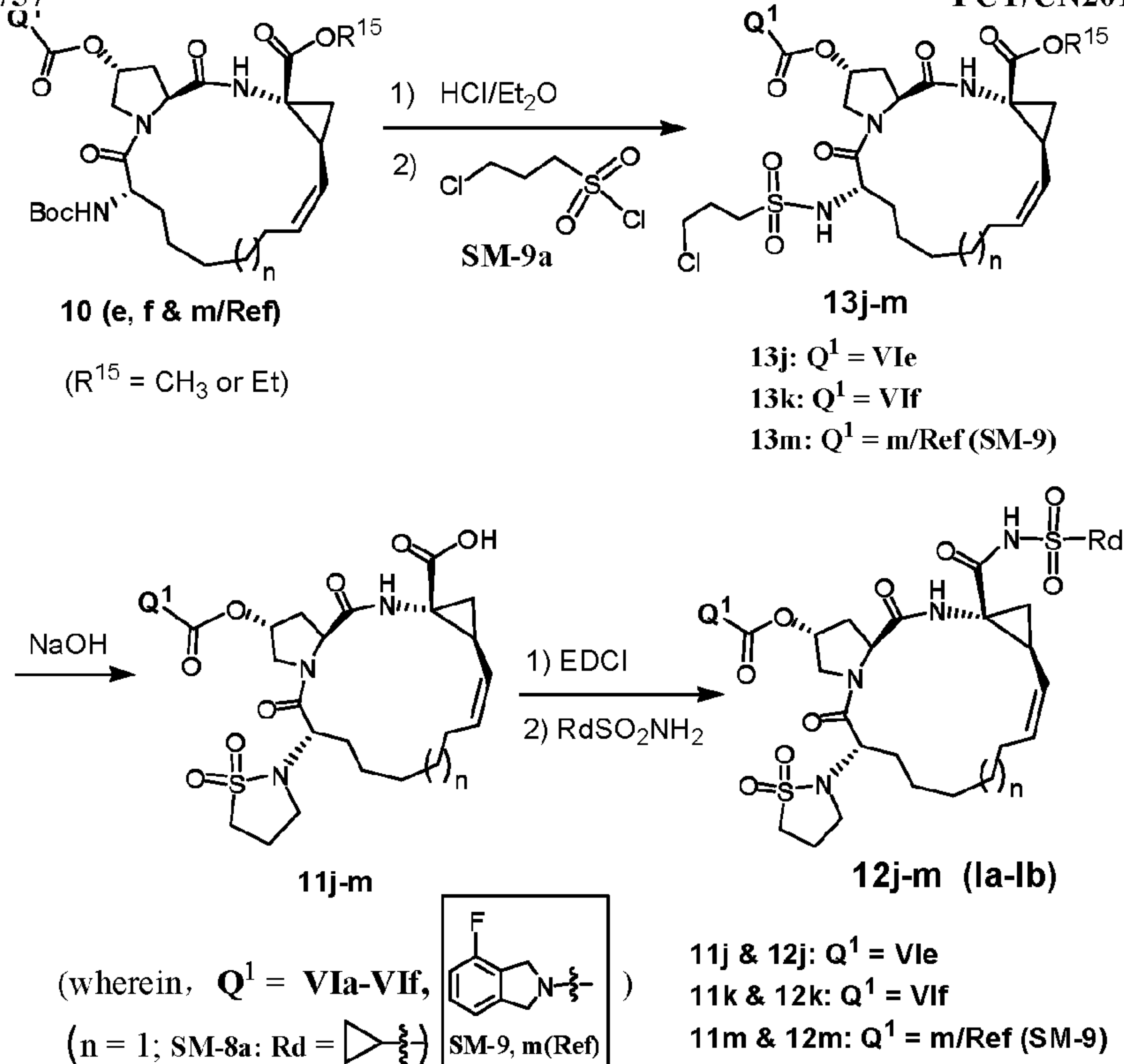
- 5 Finally, in the presence of a coupling reagent such as EDCI or HATU, the carboxylic acid product **11** reacted with different kinds of alkylsulfonamide, cycloalkylsulfonamide or arylsulfonamide [RdS(O)₂NH₂], respectively, to form a series of novel polyheterocyclic based macrocyclic compounds **1a-1b**.

10 In order to optimize efficacy and biological property of new HCV inhibitors, there are more structure modified compounds designed and synthesized in Schemes 6-11. In Scheme 6, there is a kind of cycloalkylsulfonamide products prepared for potency screening.

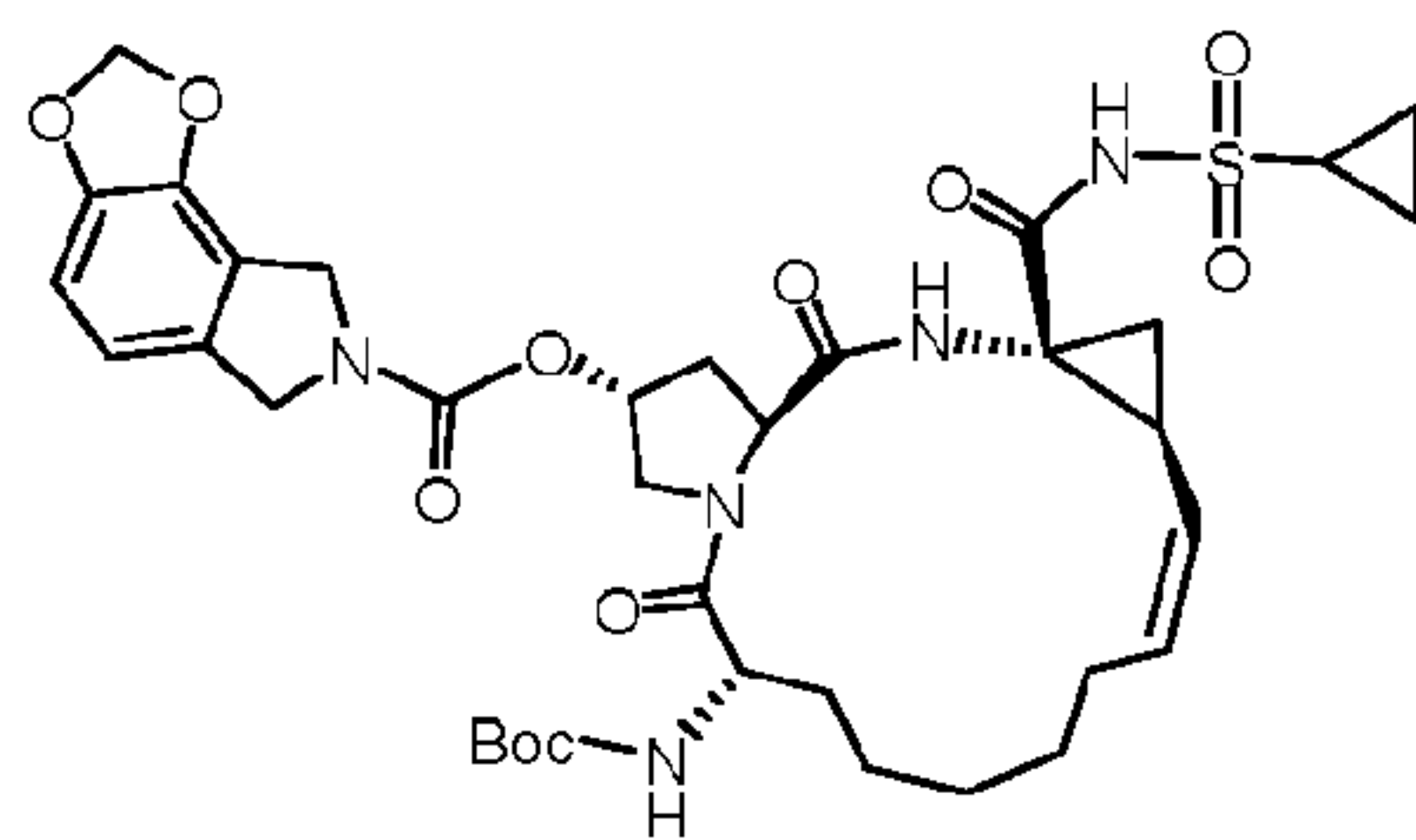
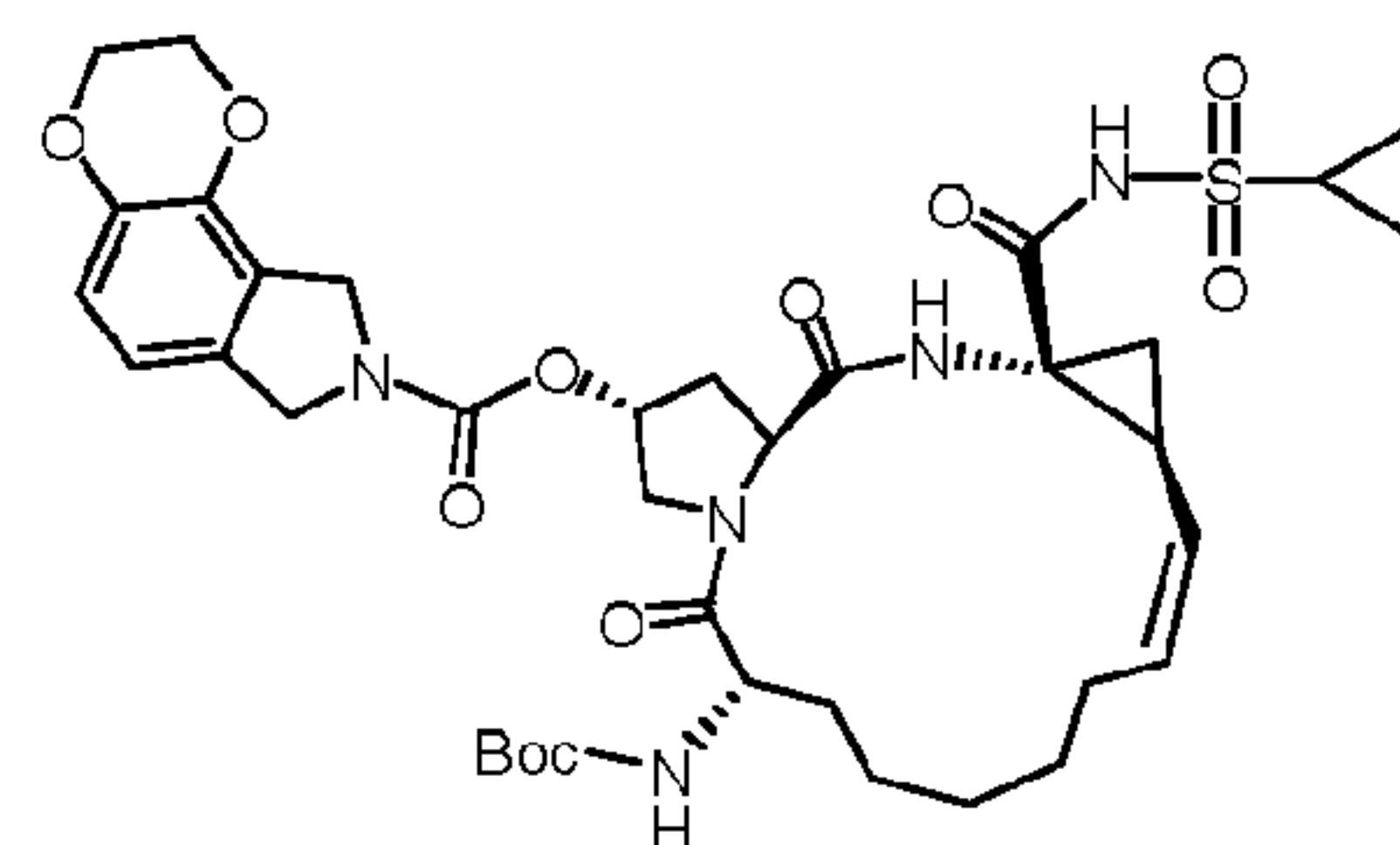
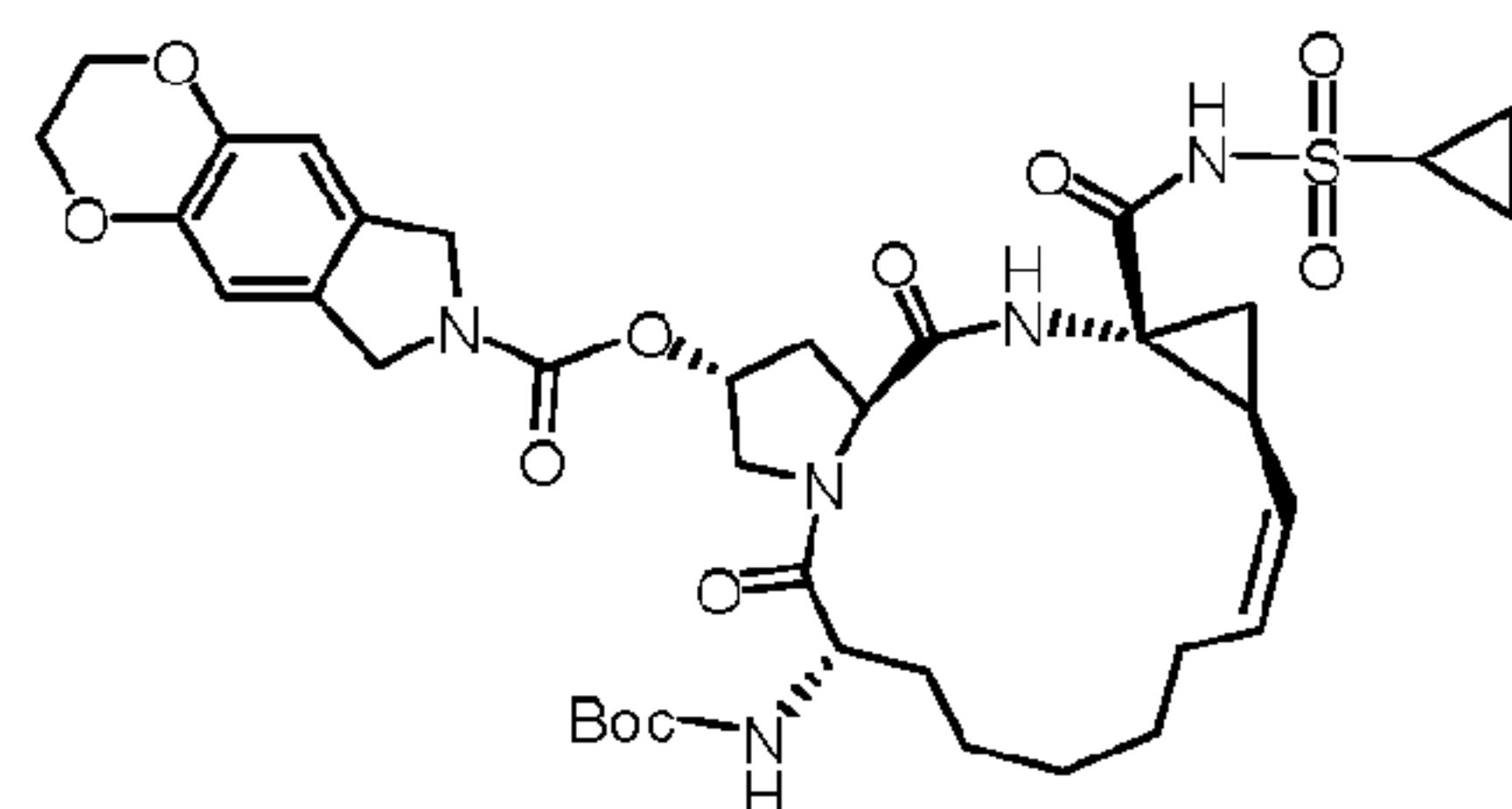
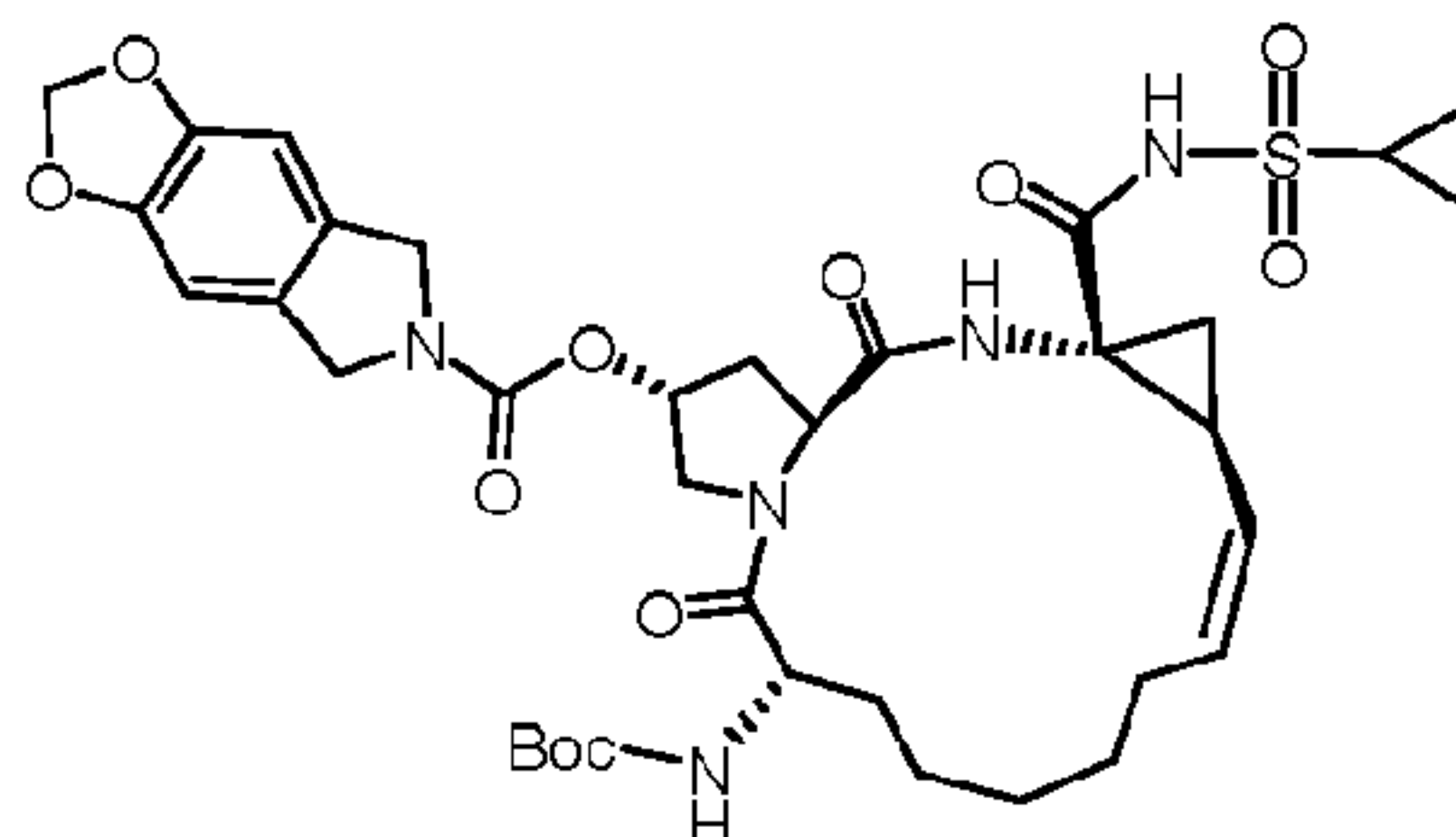
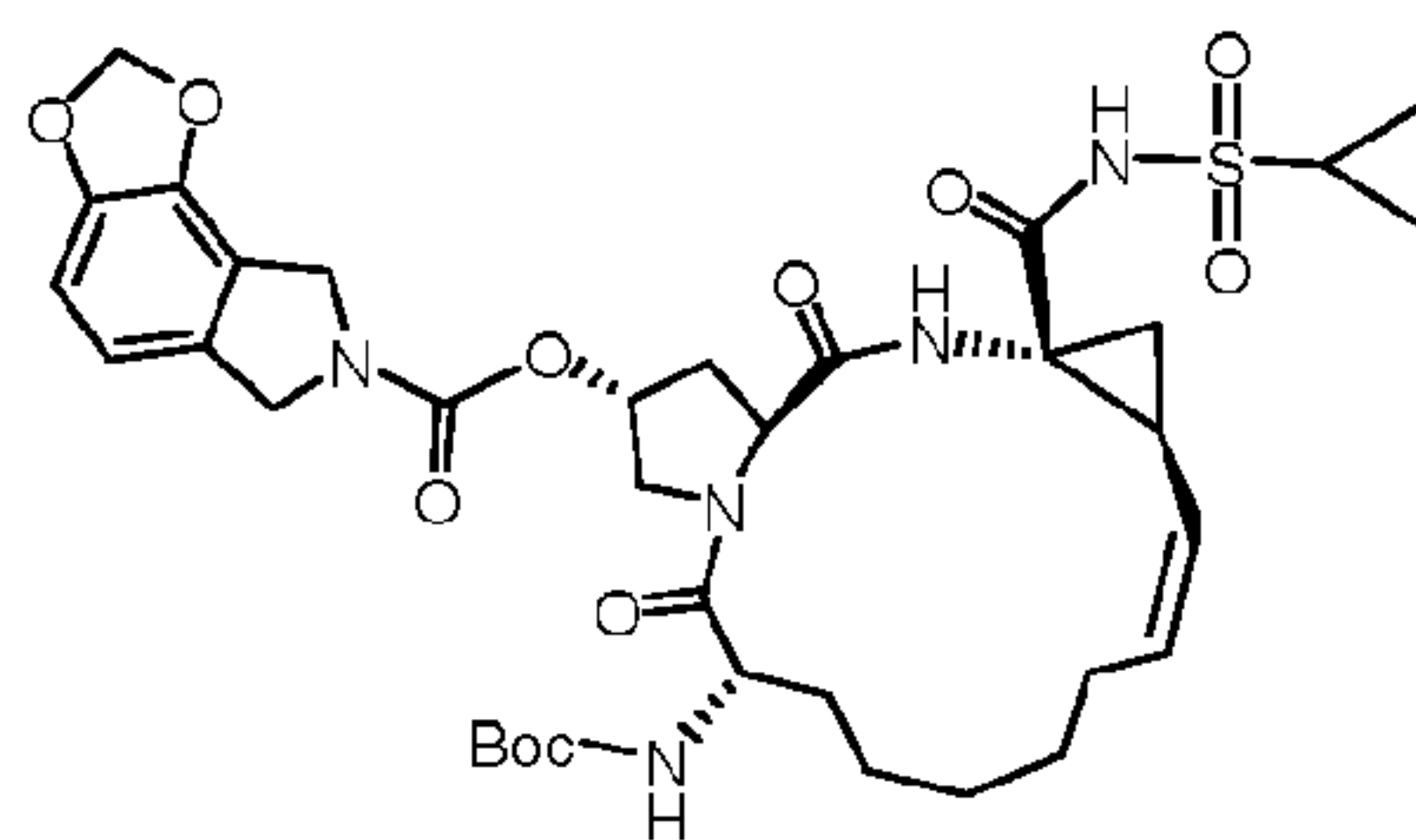
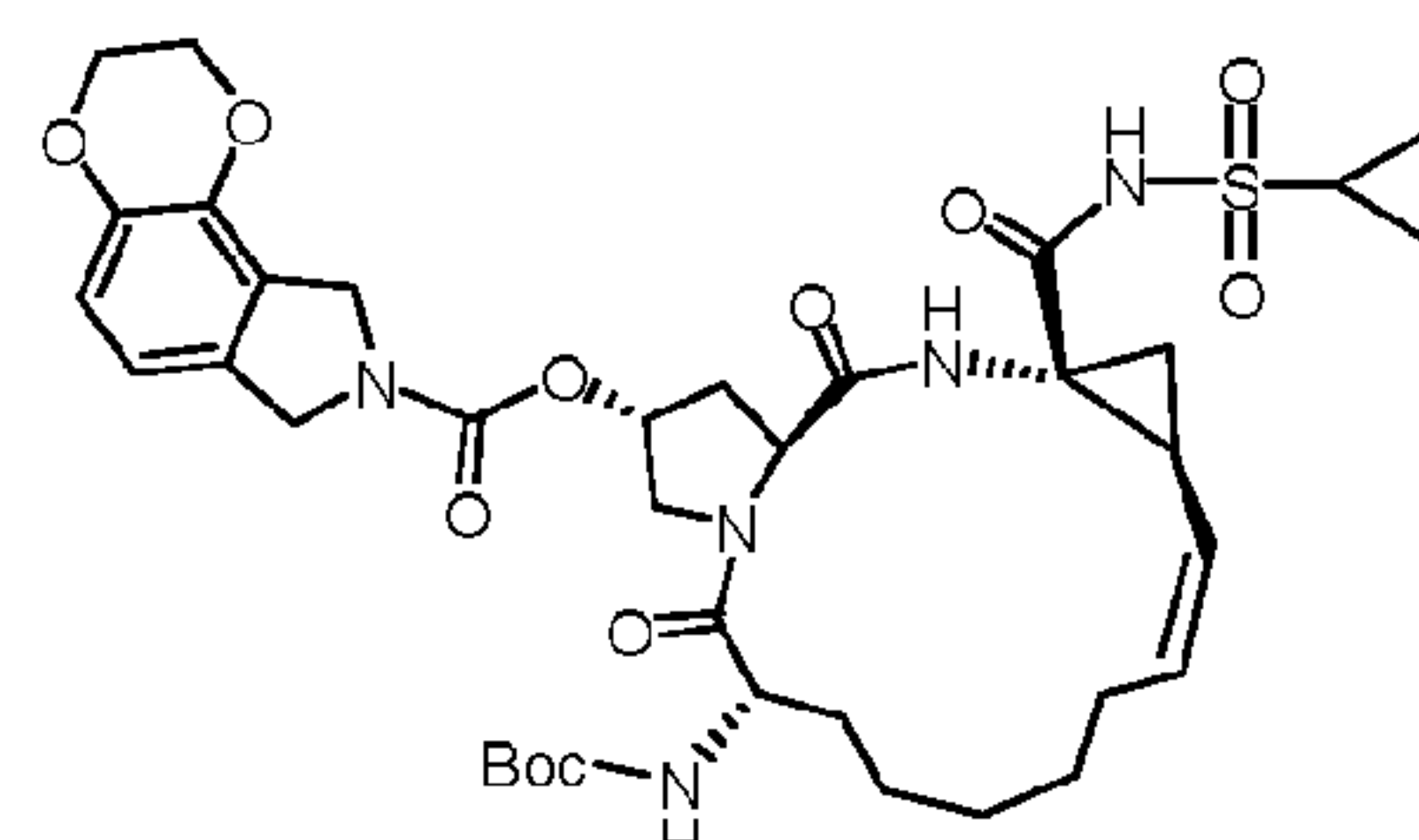
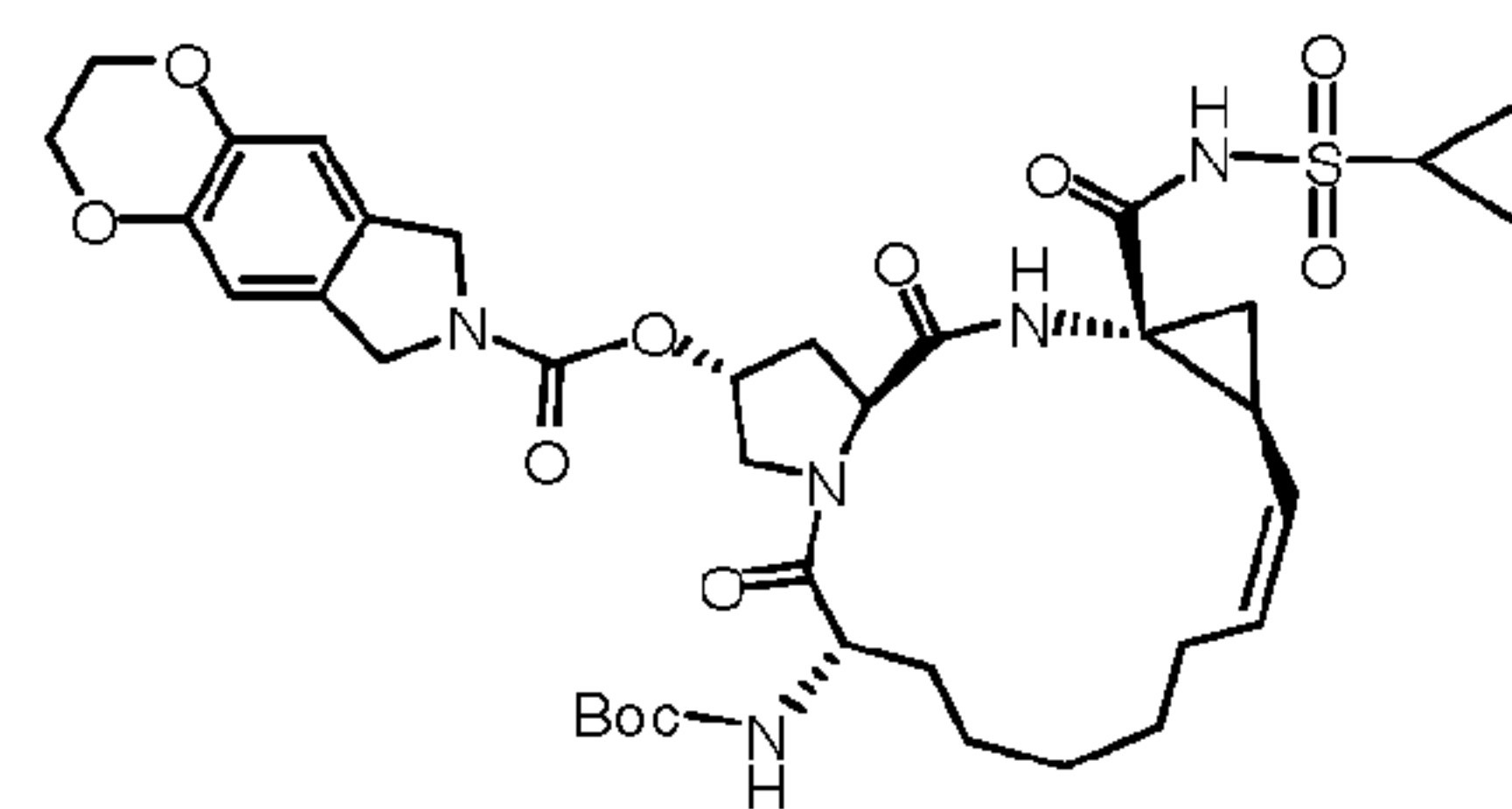
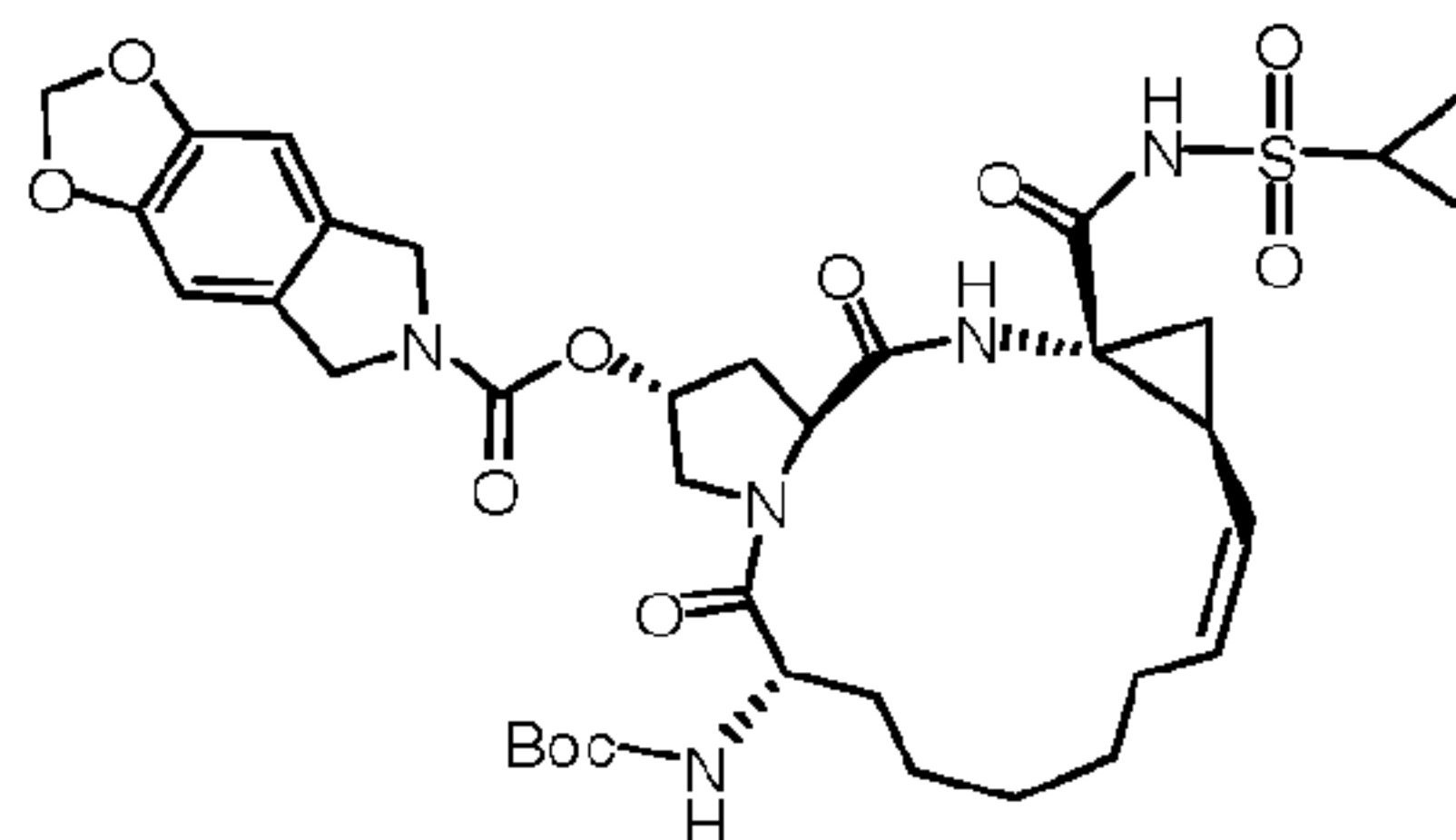
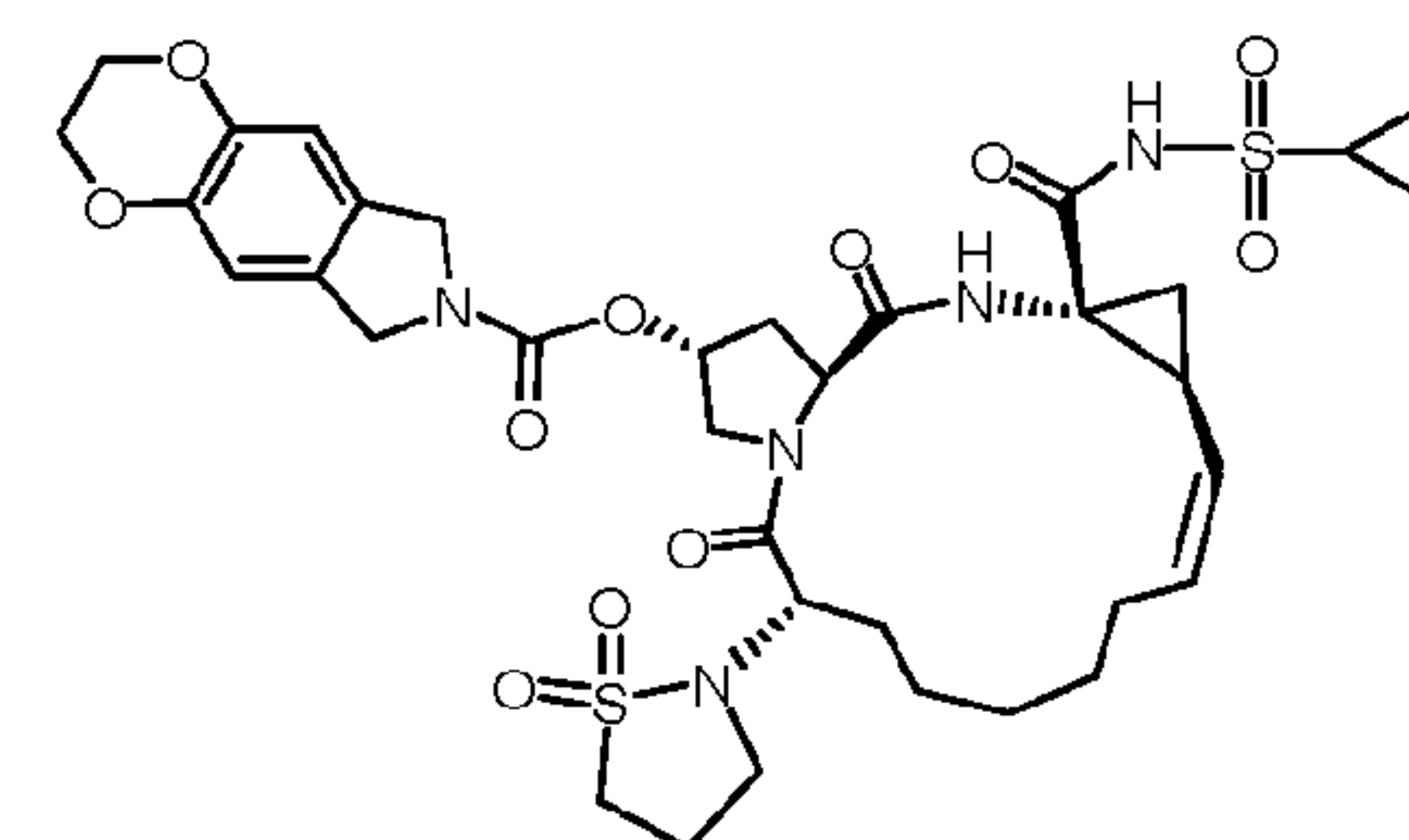
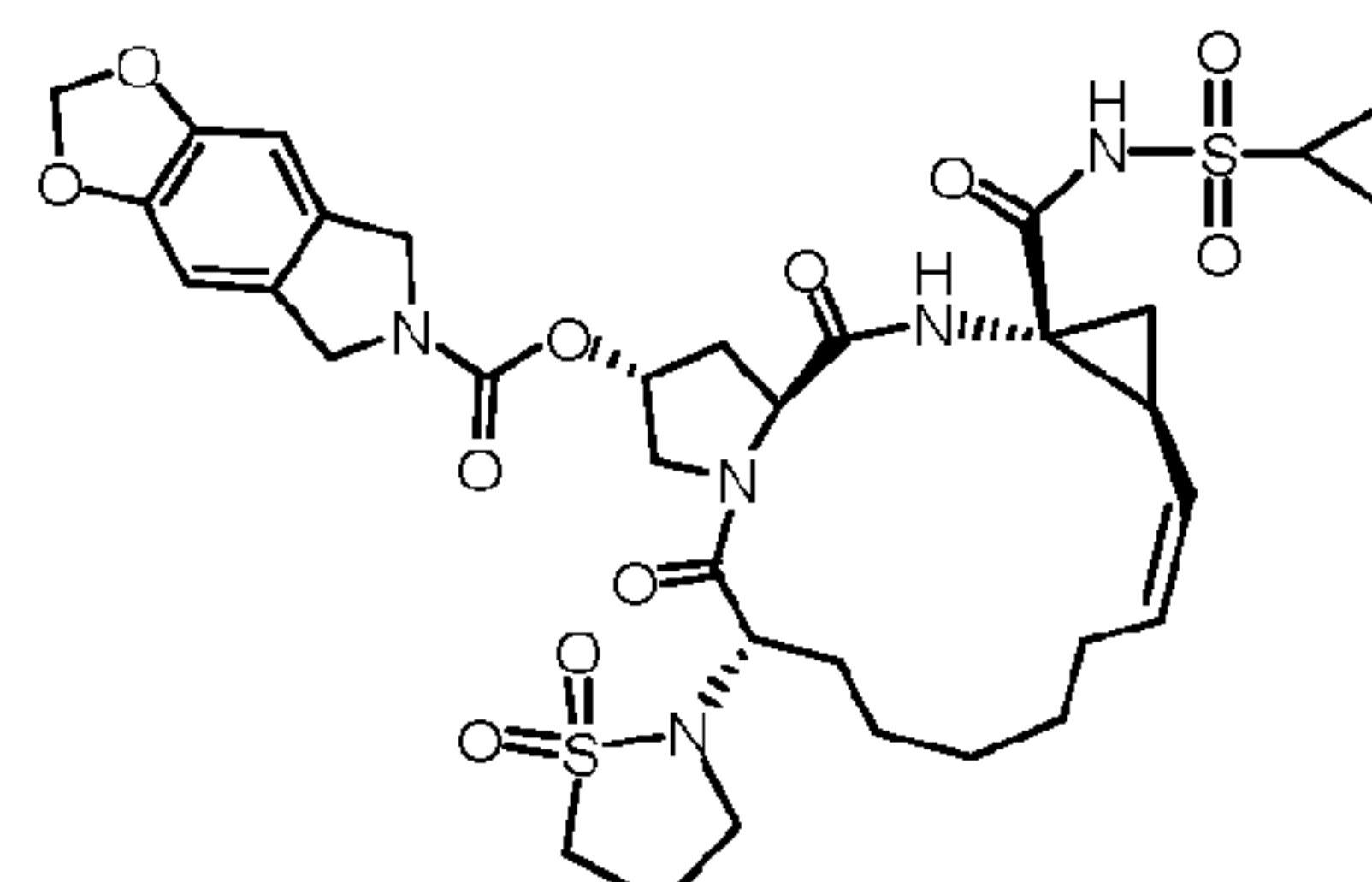
Scheme 6:

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In Scheme 6 above, the compound **10c-d** prepared in Schemes 4 and 5 were used for deprotection first by removing Boc with HCl acid, followed by amidation with an alkylsulfonyl chloride reagent (RdSO_2Cl or $\text{R}^{17}\text{SO}_2\text{Cl}$, **SM-9**) to obtain an alkylsulfonamide product **13**. In the presence of inorganic base (e.g., NaOH or KOH), the intramolecular cyclization was conducted to form sulfonamide compound **11**. Finally, in the presence of a coupling reagent such as EDCI or HATU, the carboxylic acid **11** reacted with different kinds of alkylsulfonamide, cycloalkylsulfonamide or arylsulfonamide [$\text{RdS(O)}_2\text{NH}_2$, **SM-8**], respectively, to form a series of novel polyheterocyclic based macrocyclic compounds **Ia-Ib**, such as **12j-12m** as shown in the following Figure 5. Furthermore, the compound **10c-d** was deprotected first by removing Boc with HCl acid, followed by amidation with an alkylsulfonyl chloride reagent (RdSO_2Cl or $\text{R}^{17}\text{SO}_2\text{Cl}$, **SM-9**) to obtain another kind of alkylsulfonamide product **13**, then in the presence of a base (e.g., NaH), the alkylsulfonamide product **13** was reacted with another reagent $\text{R}^{16}\text{-Cl}$ (or $\text{R}^{16}\text{-Br}$, **SM-10**) to form another kind of new desired products **Ia-Ib (12s-12u)** as shown in Figure 5, wherein, R^{16} is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_1\text{-C}_6$ alkoxy carbonyl, $\text{C}_3\text{-C}_6$ cycloalkoxy carbonyl, $\text{C}_6\text{-C}_{10}$ aryl, $\text{C}_6\text{-C}_{10}$ aryl carbonyl, $\text{C}_6\text{-C}_{10}$ aryloxy carbonyl or $\text{C}_2\text{-C}_{10}$ heterocyclic group.

**12a****12b****12c****12d****12e****12f****12g****12h****12j****12k**

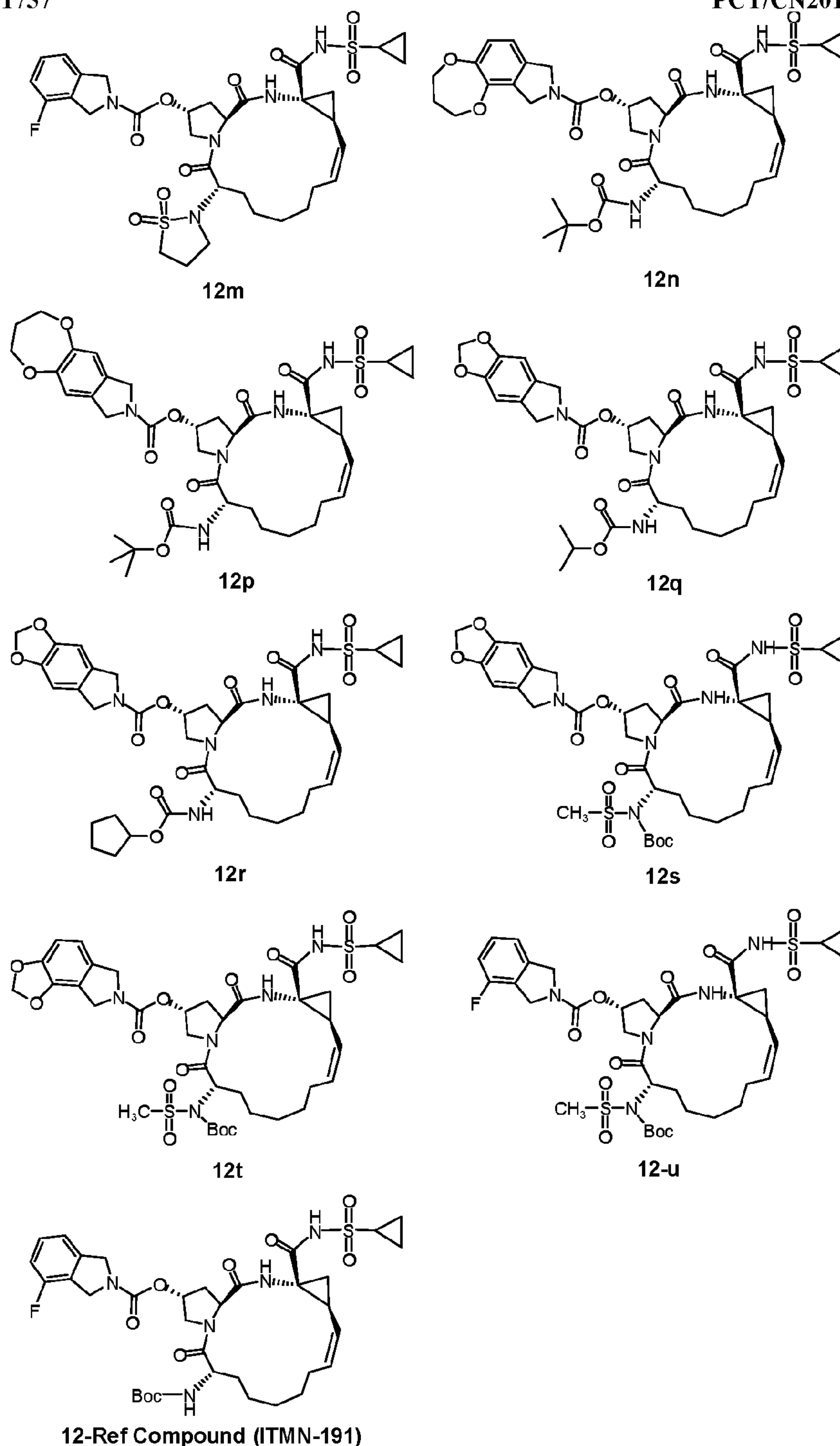
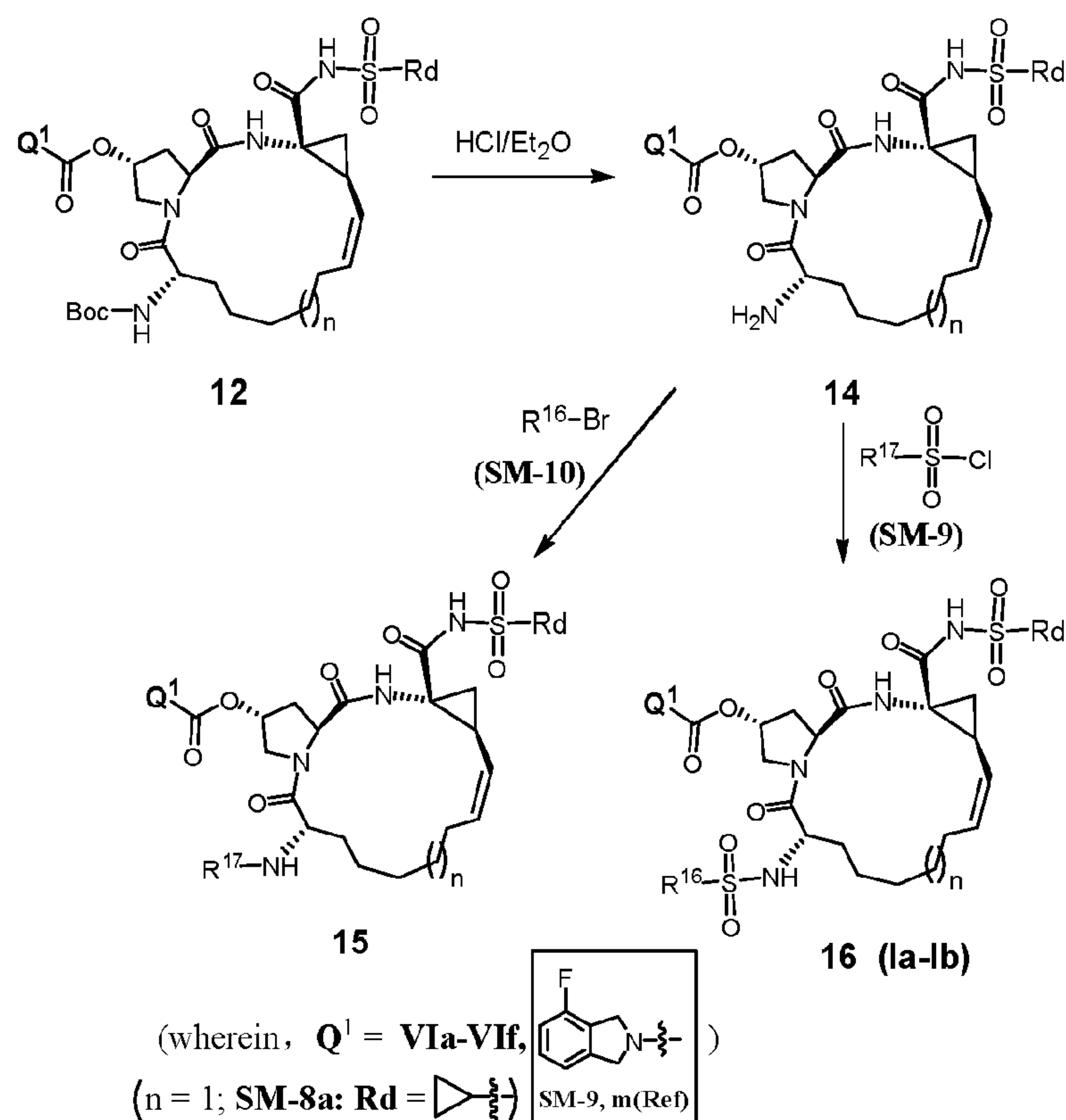


Figure 5: Structure of Compounds 12a-12u and 12-Ref

In the following Scheme 7, the product **12** (e.g., **12a-12f** and **12-Ref**) was used for
 5 deprotection first by removing Boc with HCl acid, followed by either alkylation or amidation with
 reagent **SM-10** (R^{16} -Cl or R^{16} -Br) to obtain an N-alkylated product **15** or amidation with an
 alkylsulfonyl or arylsulfonyl chloride reagent **SM-8** [R^{17} S(O)₂Cl] to form product **16**, wherein R^{16}

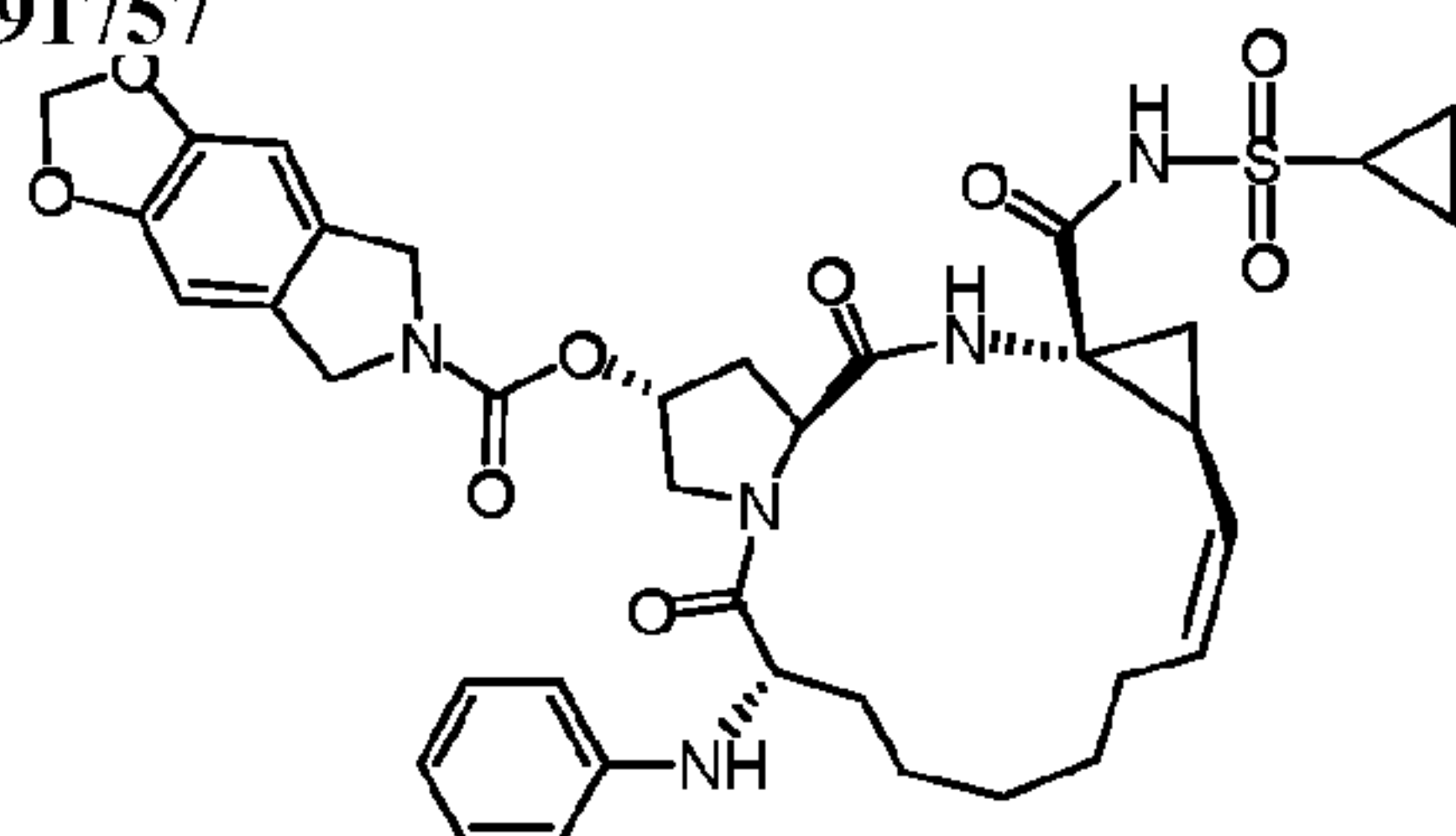
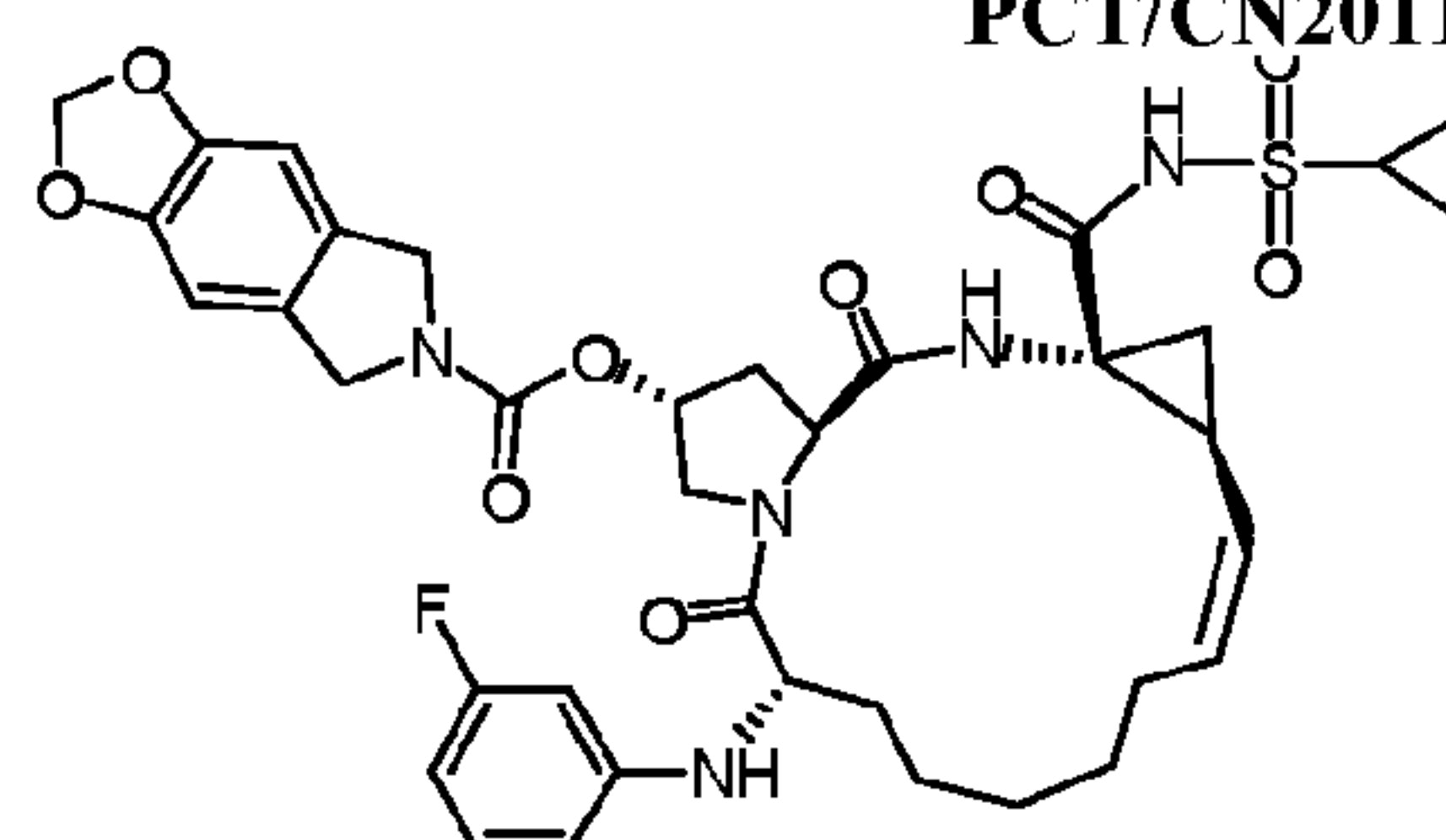
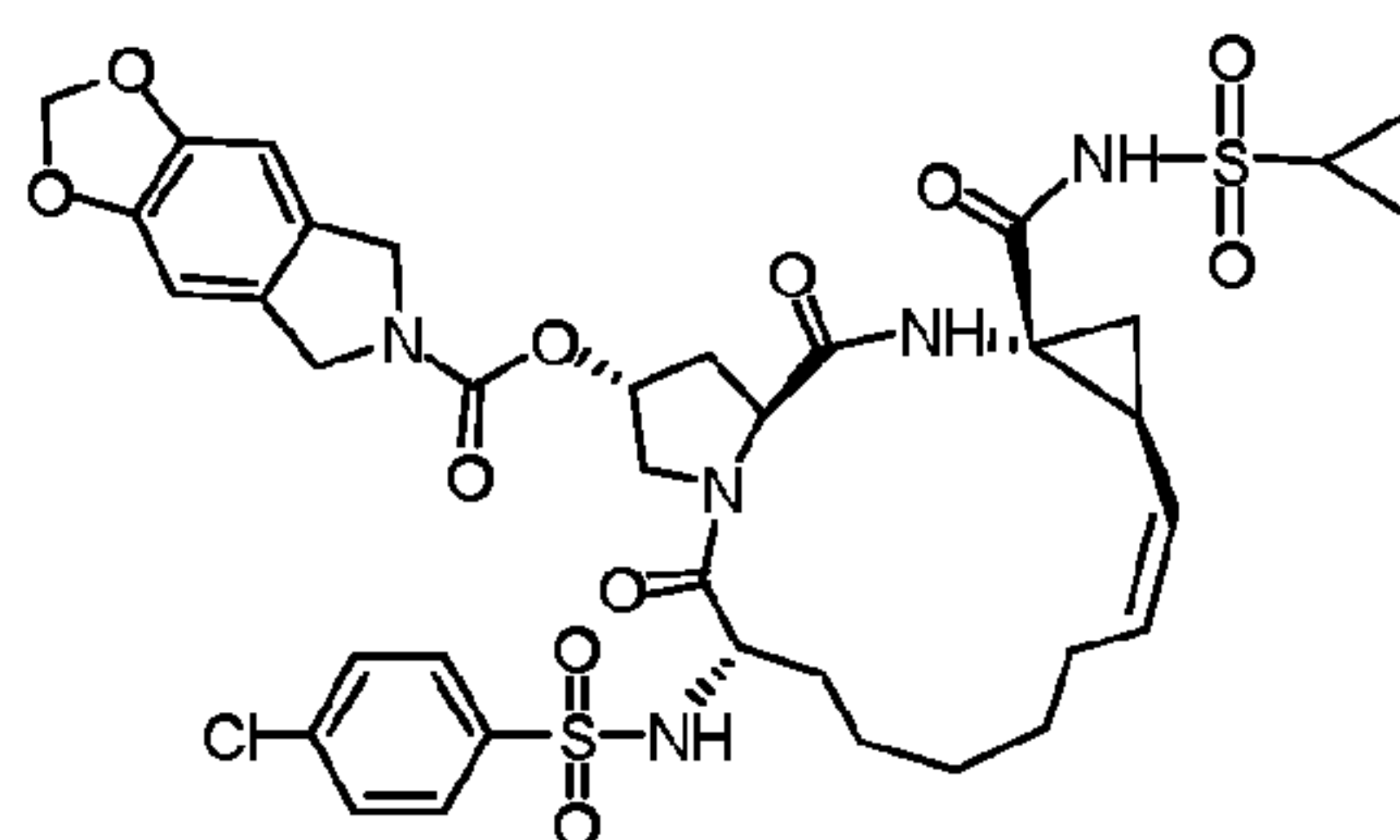
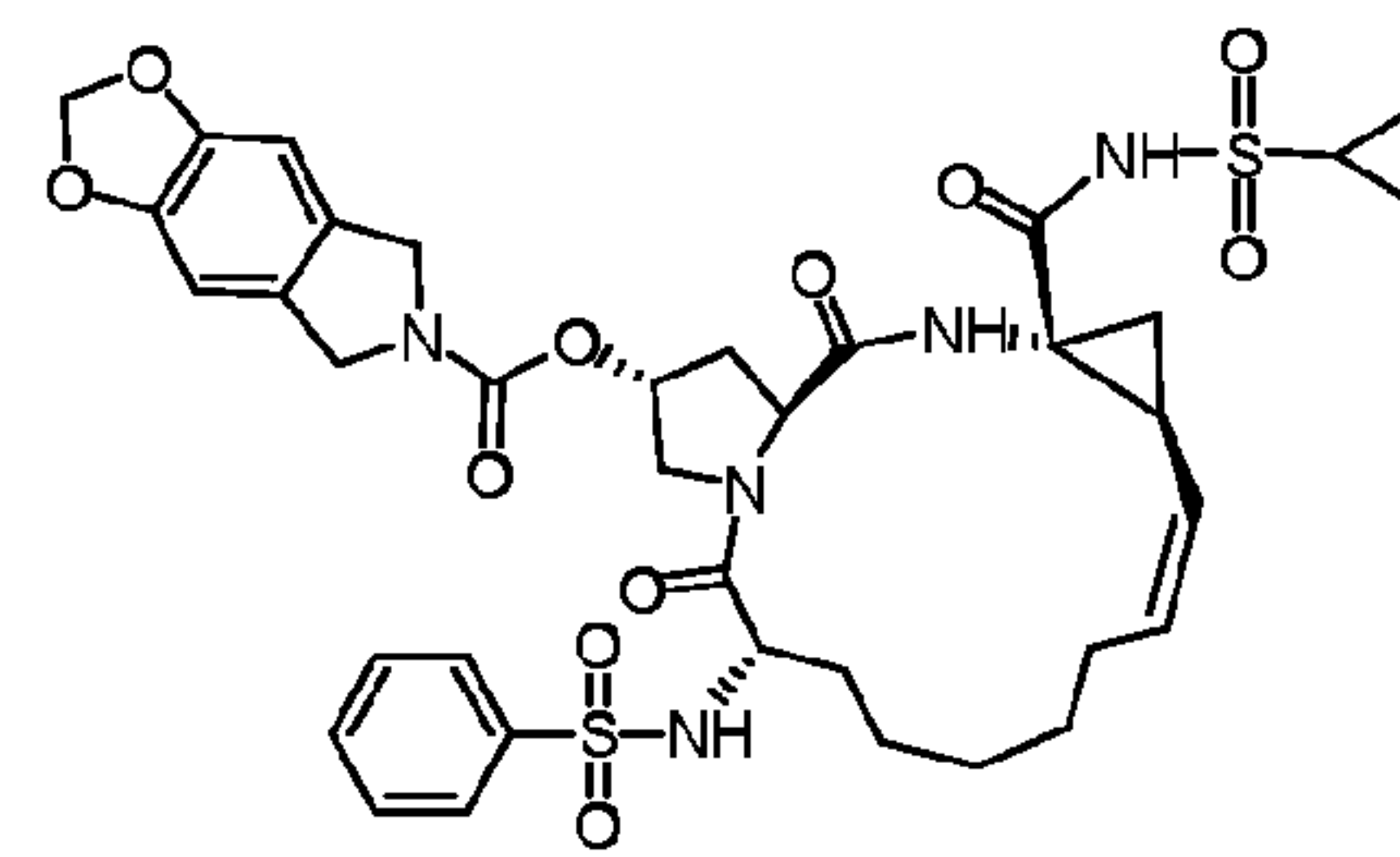
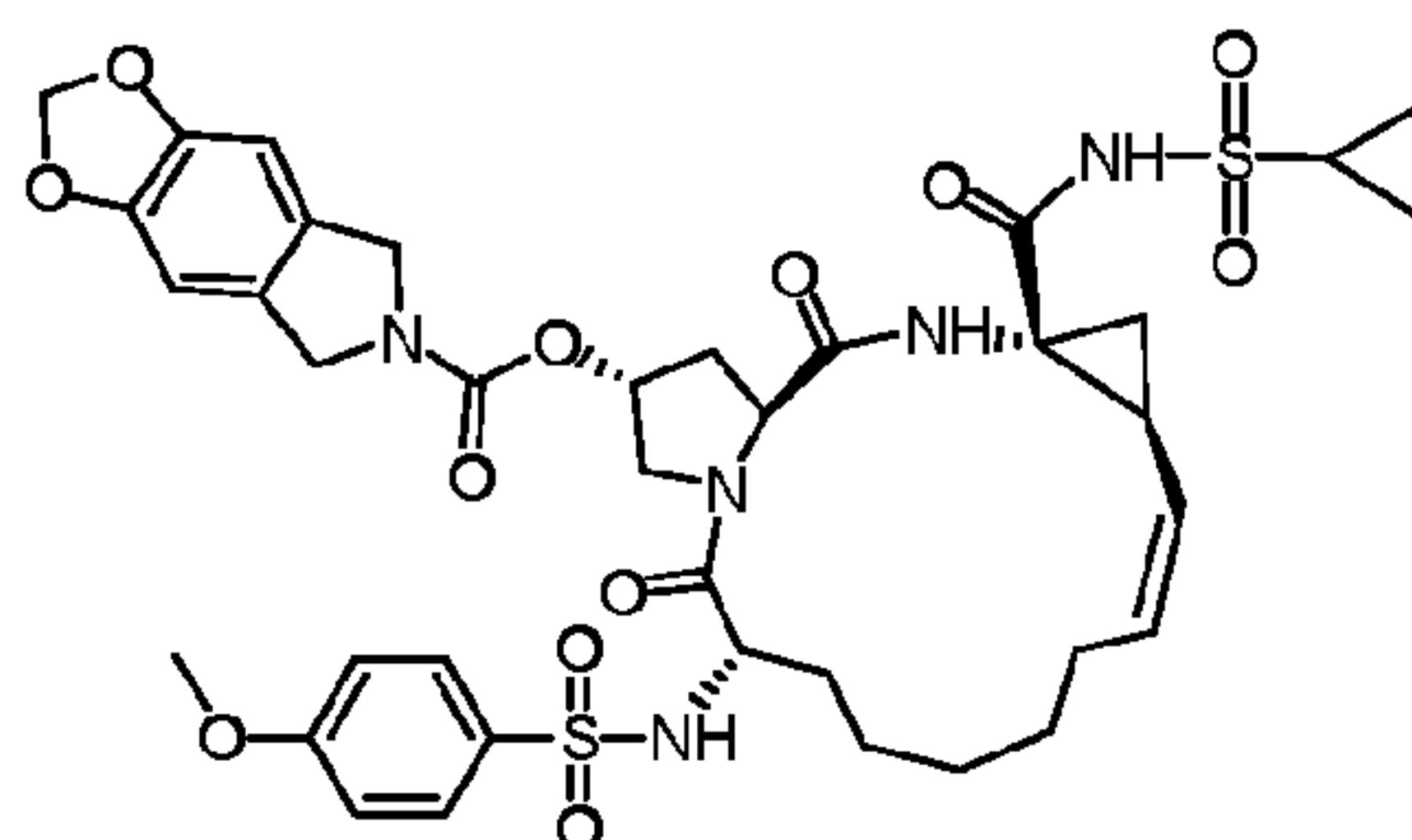
and R^{17} each is C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy carbonyl, C_3 - C_6 cycloalkoxy carbonyl, C_6 - C_{10} aryl, C_6 - C_{10} aryl carbonyl, C_6 - C_{10} aryloxy carbonyl or C_2 - C_{10} heterocyclic group, which generates more polyheterocyclic compounds **15a-15b** and **16a-16c** shown in Figure 6.

5 Scheme 7:



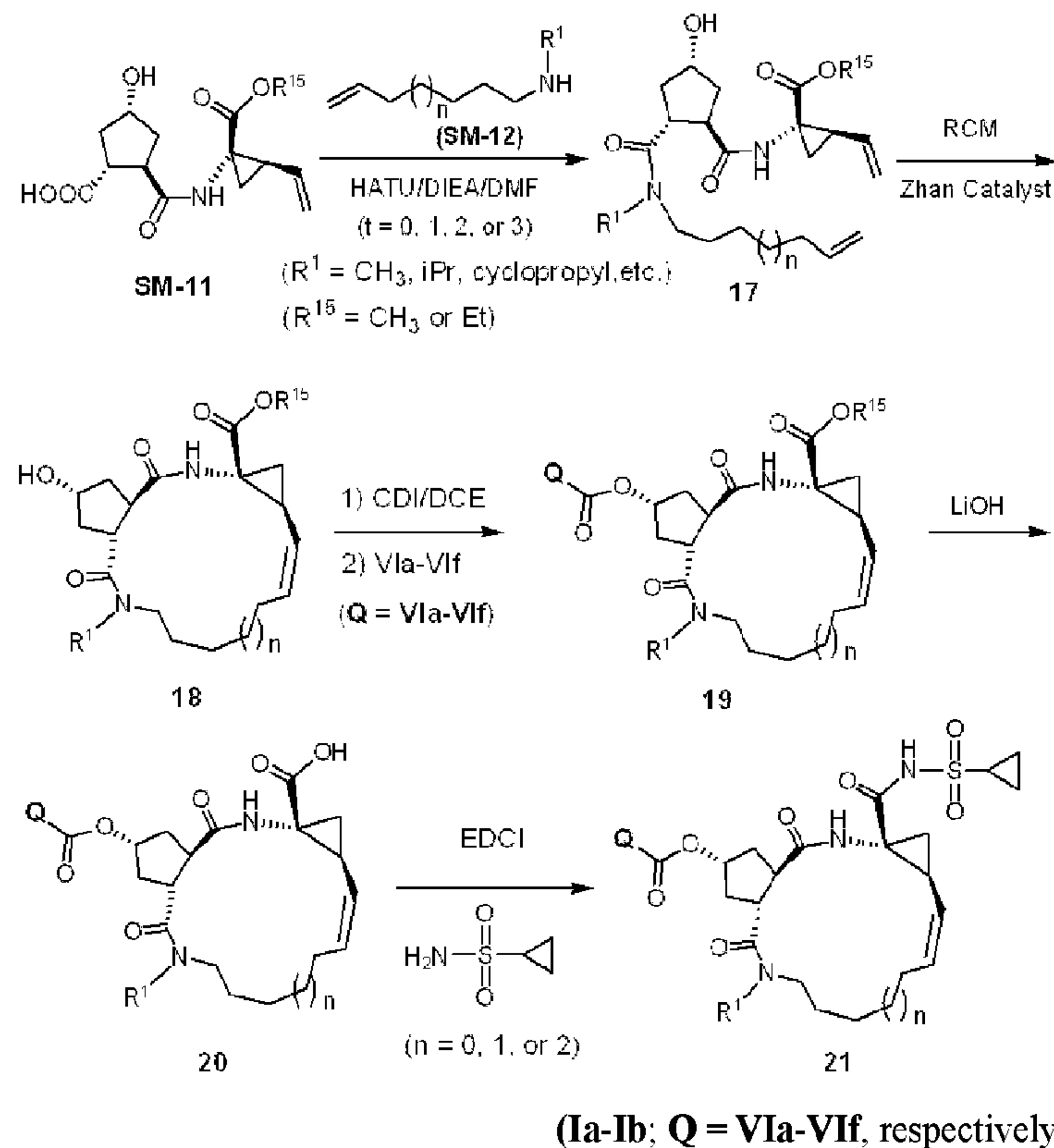
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**15a****15b****16a****16b****16c**Figure 6: Structure of Compounds **15a-15b**, **16a-16c**

In order to optimize efficacy and biological property of new HCV inhibitors, there are two
 5 more different macrocyclic structure designed and synthesized in the following Schemes 8 and 9.

Scheme 8:



In Scheme 8, in the presence of coupling reagent HATU, an acid **SM-11** was reacted with another amine **SM-12** to form a diene product **17** by amidation, followed by RCM reaction in the presence of Zhan catalyst-1B to form a 14-16 membered macrocyclic product **18**. In the presence of coupling reagent CDI, product **18** was reacted with compounds **VIa-VIi**, respectively to obtain polyheterocyclic compounds **21a-21f**, then the methyl/ethyl ester was hydrolyzed with LiOH in water-MeOH solution to offer a new carboxylic acid **11**. Finally, in the presence of a coupling reagent such as EDCI or HATU, the carboxylic acid **20** reacted with different kinds of alkylsulfonamide, cycloalkylsulfonamide or arylsulfonamide [RdS(O)₂NH₂], respectively, to form a series of novel polyheterocyclic based macrocyclic compounds **Ia-Ib (21a-21j)**, which structures are shown in the following Figure 7.

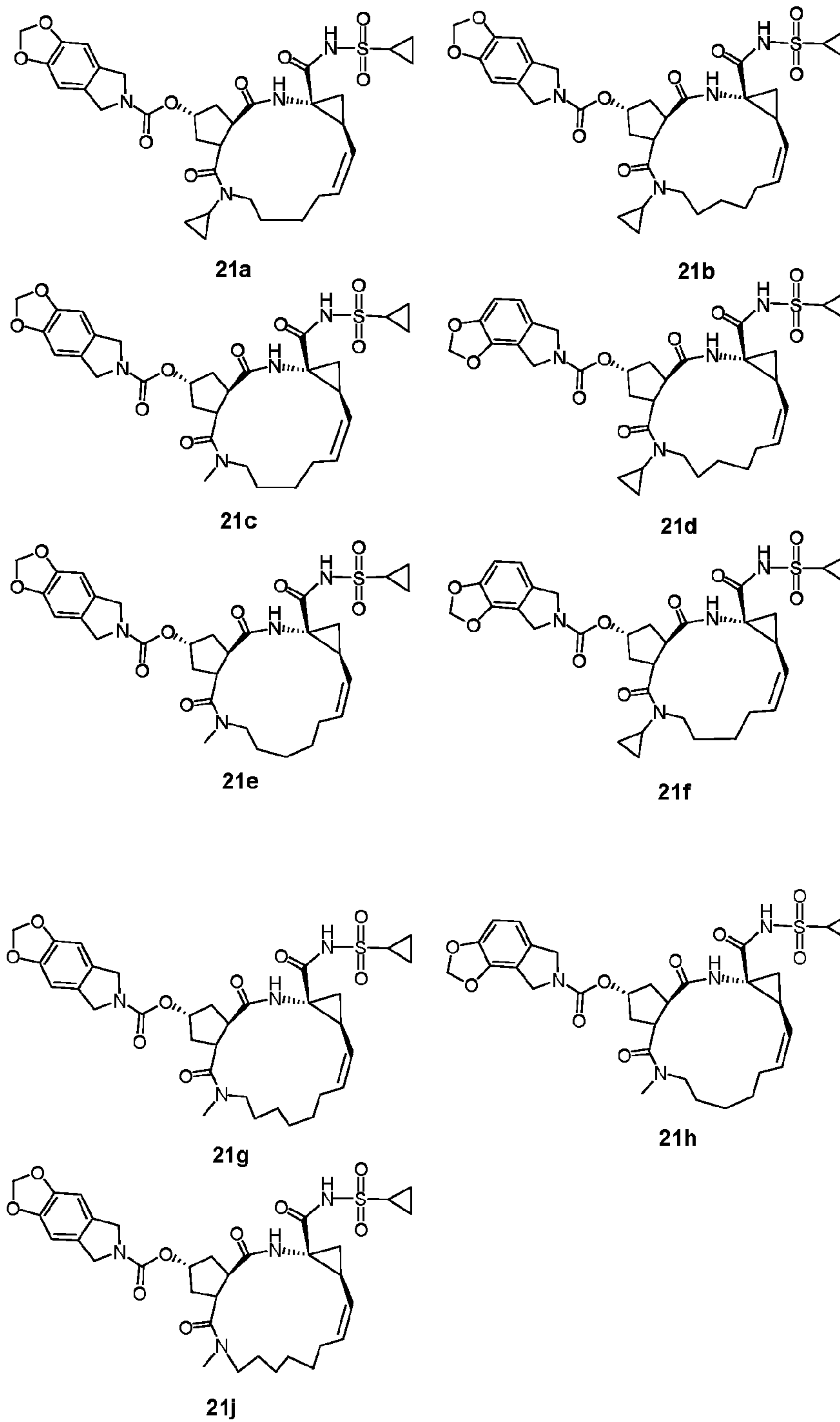
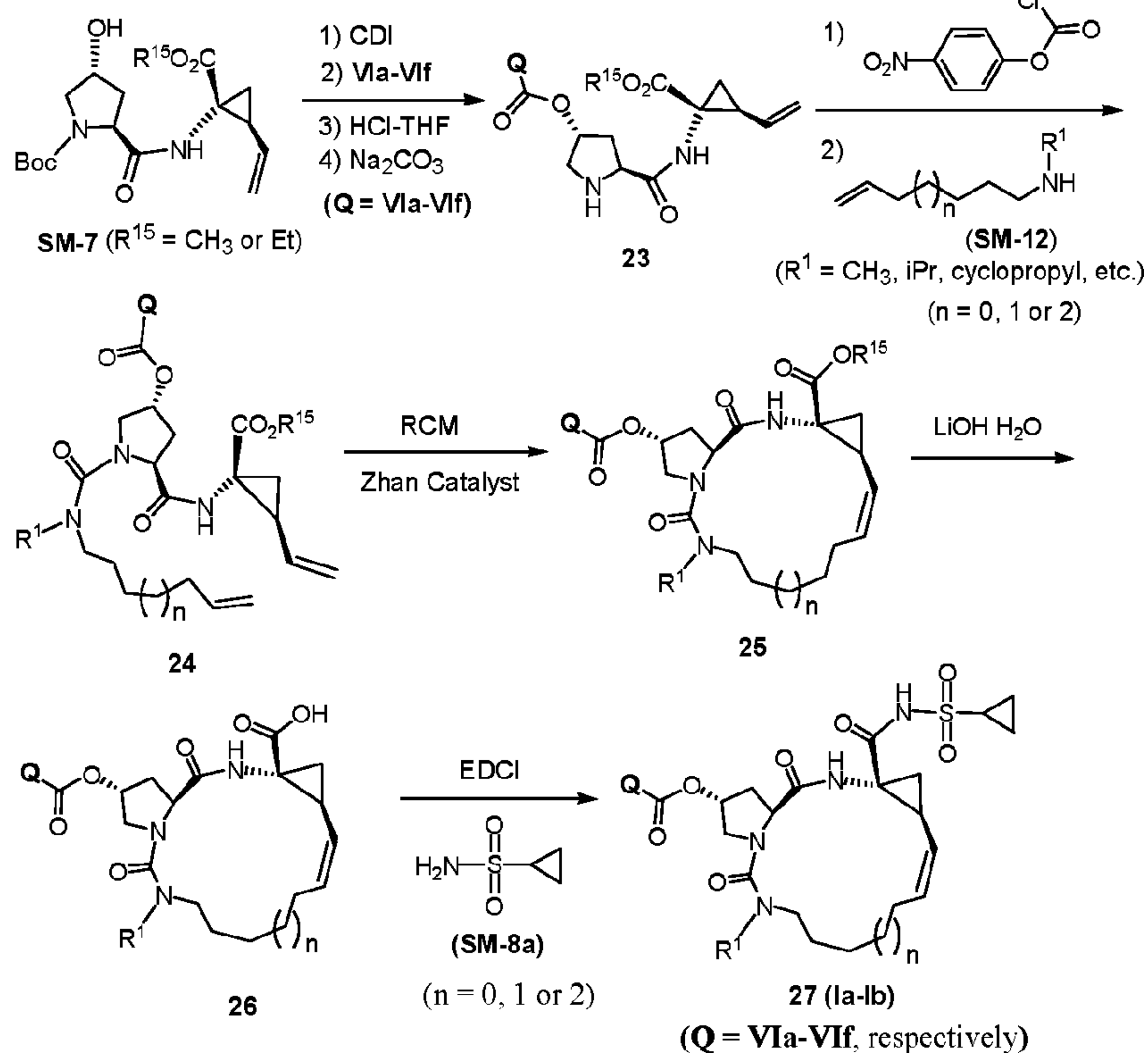


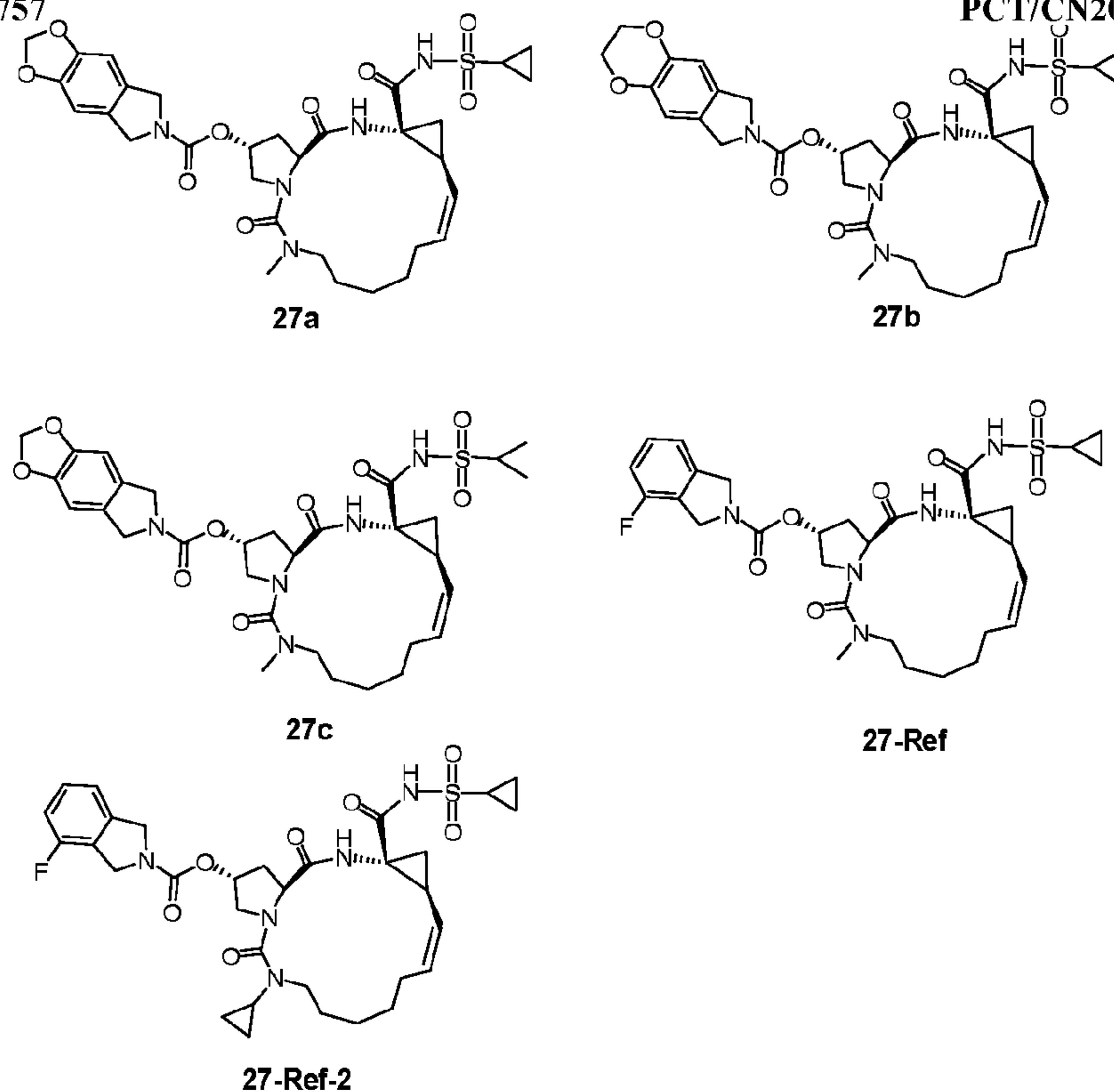
Figure 7: Structure of Compounds 21a-21j



In Scheme 9, in the presence of coupling reagent CDI, SM-7 was reacted with compounds VIa-VIi, respectively to obtain polyheterocyclic compounds 23a-23f, followed by reacting with a reagent chloroformic acid 4-nitrophenyl ester and SM-12 to form a diene product 24. In the presence of Zhan catalyst-1B, the diene product 24 was conducted a RCM reaction to form a desired macrocyclic product 25, then the methyl/ethyl ester was hydrolyzed with LiOH in water-MeOH solution to offer a new carboxylic acid 26. Finally, in the presence of a coupling reagent such as EDCI or HATU, the carboxylic acid 26 reacted with different kinds of alkylsulfonamide, cycloalkylsulfonamide or arylsulfonamide [$\text{RdS}(\text{O})_2\text{NH}_2$], respectively, to form a series of novel polyheterocyclic based macrocyclic compounds Ia-Ib (27a-27c and 27-Ref), which structures are shown in the following Figure 8.

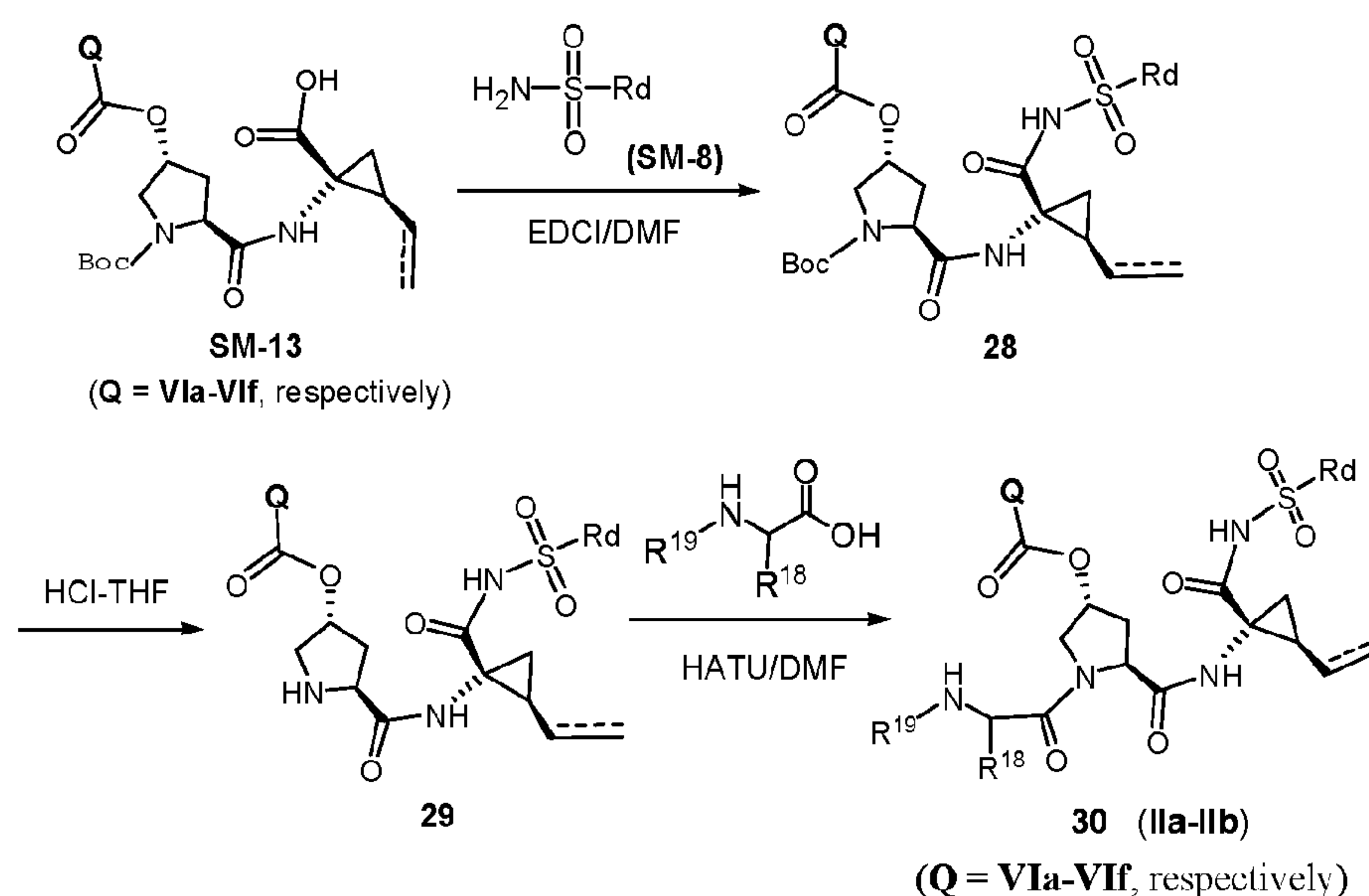
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Figure 8: Structure of Compounds **27a-27c** and **27-Ref**

To evaluate the difference in potency and other biological activities between the macrocyclic and linear structures for the novel polyheterocyclic based HCV inhibitors, there are different kinds of linear compounds **IIa-IIb** (**30** and **33**) with polyheterocyclic groups **VIa-VI** prepared as shown in the following Schemes 10 and 11, respectively.

Scheme 10:



In Scheme 10 above, in the presence of coupling reagent EDCI, an amine **SM-13** was reacted with a sulfonamide $\text{RdS(O)}_2\text{NH}_2$ (**SM-8**) to form product **28**, followed by removing Boc protecting group to obtain a de-Boc product **29**. Finally, in the presence of a coupling reagent such as EDCI or HATU, the amine intermediate **29** was reacted with different kinds of amino acid derivatives **SM-14** selected from a list of chemical reagents shown in the following Figure 9 to form various products **IIa-IIb (30a-30ar)** as shown as follows, wherein Rd and R^{18} each is $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_3\text{-C}_6$ cycloalkyl group, and R^{19} is $\text{C}_1\text{-C}_{20}$ alkyl, $\text{C}_1\text{-C}_{20}$ alkylcarbonyl, $\text{C}_1\text{-C}_{20}$ alkoxy carbonyl, or $\text{C}_1\text{-C}_{20}$ alkylsulfonamido groups as shown below from compounds **30a-30ar**.

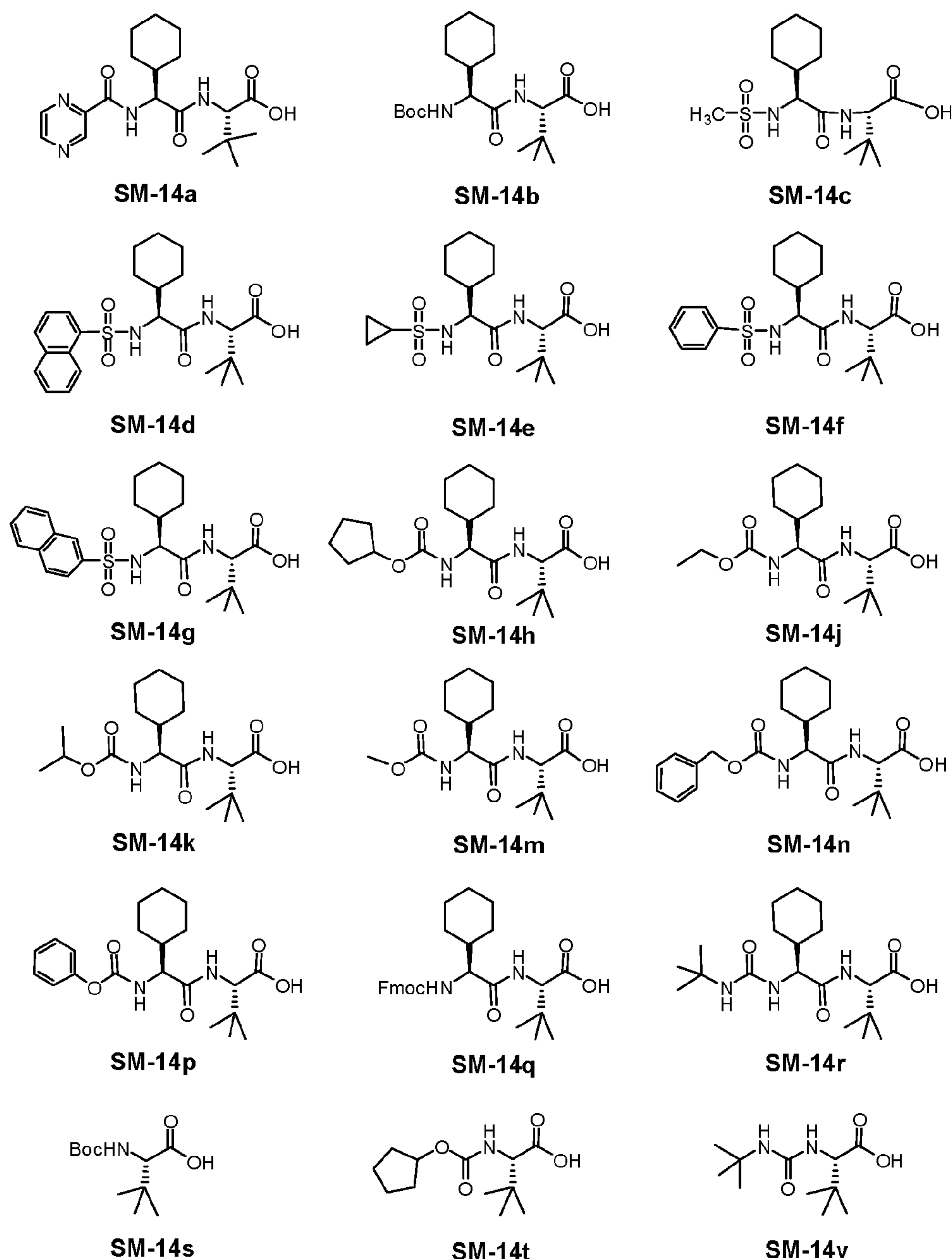
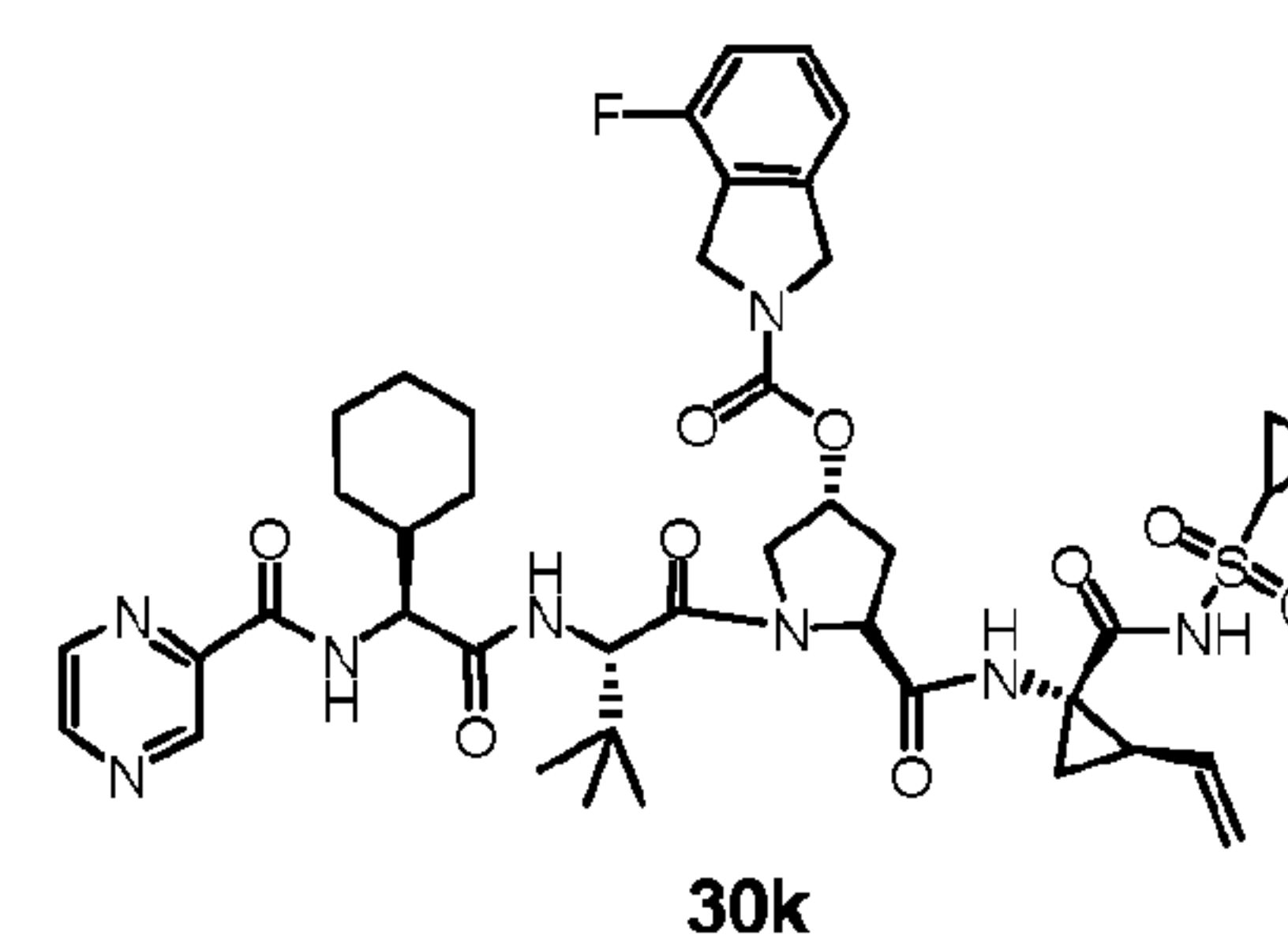
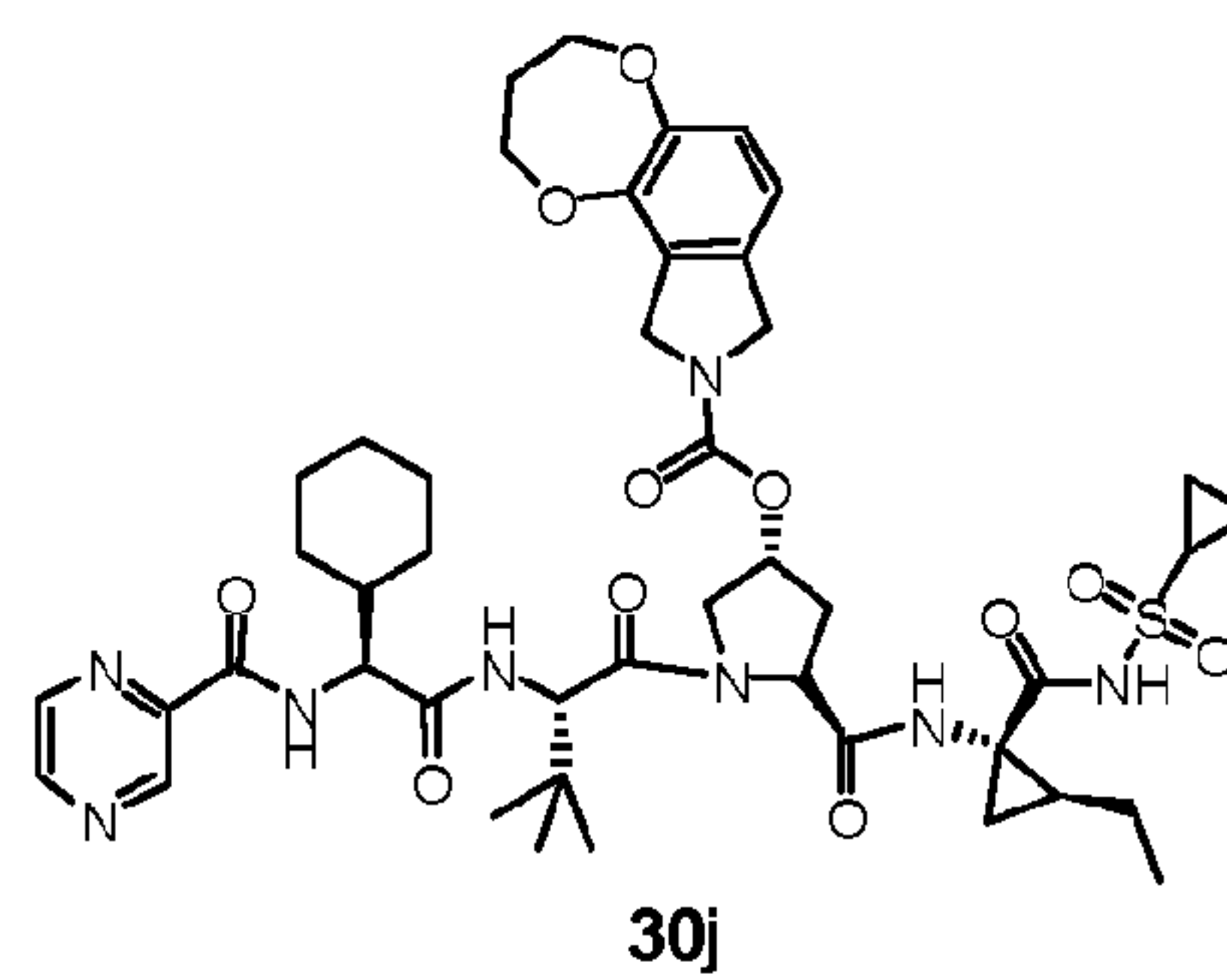
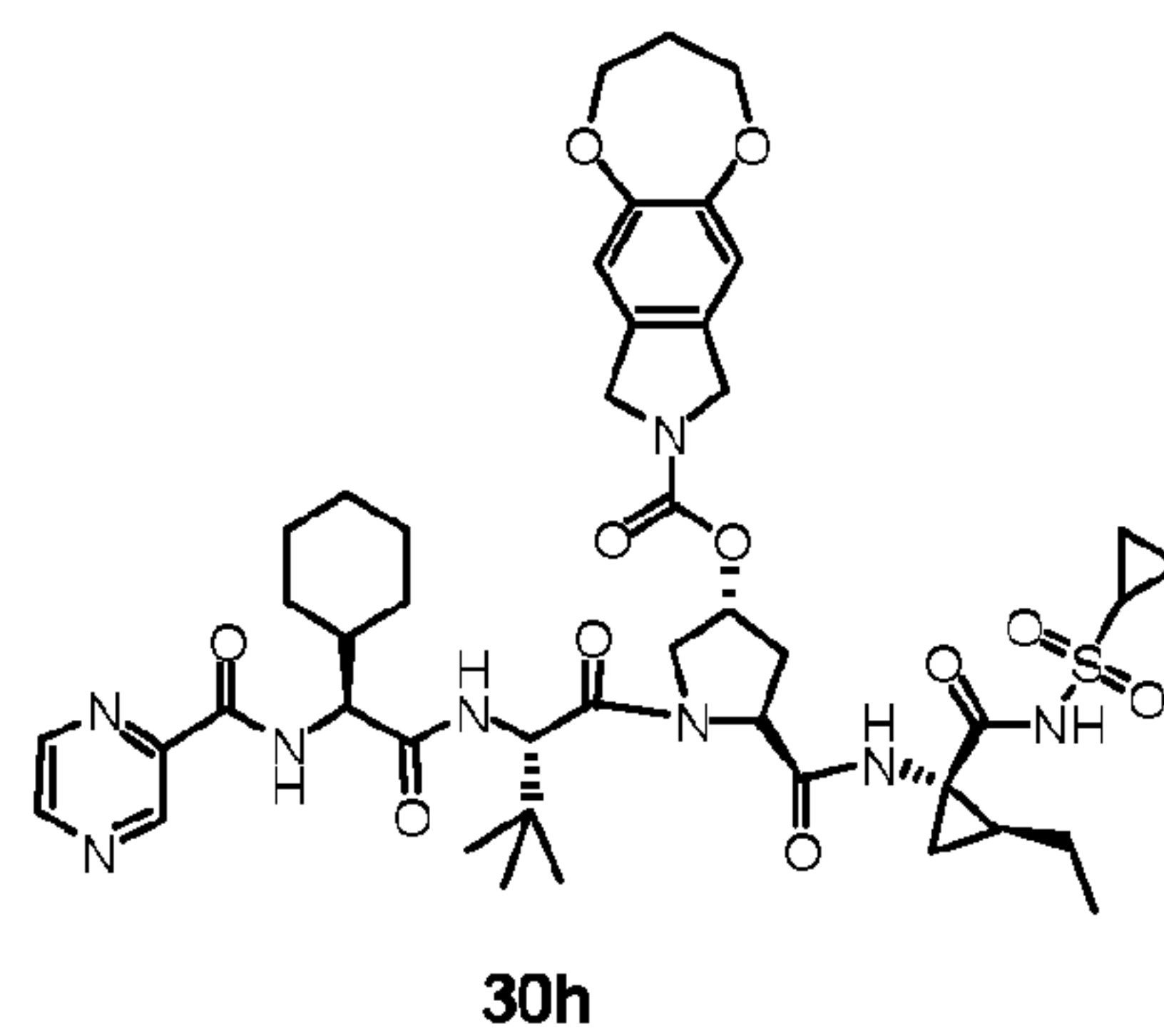
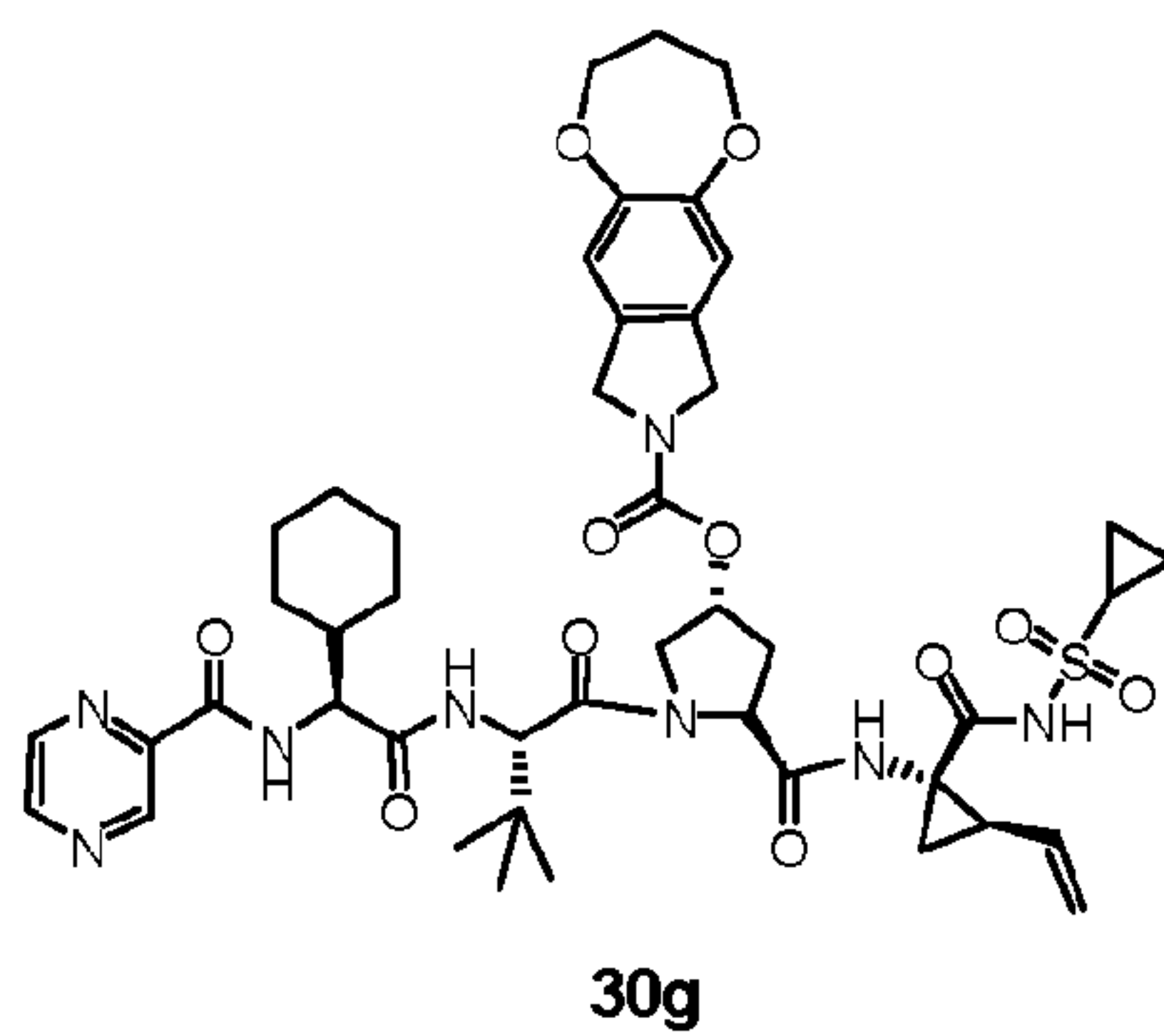
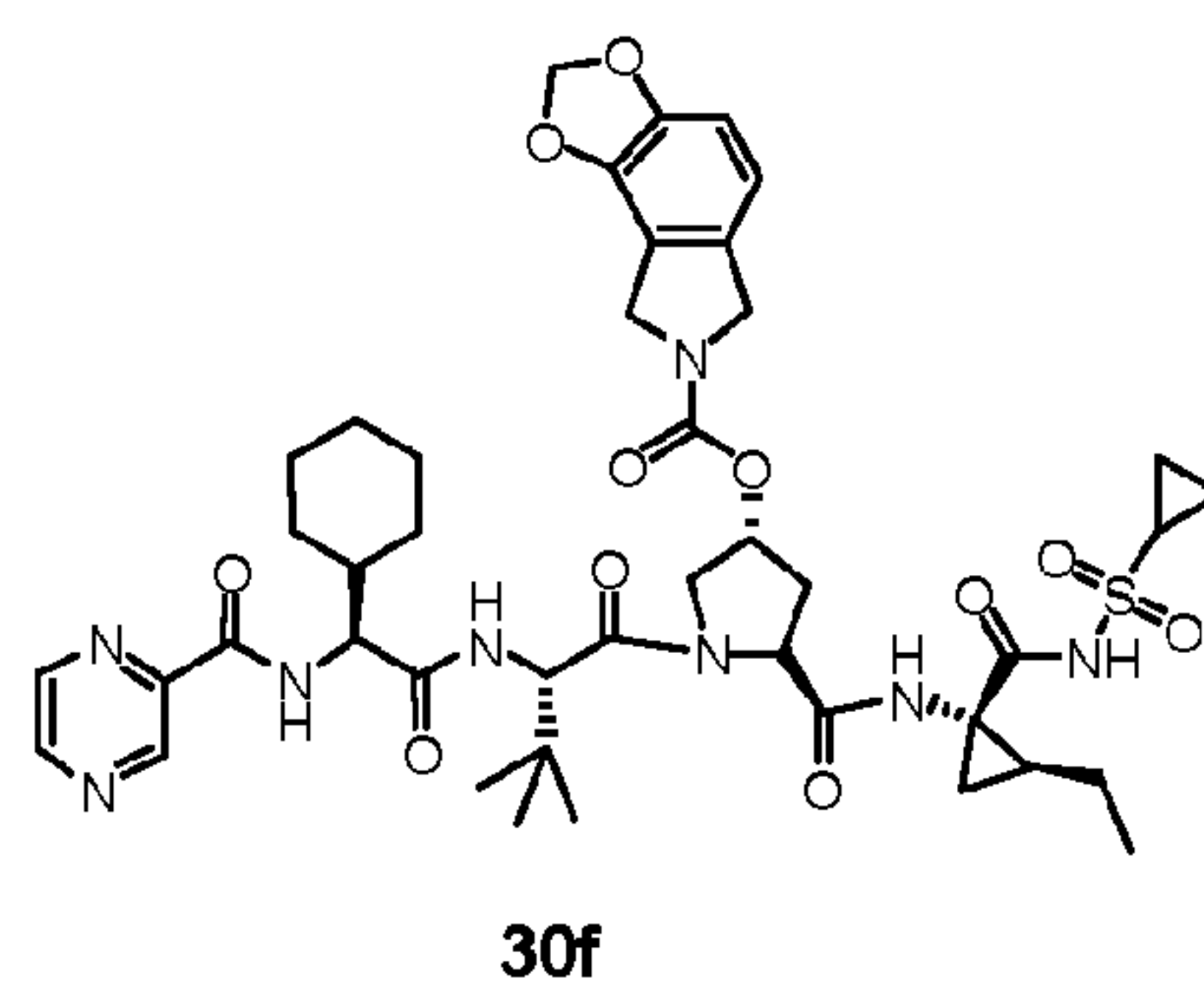
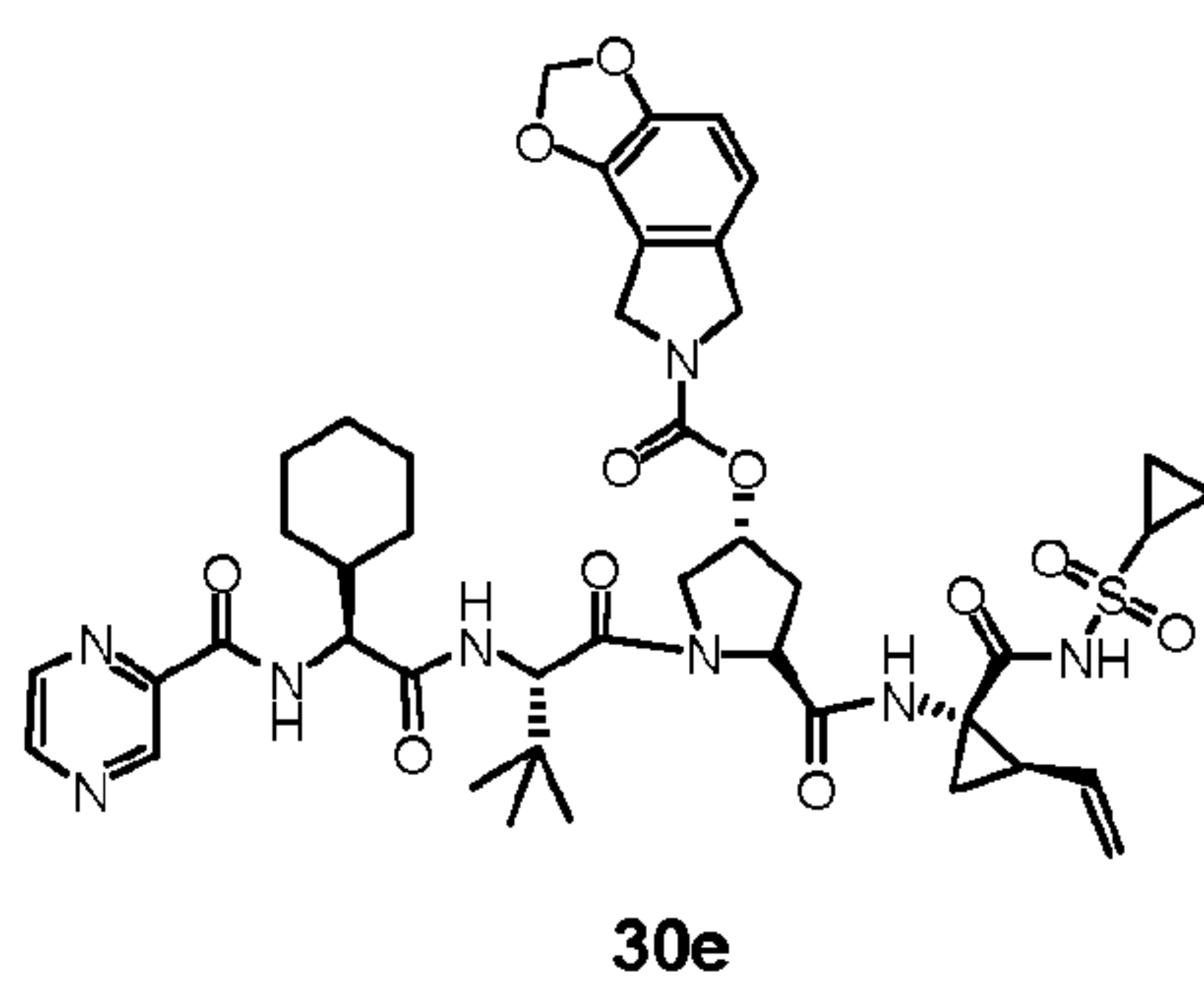
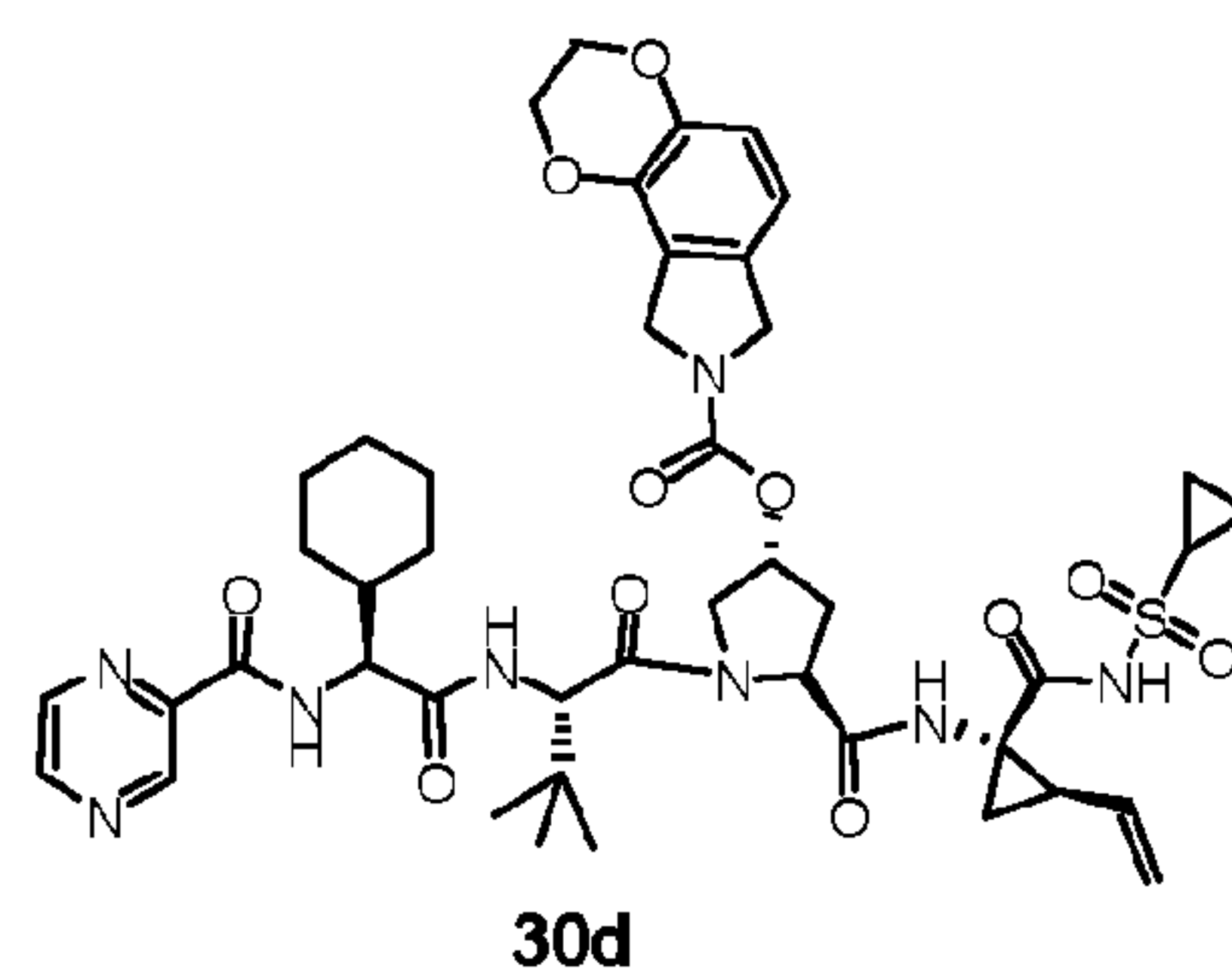
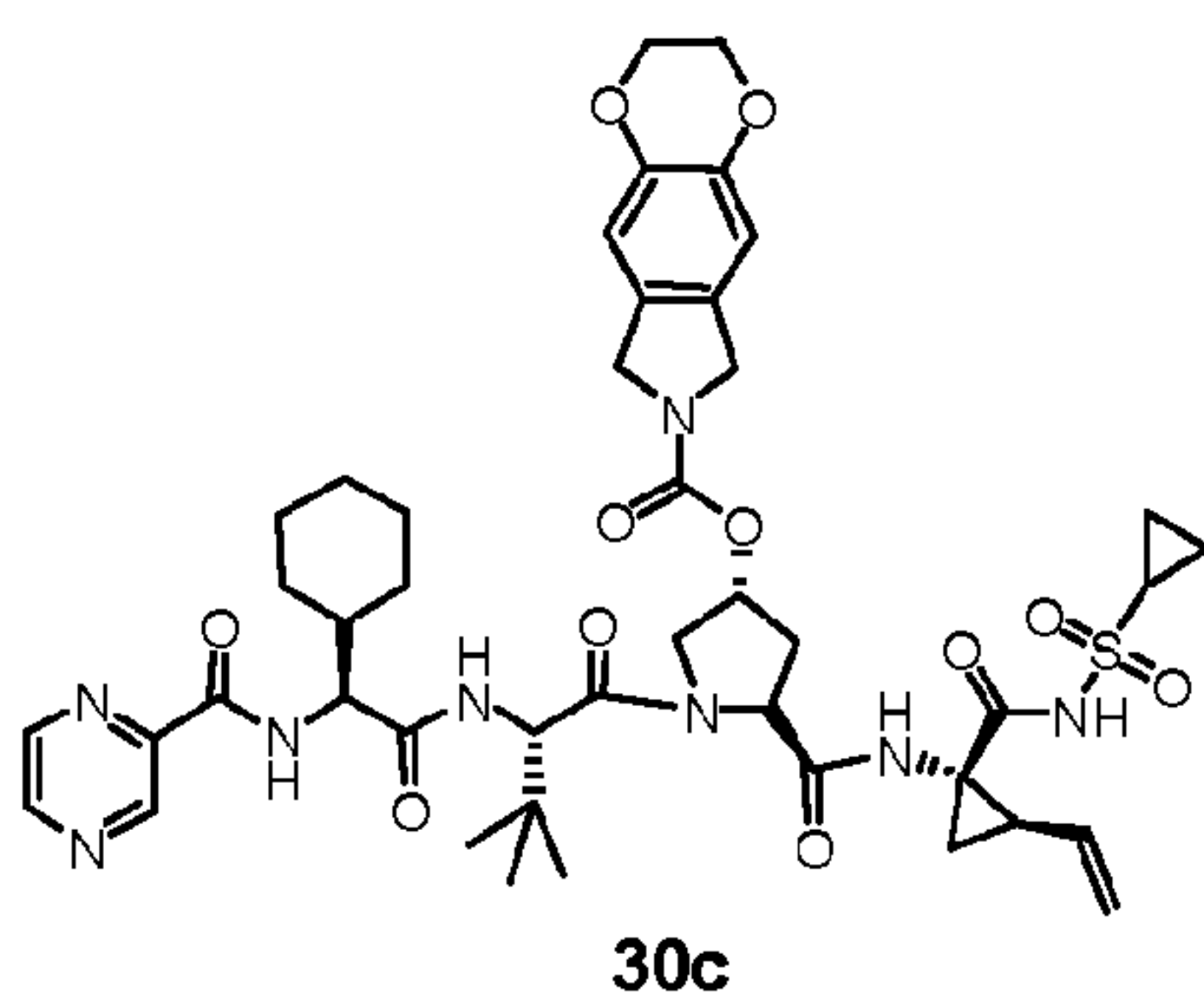
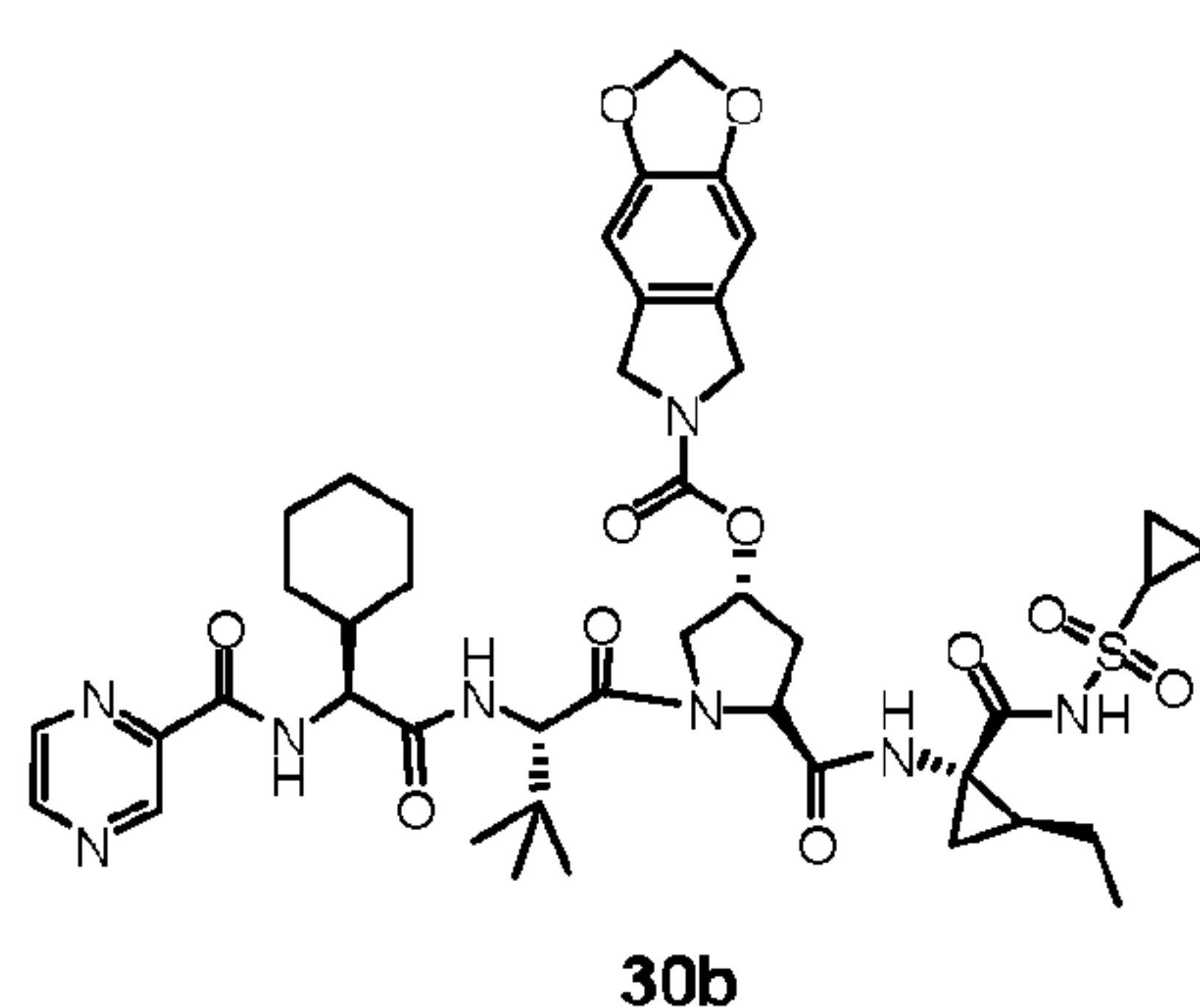
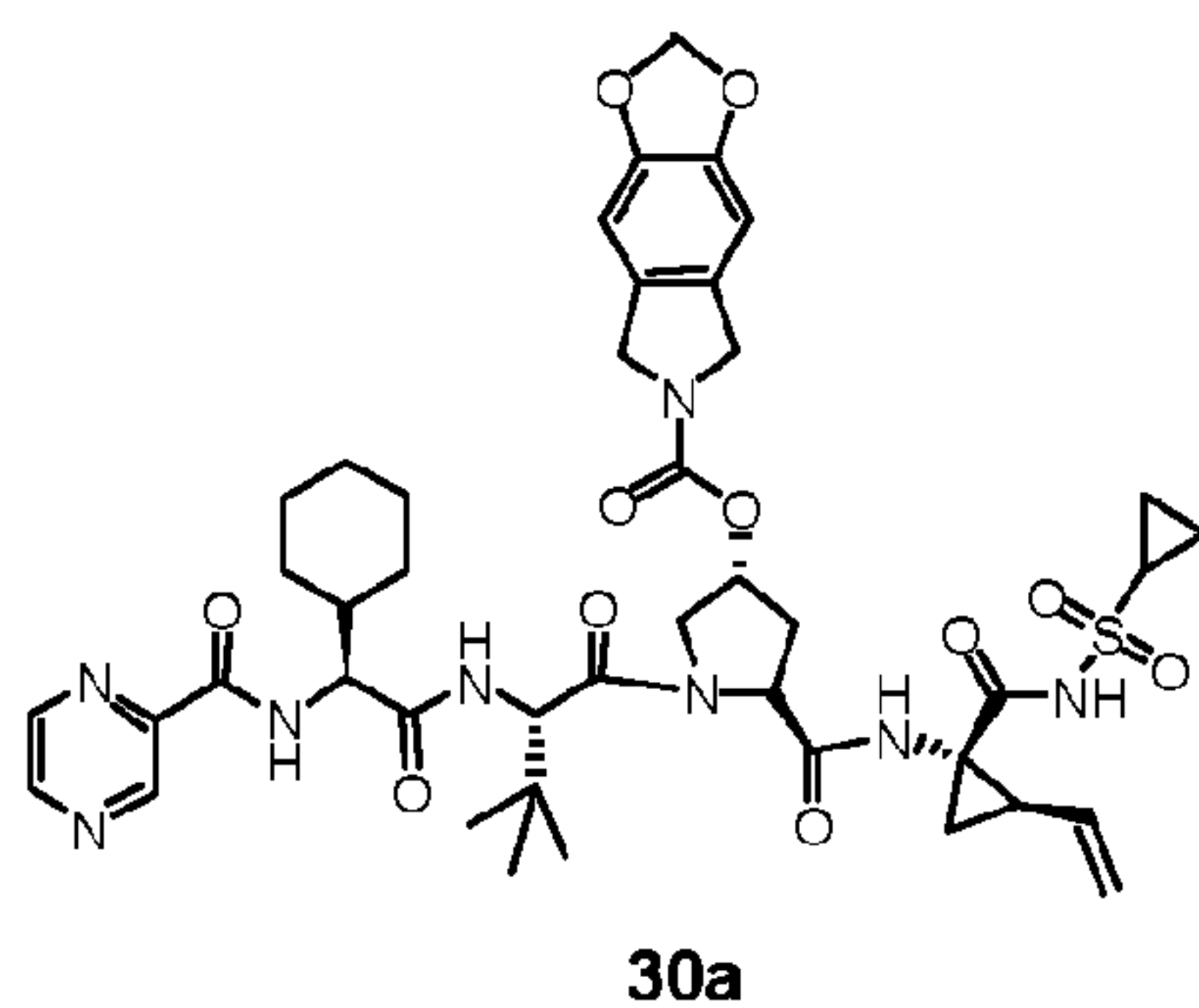
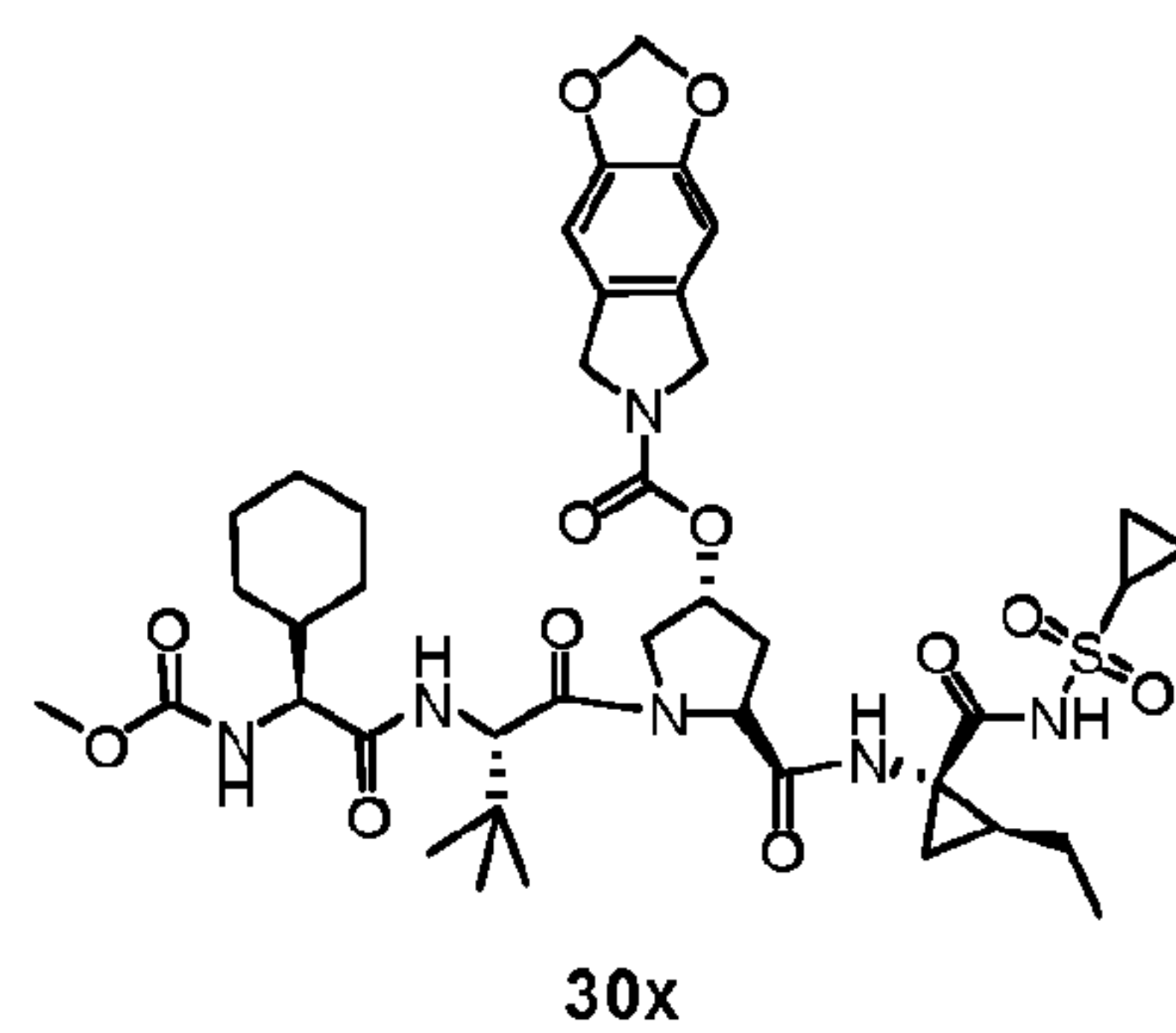
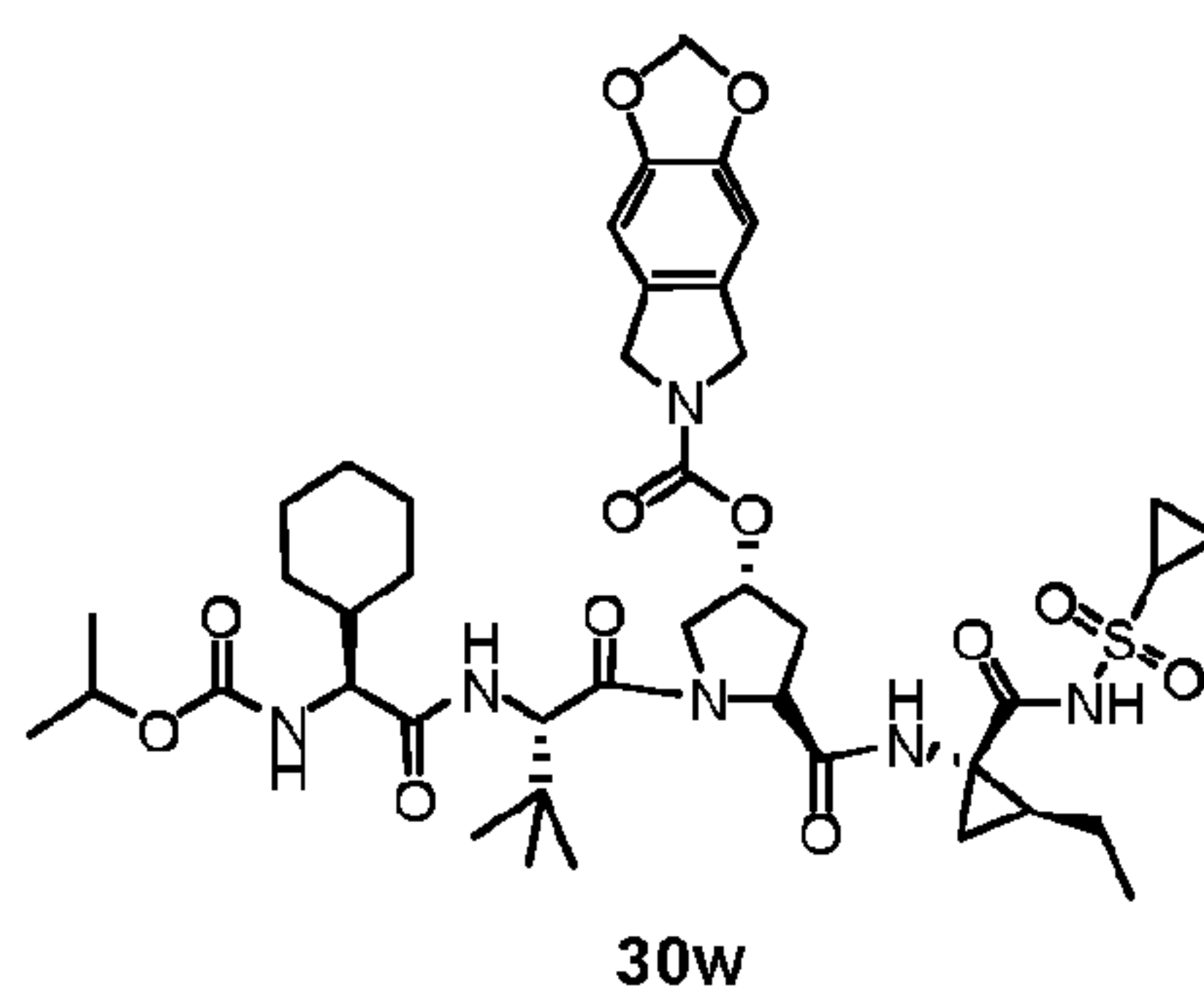
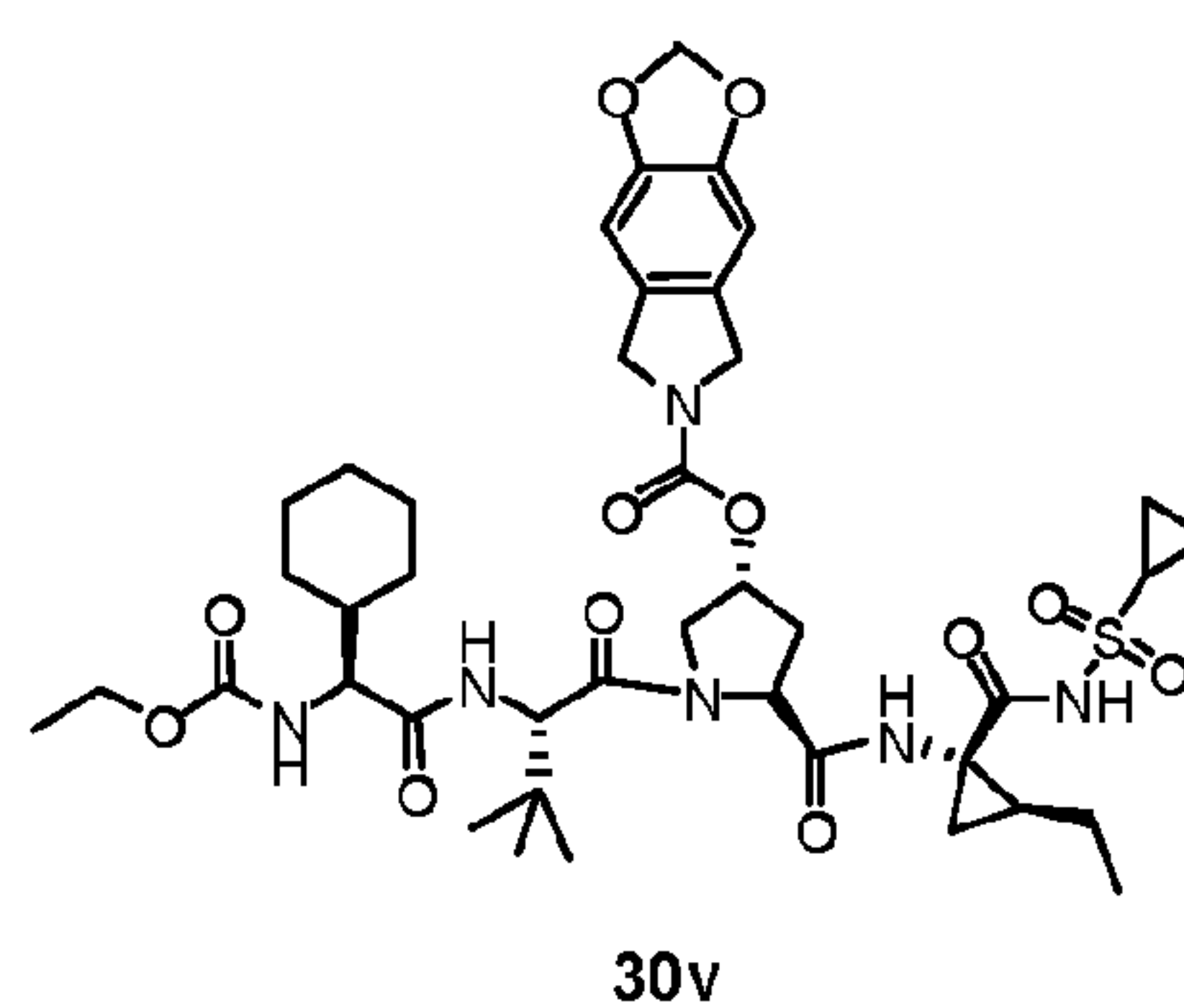
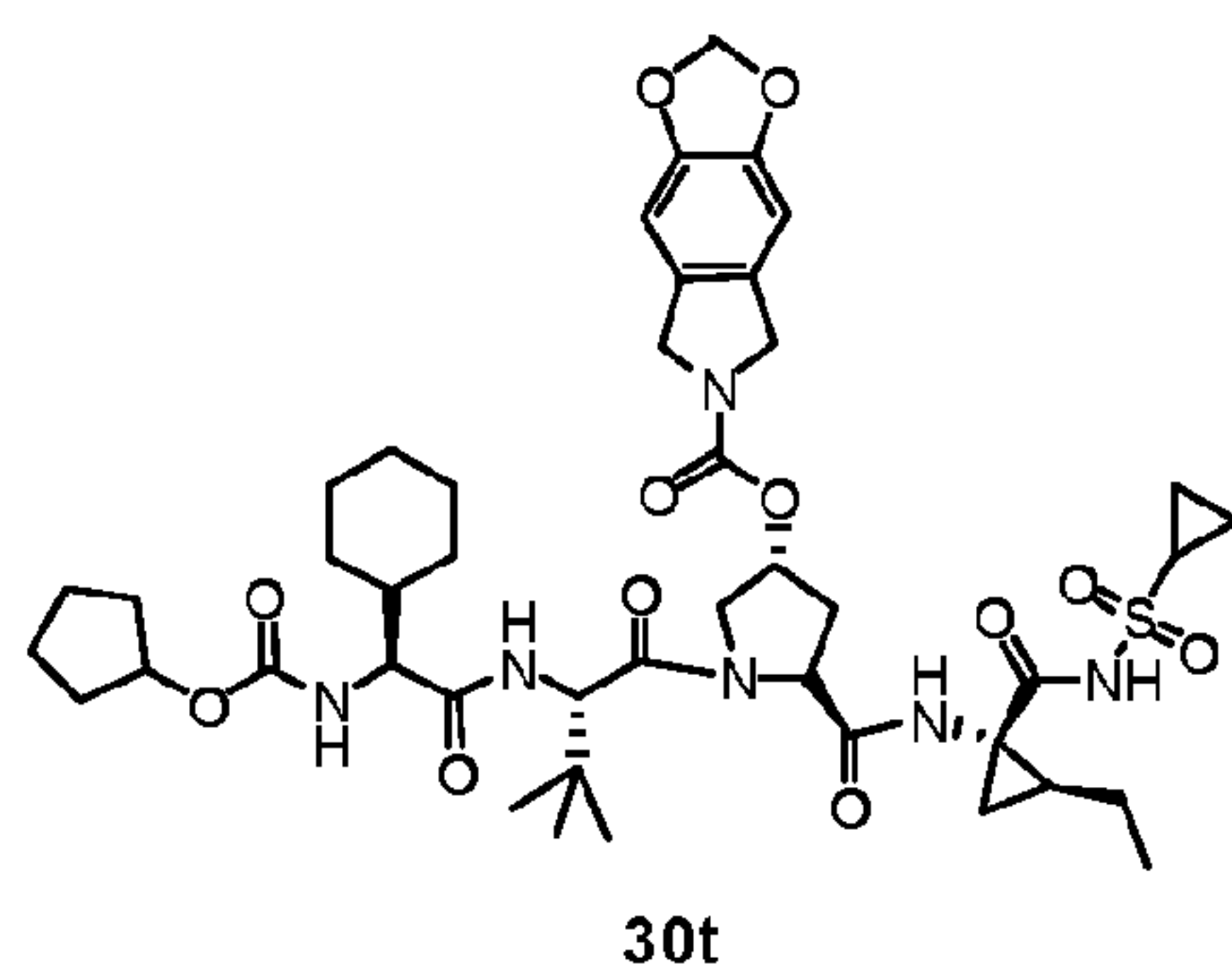
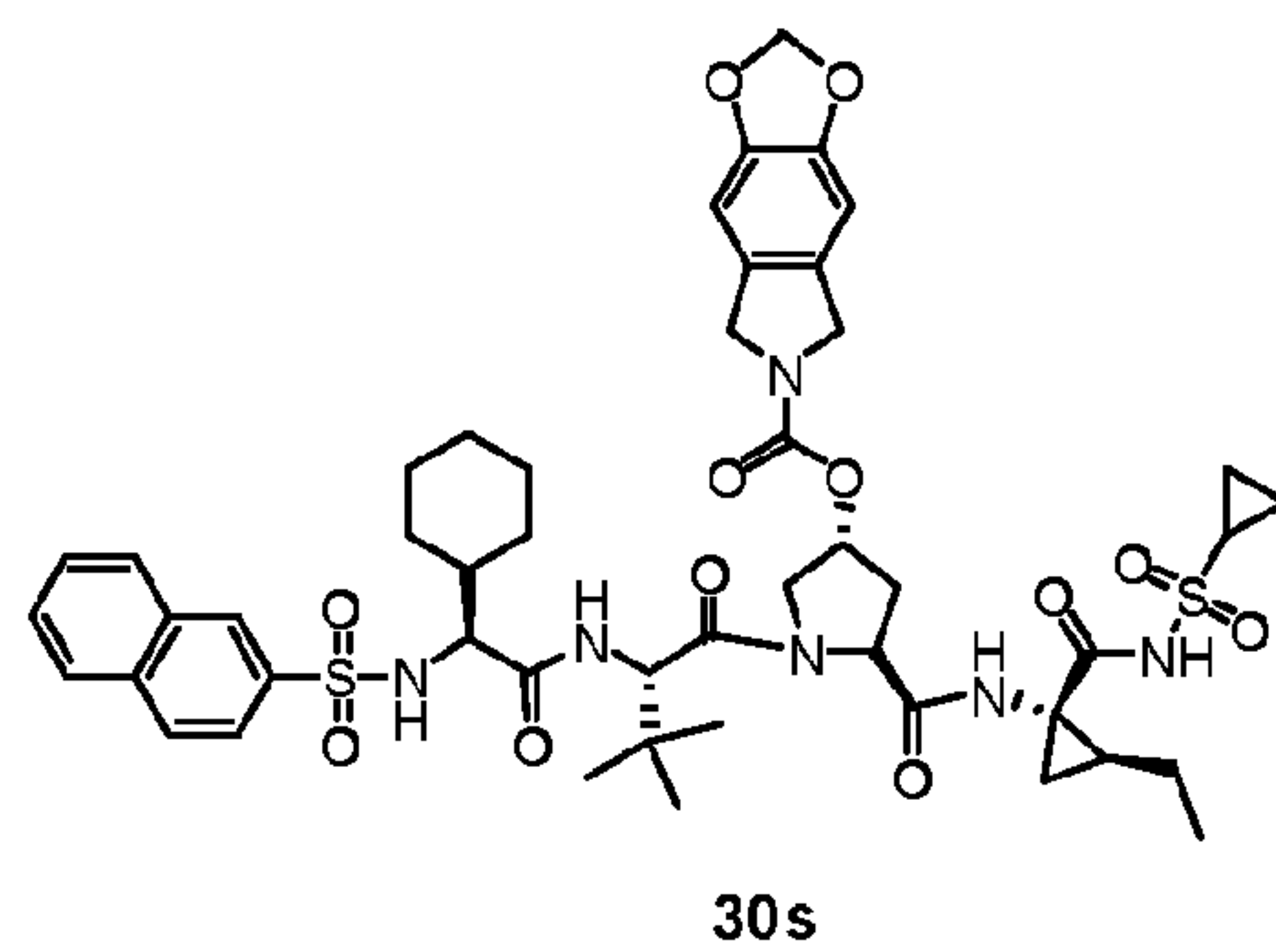
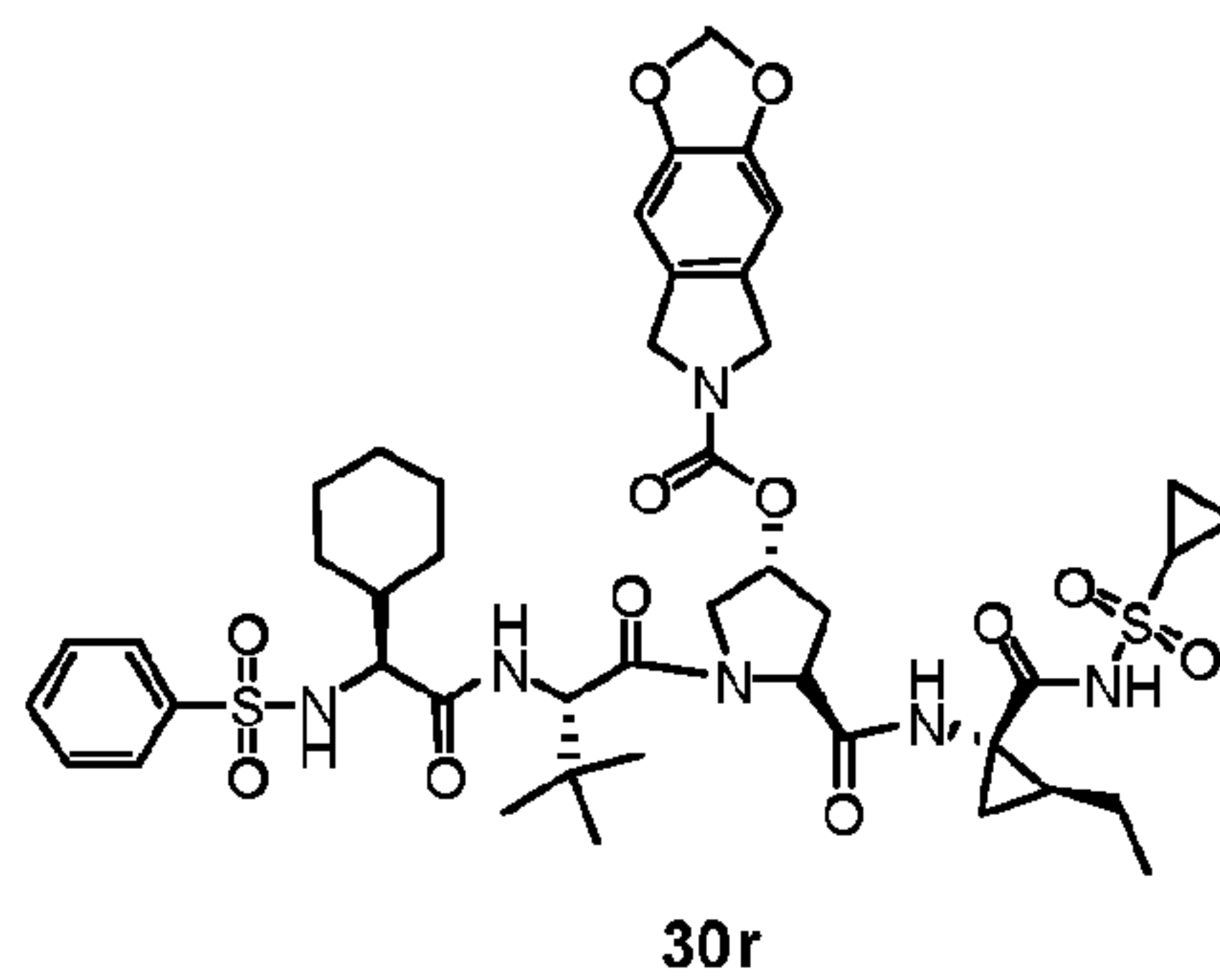
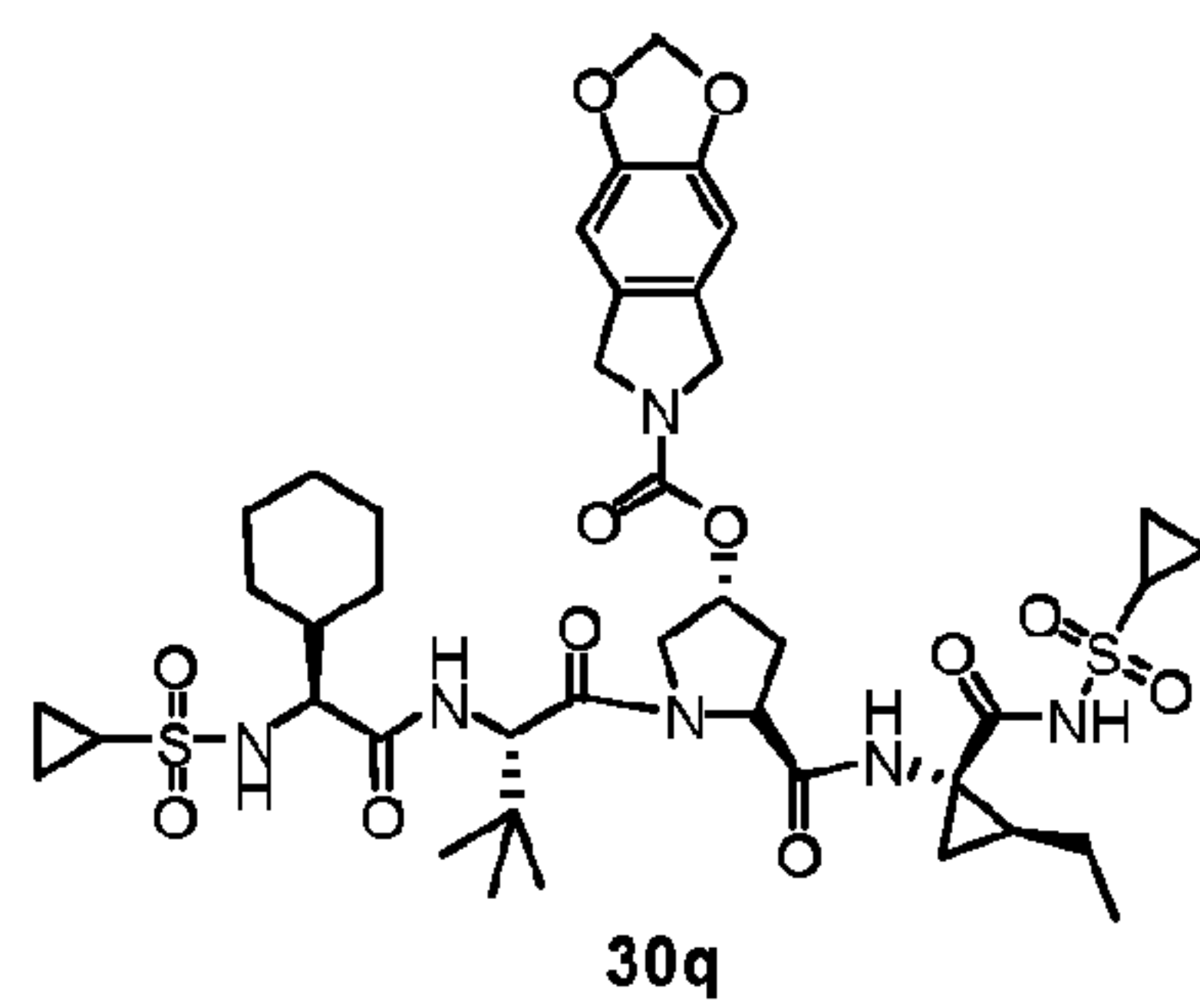
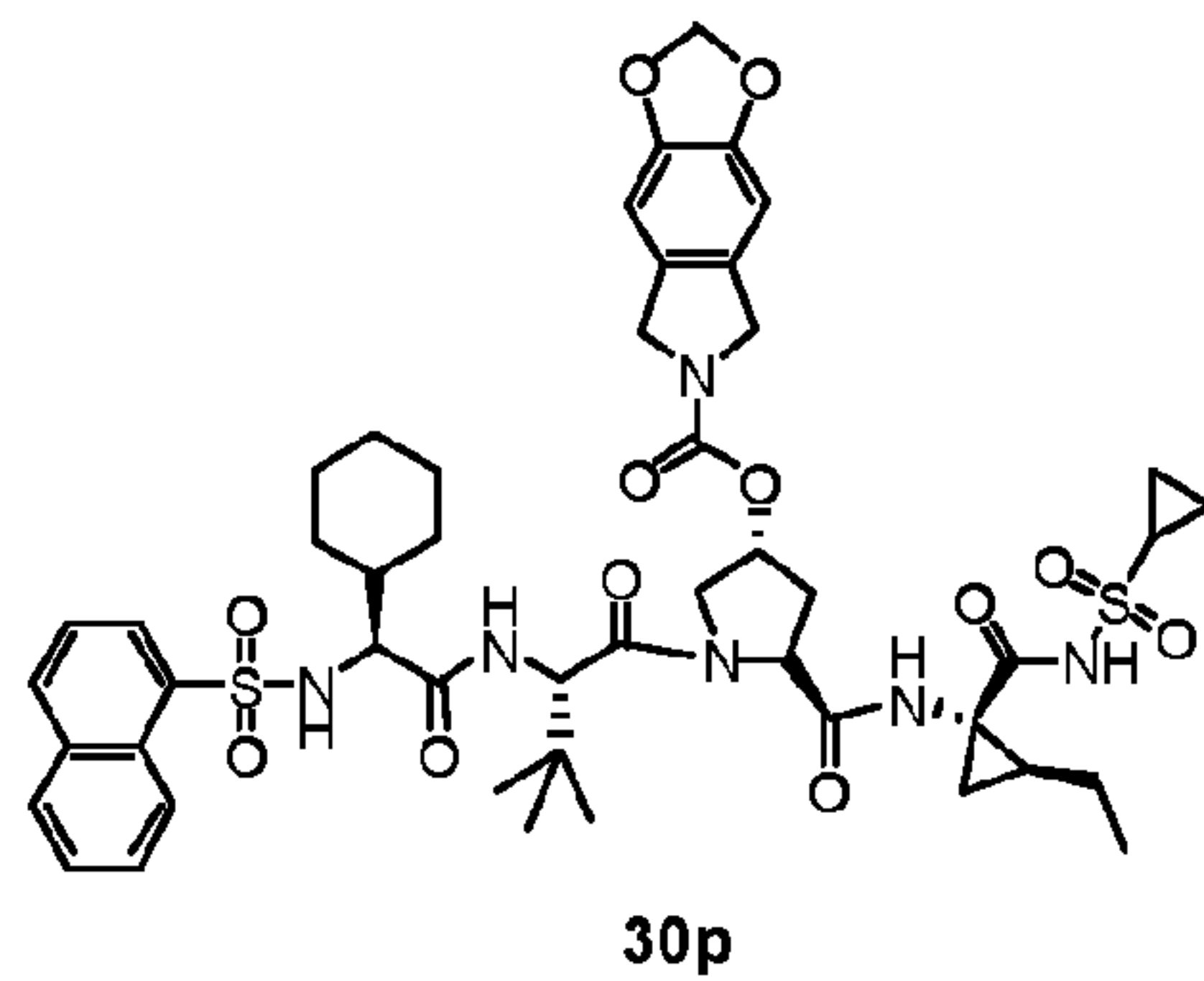
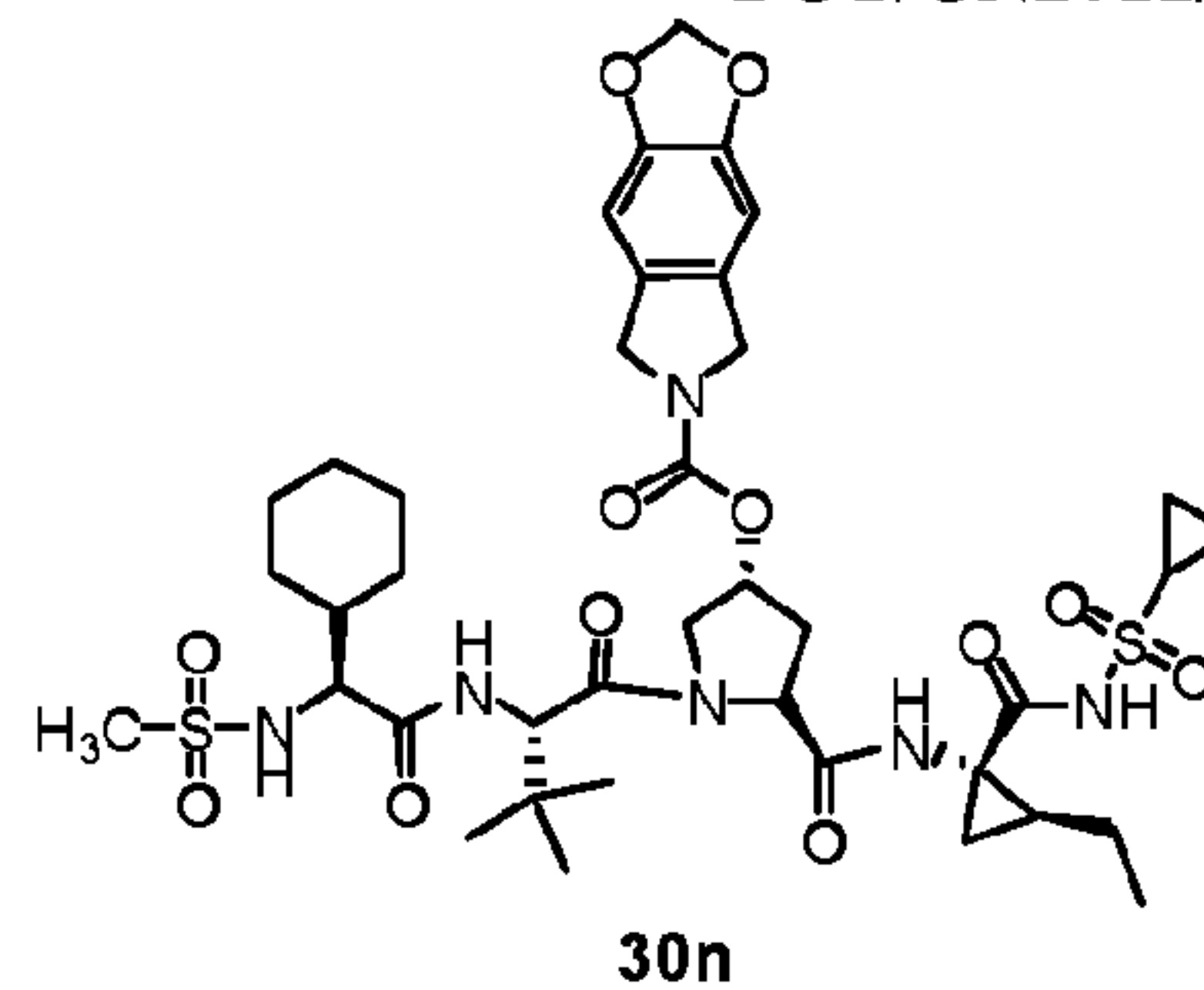
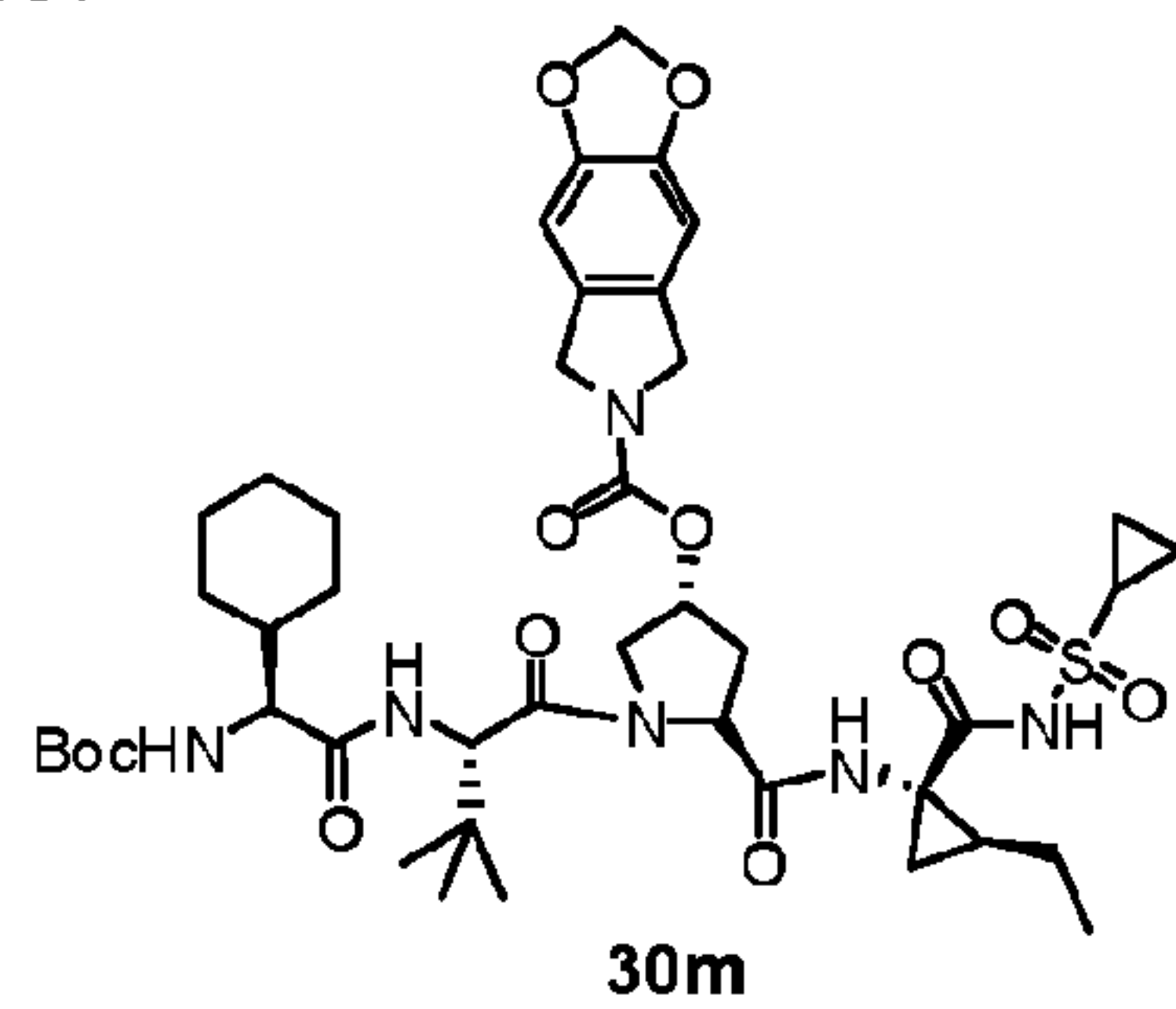
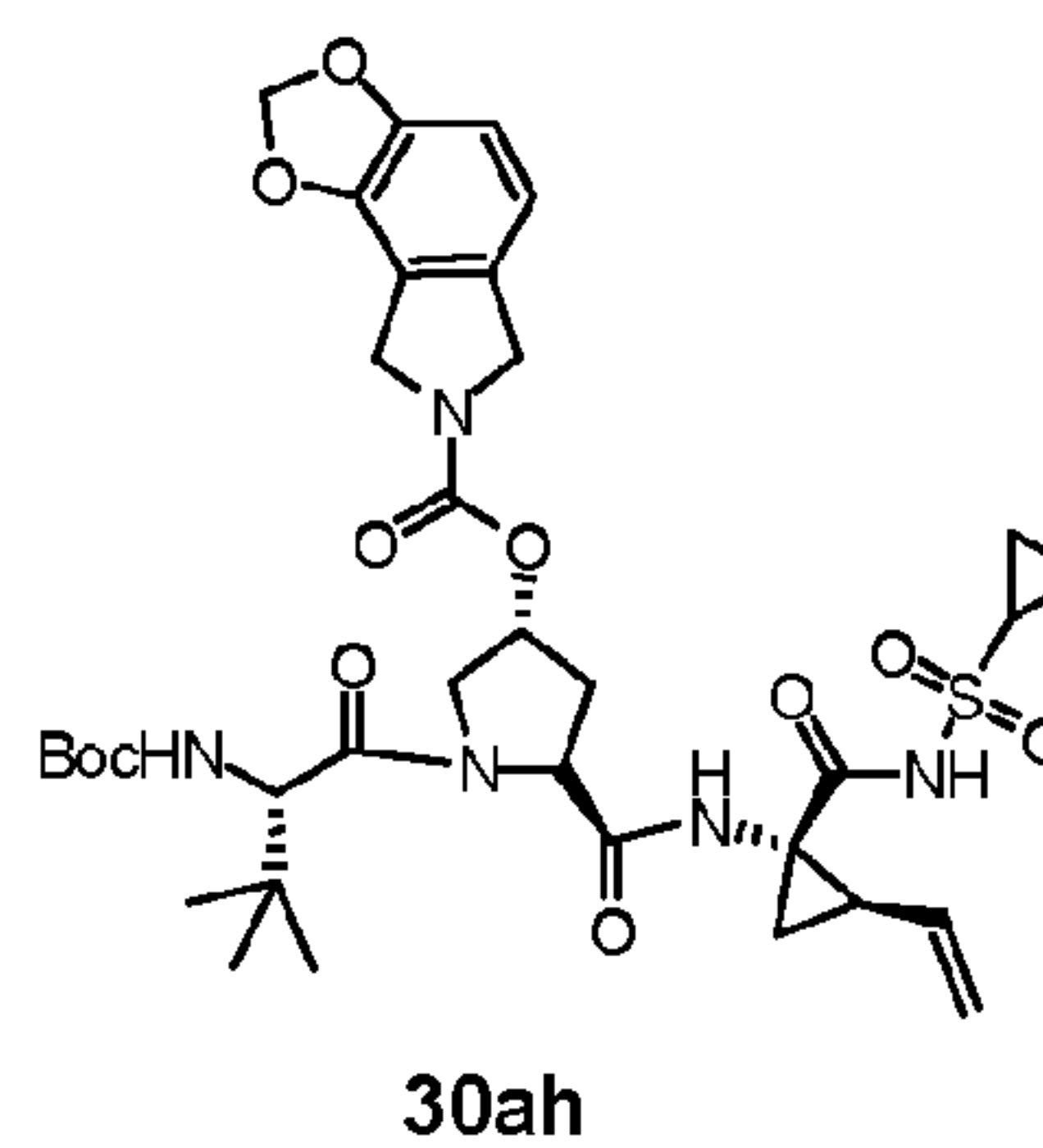
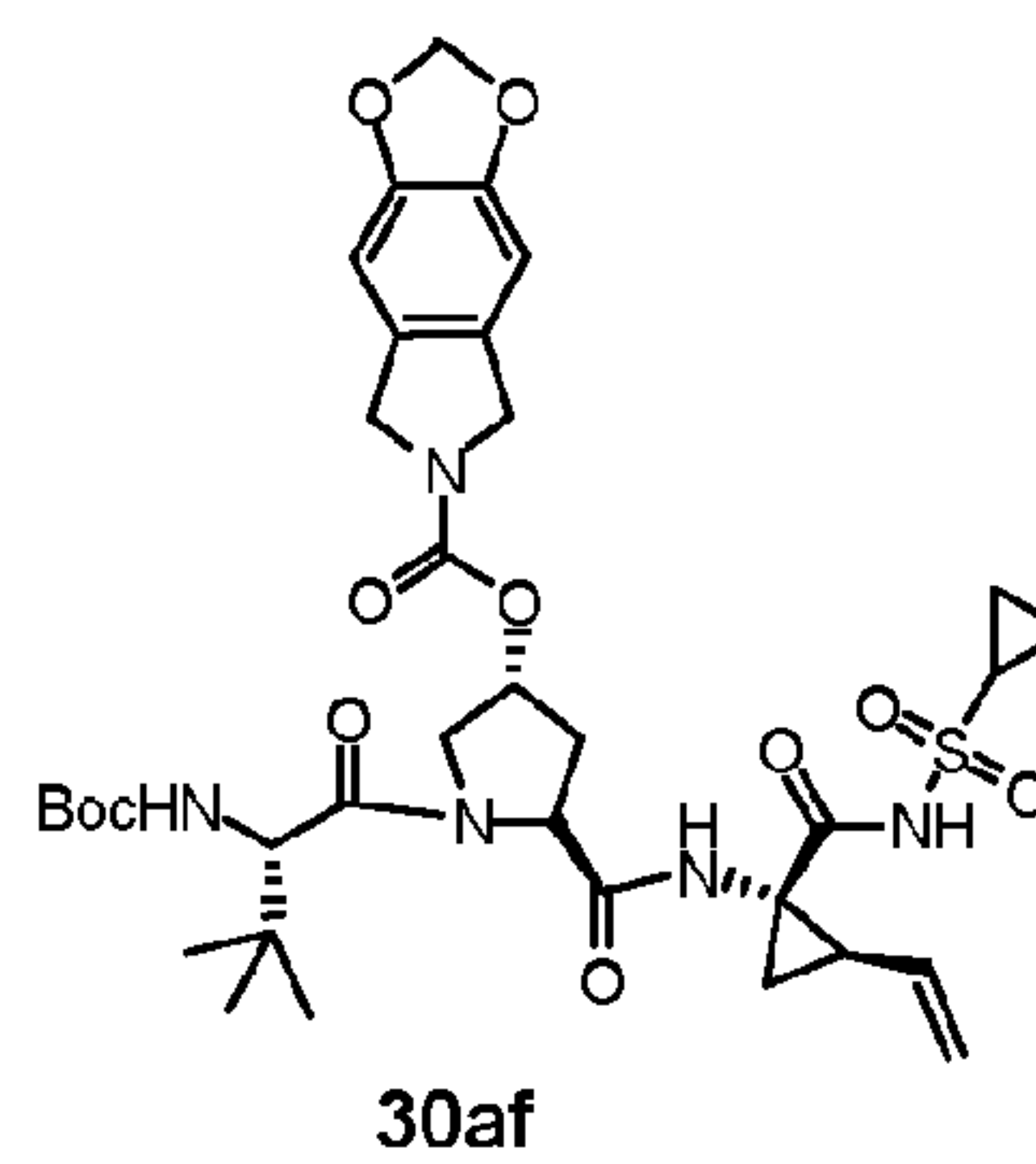
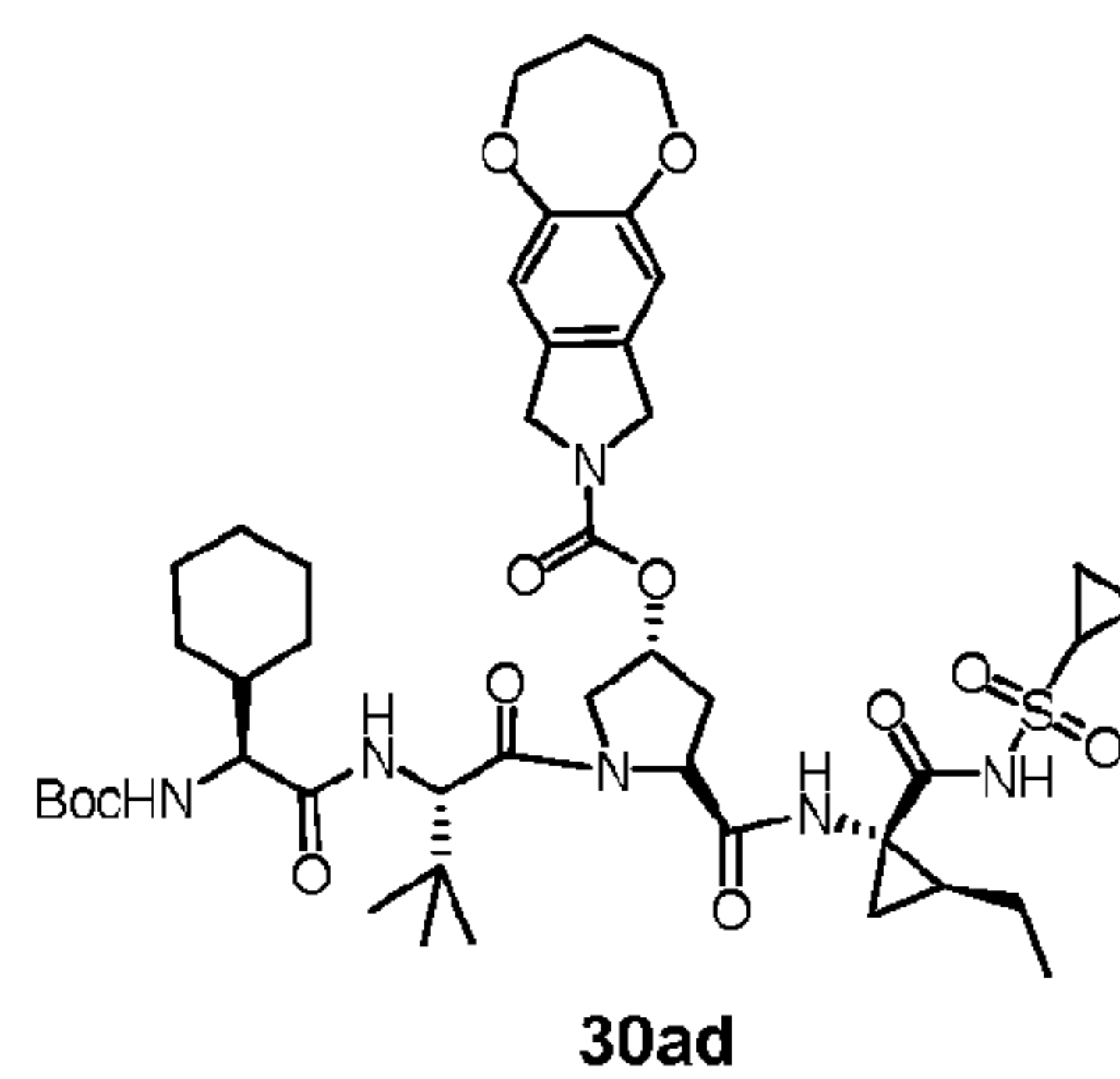
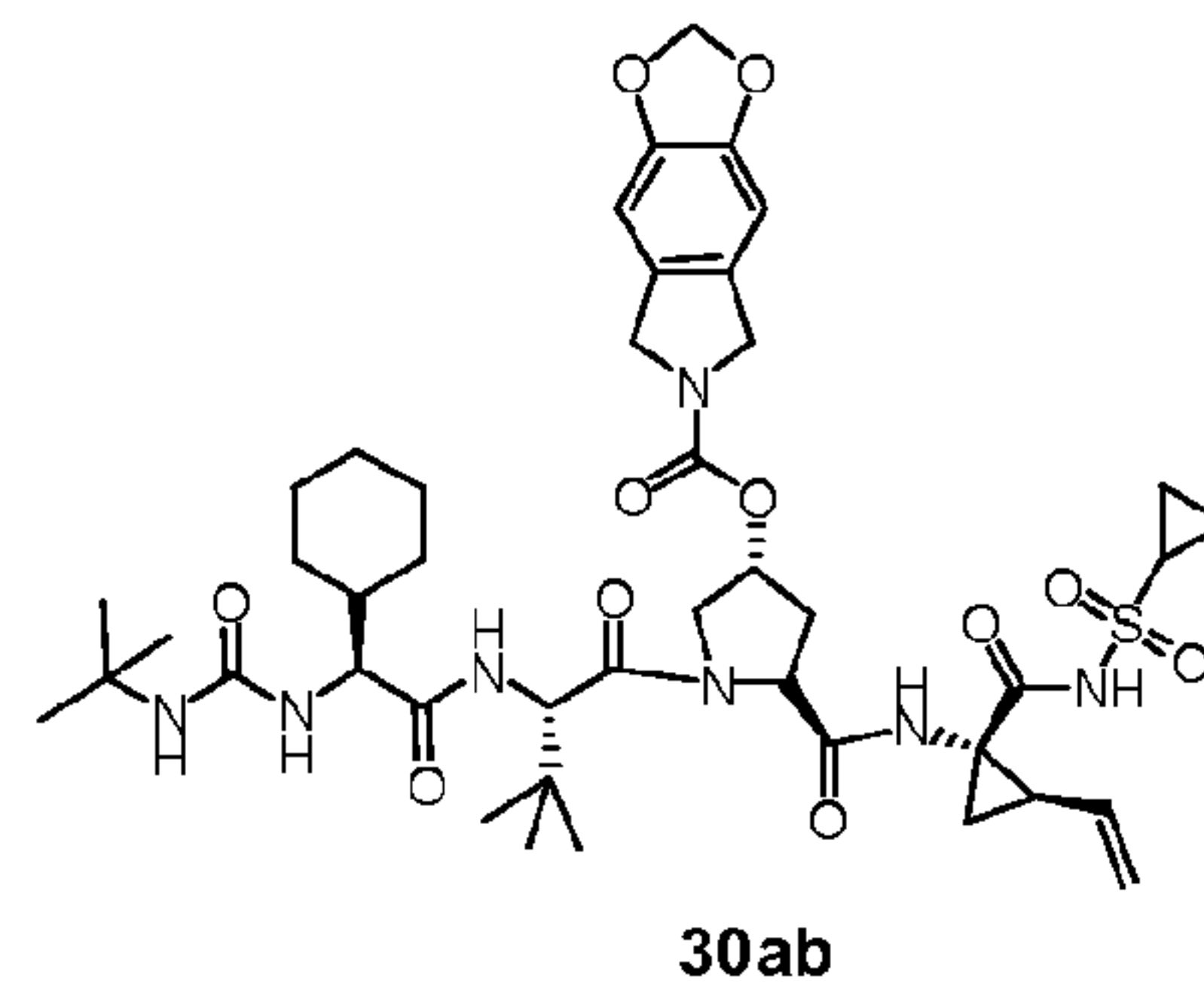
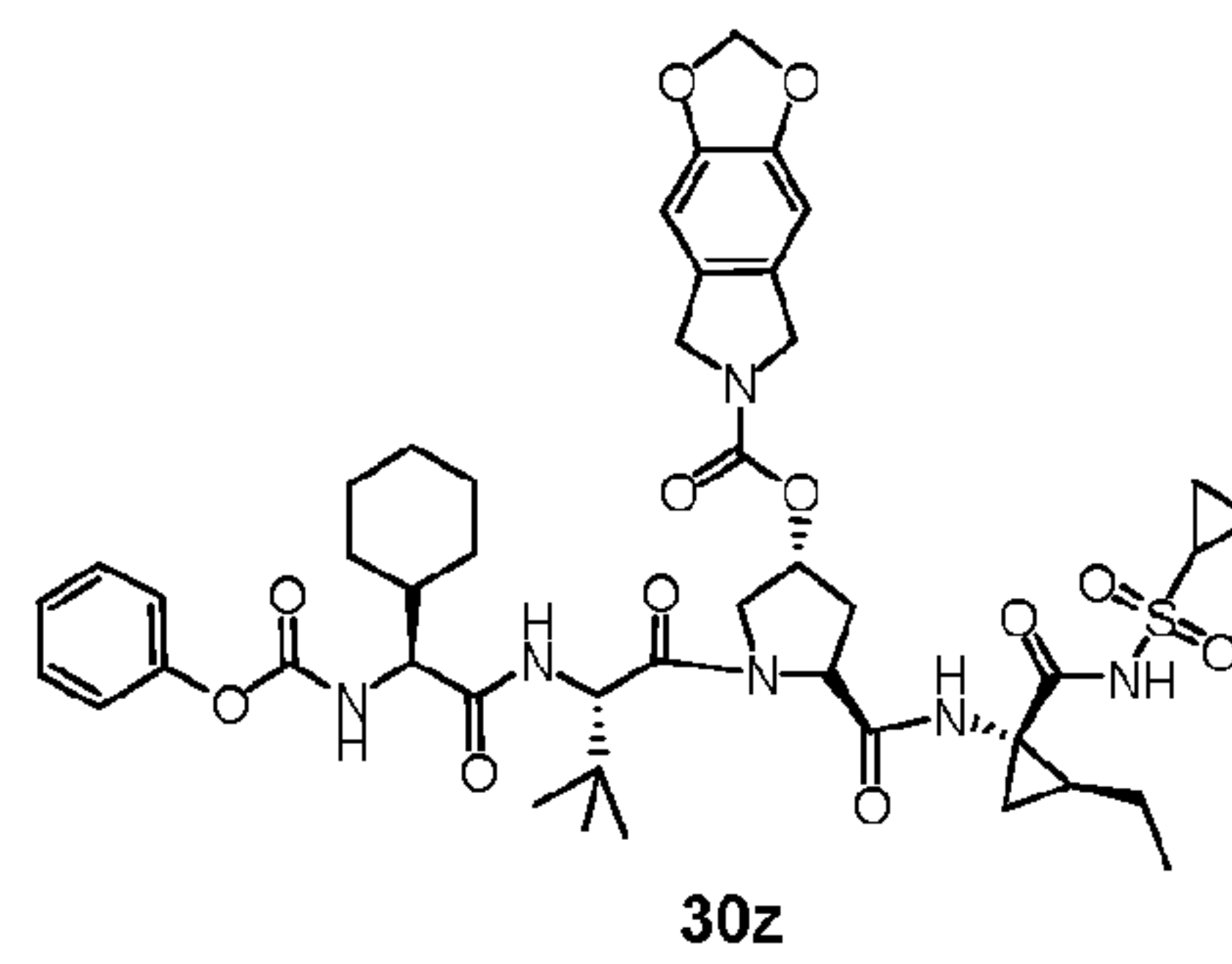


Figure 9: A list of Selected Amino Acid Building Blocks (**SM-14a-SM-14v**)







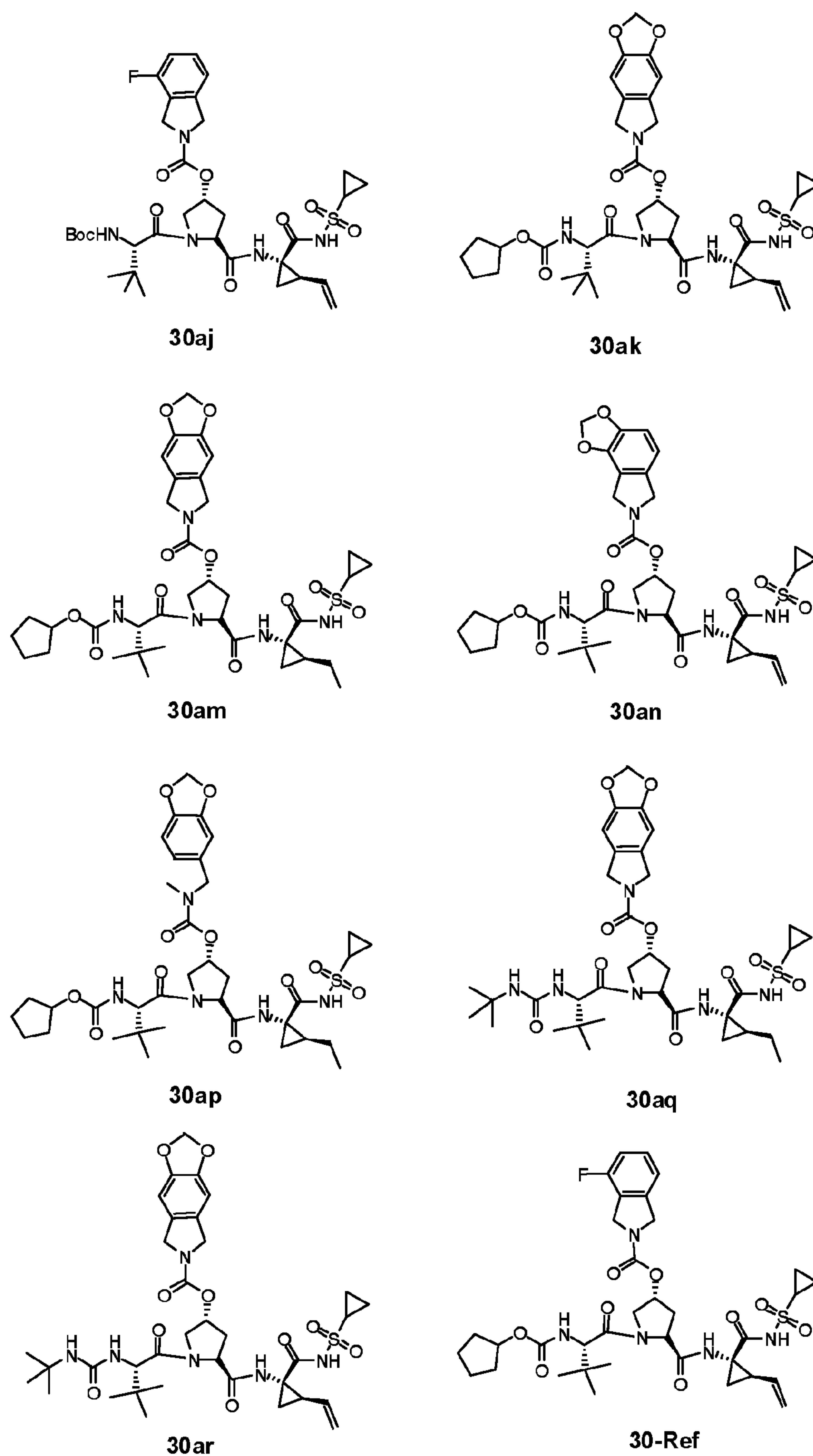
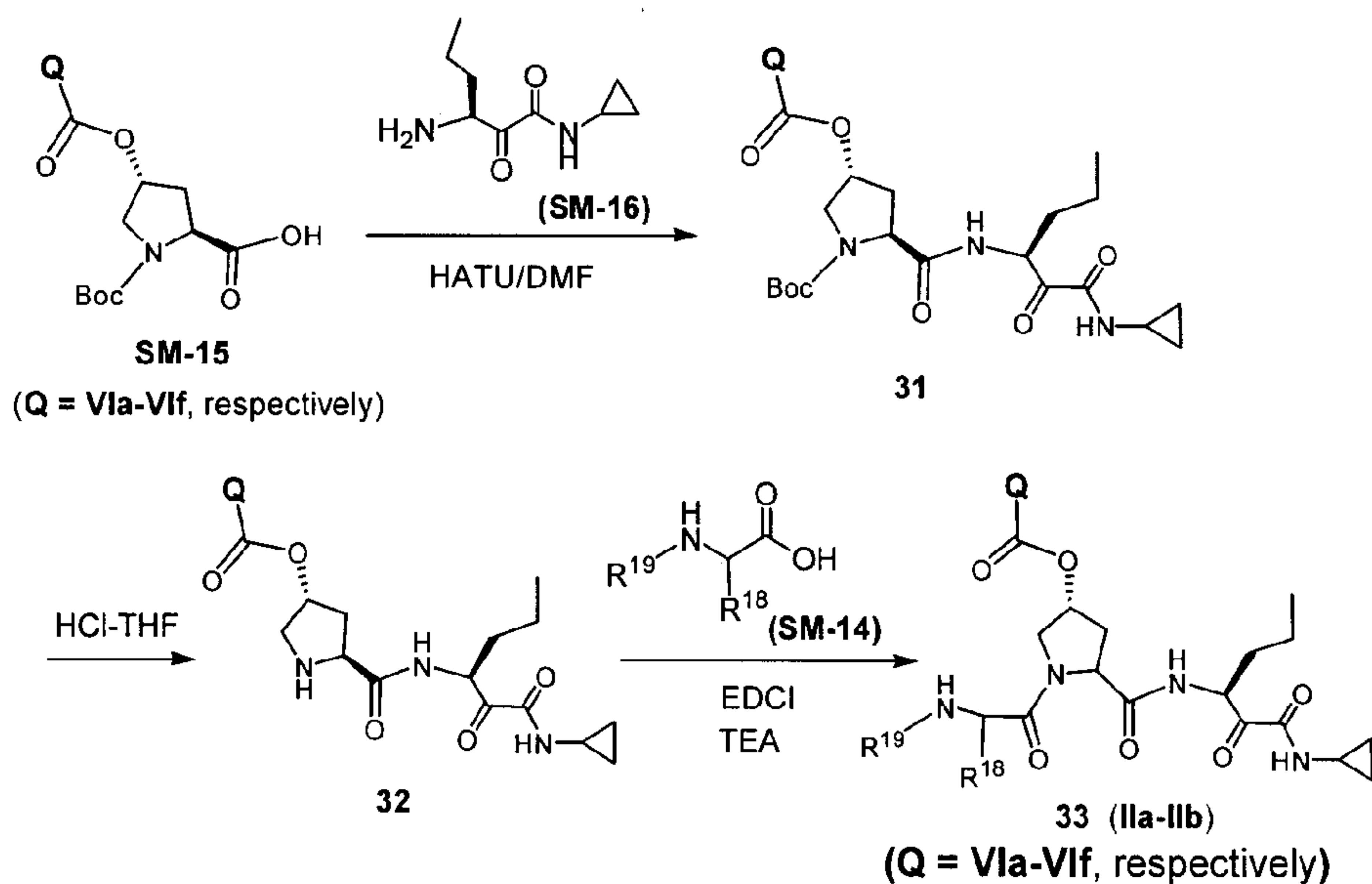
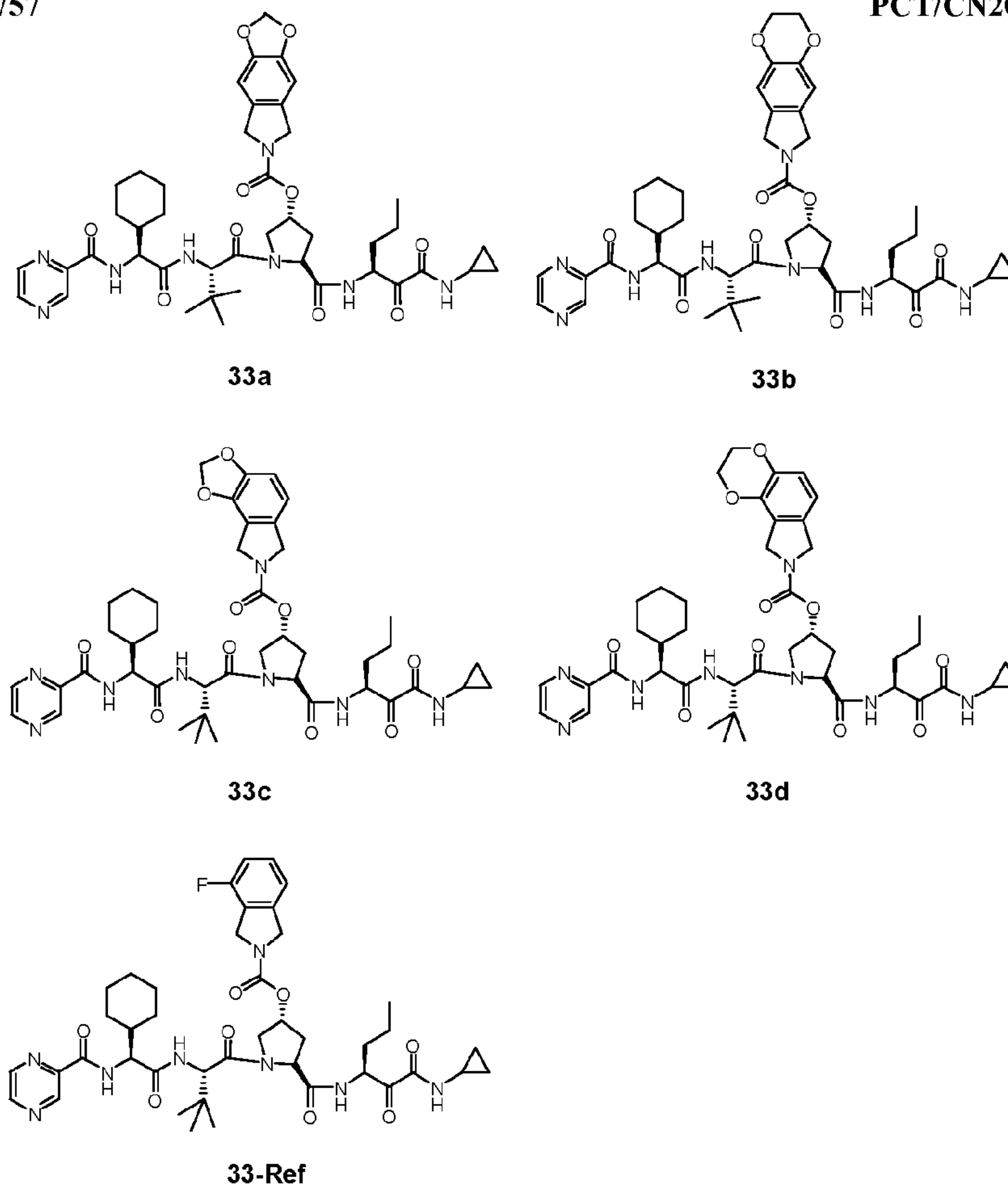


Figure 10: Structure of Compounds 30a-30ar and 30-Ref



In Scheme 11 above, in the presence of coupling reagent HATU in DMF, an acid **SM-15** was reacted with another amine reagent **SM-16** to form an amide product **31** by
 5 amidation, followed by removing Boc protecting group with HCl-THF solution to obtain an amine product **32**. Finally, in the presence of a coupling reagent such as EDCI or HATU, the amine intermediate **32** reacted with various carboxylic acids **SM-14**, respectively to form different kinds of novel polyheterocyclic based linear compounds **IIa-IIb (33a-33d)** as shown in the following Figure 11, wherein R^{20} and R^{21} each is hydrogen, C_1 - C_6 alkyl or
 10 C_3 - C_6 cycloalkyl group, R^{22} is C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkyl sulfonylamido or C_3 - C_6 cycloalkyl sulfonylamido group.

Figure 11: Structure of Compounds **33a-33d** and **33-Ref**

There are more polyheterocyclic based compounds described in this invention can be prepared using other suitable starting materials through the above synthetic routes or other developed procedures as reported from different references. The methods described in Schemes 1-11 above may also additionally include steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compounds in this invention. In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds.

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

for *Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

The compounds mentioned herein may contain a non-aromatic double bond and one or more asymmetric centers. Thus, they can occur as racemates and racemic mixtures, single enantiomers, individual diastereomers, diastereomeric mixtures, tautomers, and cis- or trans-isomeric forms, and/or hydrates. All such isomeric forms are contemplated.

So far, there is no any effective animal model for scientists to evaluate the efficacy of new compounds for inhibiting the HCV NS3 protease. The compounds described above in the present invention can be preliminarily screened by evaluating the IC_{50} and/or EC_{50} results for their activity and efficacy in treating HCV infection by an *in vitro* and/or *in vivo* assay as follows, then have some highly potent HCV inhibitors selected for other PK and toxicity studies before clinic trial during new drug development. Other methods will also be apparent for scientists in pharmaceuticals.

HCV NS3-4A protease assay in vitro. The assay was conducted in Buffer A containing 30mM NaCl, 5mM $CaCl_2$, 10mM DTT, 50mM Tris (pH7.8), using the Ac-Asp-Glu-Asp(EDANS)-Glu-Glu-Abu- ψ -[COO]-Ala-Ser-Lys (DABCYL)- NH_2 (FRET-S) fluorescent peptide (AnaSpec, USA) as substrate. Briefly, 140 μ L buffer A, 20 μ L compounds dissolved in buffer A with different concentration and 20 μ L HCV NS3-4A protease diluted in buffer A were added into 96-well plate respectively and mixed well. The reaction was initiate with adding 20 μ L of FRET-S. Reactions were continuously monitored at 37°C using a BMG Polarstar Galaxy (MTX Lab Systems, Inc. USA), with excitation and emission filters of 355 nm and 520 nm, respectively. The 50% inhibitory concentration (IC_{50}) was calculated with Reed & Muench methods.

Antiviral assay: Antiviral assays were carried out in black-walled, clear bottomed 96-well plates. Renilla luciferase reporter replicon cells were seeded at a density of 7×10^3 cells/well in 100 μ L complete DMEM culture without selection antibiotics. Eight twofold serial dilutions of compounds were prepared in complete DMEM and added to the appropriate wells, yielding final concentrations in 200 μ L of complete DMEM culture. Following 3 days of incubation, cells were incubated with 100 μ L fresh culture containing EnduRen™ Live Cell Substrate (Promega) at final concentrations of 60 μ M at 37 °C in 5% CO_2 for 2 h in the dark. Luminescence was then measured using an EnVision (Perkin-Elmer) microplate reader. Data were normalized to percentage of the control, and the the 50% effective concentration (EC_{50}) values were calculated using the method of Reed-Muench.

Acute Toxicity Study (MTD): Materials and Methods for MTD Study are as follows:

Animals: 320 KM mice, Certificate Number: 2007000510144, male and female were each half, 40 Wistar rats, certificate number: 2007000510555, male and female were each half. Animals were purchased from SLAC Laboratory Animal Limited Co., **Feed:** Breeding fodder of Radiation, special for rats and mice, was purchased from SLAC Laboratory Animal Limited Co.

Test Group: Animals were fed freely for adaptation more than 1 week. Healthy rats, body weight between 170-190g, were divided randomly into 3 groups, 5 male and 5 female in each group. Healthy mice, body weight between 18-20g, were divided randomly into 22 groups, 5 male and 5 female in each group.

Administration Method: In rats, the compound weighing 21.00g, serial number 1-3 respectively, adding 0.7% sodium carboxymethyl cellulose solution 30.00g, high-speed homogenizer machine 15000RPM, 10 min mixing, the rats were fed once, oral dose 10000mg/kg. In mice, the compound weighing 2.00g, serial number 4-25 respectively, adding 0.7% sodium carboxymethyl cellulose solution 8.00g, high-speed homogenizer machine 10000RPM, 10 min mixing, the mice were fed once, oral dose 10000mg/kg.

Clinical observation: Animals were observed every hour after administration in the first day, and behavior observation daily continuous for a week. Dead animals were necropsied, gross pathology of the organs were observed and recorded.

Evaluation of toxicity: Toxicity was evaluated by animal mortality, signs of clinical behavior and others.

Among all of synthesized polyheterocyclic compounds **11a-11p**, **12a-12u**, **15a-15b**, and **16a-16c**, **30a-30ar**, **33a-33d** and some reference compounds **12-Ref**, **21-Ref**, **27-Ref**, the results of HCV protease (HCV NS3-4A) inhibition test are listed in Table 1; where the scope of potent activity (IC_{50}): $\geq 200nM$ labeled "A", active in the range of 30-200nM labeled "B", active range $\leq 30nM$ labeled "C".

Table 1: Activity of Novel Polyheterocyclic Based Compounds
for Inhibiting HCV NS3 Protease

Entry	Compound	NS3-NS4A IC_{50}
1	11a	A

2	11b	A
3	11c	A
4	11d	A
5	12a	C
6	12b	C
7	12c	C
8	12d	C
9	12e	C
10	12f	C
11	12g	C
12	12h	C
13	12j	B
14	12k	C
15	12m	B
16	12n	C
17	12p	C
18	12q	C
19	12r	C
20	12s	C
21	12t	C
22	12u	C
23	12-Ref	C
24	15a	C
25	15b	C
26	16a	C
27	16b	C
28	16c	C
29	21a	B
30	21b	B
31	21c	C

32	21d	B
33	21e	C
34	21f	B
35	27a	B
36	27b	B
37	27c	B
38	27-Ref	B
39	27-Ref-2	B
40	30a	C
41	30b	C
42	30c	C
43	30d	C
44	30e	C
45	30f	C
46	30g	C
47	30h	C
48	30j	C
49	30k	C
50	30m	C
51	30n	C
52	30p	C
53	30r	C
54	30s	C
55	30t	C
51	30v	C
52	30w	C
53	30x	C
54	30y	C
55	30z	C
56	30aa	C

57	30ab	C
58	30ac	C
59	30ad	B
60	30ae	B
61	30af	C
62	30ag	C
63	30ah	C
64	30aj	C
65	30ak	C
66	30am	C
67	30an	C
68	30ap	C
69	30aq	C
70	30ar	C
71	30-Ref	C
72	33a	B
73	33b	B
74	33c	B
75	33d	A
76	33-Ref	B

The potent screening results in Table 1 show that: (1) the polyheterocyclic based macrocyclic compounds (e.g., **12a-12u**) containing cyclopropyl sulfonamide and isopropylsulfonamide have much better HCV inhibition activity than the polyheterocyclic based carboxyl acid products (e.g., **11a-11m**) that do not have cyclopropylsulfonamide or isopropylsulfonamide group incorporated by amidation, (2) in general, the polyheterocyclic based macrocyclic compounds **Ia-Ib** (e.g., **12a-12u**) have better efficacy and biological activity than the polyheterocyclic based linear compounds **IIa-IIb** (e.g., **30a-30ar** and **33a-33d**), and (3) several of the novel polyheterocyclic based macrocyclic sulfonamide compounds **Ia-Ib** (e.g., **12a-12d**, **12q-12u**) are highly effective (EC₅₀: 0.001-1.0uM) as HCV inhibitors, and many of new

polyheterocyclo based HCV inhibitors have excellent biological activities to inhibit HCV in comparison with some referred HCV inhibitors already in clinical Phase II and III, such as InterMune (ITMN-191, **12Ref**)-Roche, and Merck MK-7009.

Overall, all prepared new polyheterocyclic based compounds have been evaluated for their potency and efficacy *in vitro* and/or *in vivo*, and there are two novel classes of polyheterocyclic based compounds found highly effective to inhibit HCV. Moreover, the present invention explores the insight relationship between the structures of new polyheterocyclic compounds and efficacy of HCV inhibition, which provides valuable clue to develop an effective potential HCV inhibitors among the developed novel polyheterocyclic compounds **Ia-Ib** and **IIa-IIb**.

Abbreviations of chemical materials, reagents, and solvents related to the present invention are listed as follows:

SM4: N-Boc-trans-4-hydroxy-L-proline methyl ester

SM5: Boc-L-2-amino-8-azelaic acid

SM6: (1R, 2S)-1-amino-2-cyclopropyl methyl vinyl

AIBN: azobisisobutyronitrile

(Boc) 2O: di-tert-butyl carbonate

CDI: N, N'-carbonyldiimidazole imidazole

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

EDCI: N-ethyl-N-(3-dimethyl aminopropyl) carbodiimide hydrochloride

HATU: 2-(7-benzotriazole azo)-N,N,N',N'-tetramethyl urea phosphate hexafluoride

NBS: N-bromosuccinimide

DMAP: 4-dimethylaminopyridine

DIEA: N, N-diisopropyl ethylamine

SOCl₂: thionyl chloride

Pd /C: Palladium carbon

HMTA: hexamethylene tetramine

HOAc: acetic acid

HBr: Hydrobromic acid

HCl: hydrochloric acid

TFA: trifluoroacetic acid

TsOH: p-toluenesulfonate

NaOH: sodium hydroxide

ACN: acetonitrile

DCM: dichloromethane

5 DCE: dichloroethane

DMF: N, N-dimethylformamide

DMSO: dimethyl sulfoxide

Et₂O: diethyl ether

EA: ethyl acetate

10 PE: petroleum ether

THF: tetrahydrofuran

TBME: tert-butyl methyl ether

EXAMPLES

15 **General:** Infrared (IR) spectra were recorded on a Fourier Transform AVATARTM 360 E.S.PTM spectrophotometer (Unit: cm⁻¹). Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ¹H NMR spectra were recorded on a Varian-400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl₃: 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s =
20 singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration, and assignment. ¹⁹F and ³¹P NMR spectra were recorded on a Varian-400 (400 MHz) and Varian-500 (500MHz) spectrometers. The chemical shifts of the fluoro resonances were determined relative to trifluoroacetic acid as the external standard (CF₃CO₂H: 0.00 ppm), and the chemical shifts of the phosphorus resonances were determined relative to phosphoric acid as the
25 external standard (H₃PO₄: 0.00 ppm). Mass spectra were obtained at Thermo Finnigan LCQ Advantage. Unless otherwise noted, all reactions were conducted in oven- (135°C) and flame-dried glassware with vacuum-line techniques under an inert atmosphere of dry Ar. THF and Et₂O were distilled from sodium metal dried flask, DCM, pentane, and hexanes were distilled from calcium hydride. Most chemicals were obtained from commercial sources or ordered by contract synthesis
30 from Zannan SciTech Co., Ltd. in China. General procedures for preparation of different polyheterocyclic intermediates and products (**Ia-Ib** and **IIa-IIb**) are described in the following

Example 1Synthesis of compound **VIa**:

SM-1 (12.2g, 0.5mol) and 100mL DCM were added into a 250mL reaction flask, then NaOH (5g) and DMSO (50mL) were added and heated to 100 °C. After the reaction was completed, the mixture was poured into ice water and extracted three times with DCM. The combined organic layer was washed with brine, then dried and concentrated, finally purified by column chromatography with silica gel to obtain the cyclized product **1-1** (7.7g), yield 61%. ESI-MS ($M+H^+$): m/z calculated 253.1, founded 253.2.

The product **1-1** (5.0g, 0.2mol) was dissolved in ethanol, catalyst Pd / C (0.5g) was added under hydrogen pressure (0.6MPa). When the reaction was completed, the mixture was filtered and washed with ethanol, then the filtrate was concentrated to offer crude product (3.0g). After purified by flash column, the desired product **VIa** (2.5g) was obtained with purity over 99%, yield 76%. Total yield for two steps: 46%.

$^1\text{H-NMR}$ for the product **VIa** (CDCl_3 , 500MHz): δ 6.71(s, 2H), 5.91(s, 2H), 4.20(s, 2H), 4.15(s, 2H), 2.22(s, 1H, NH). ESI-MS ($M+H^+$): m/z calculated 164.1, founded 164.2.

Example 2Synthesis of compound **VIb**:

SM-1 (12g, 0.5mol) and 30mL DCE were added to a 250mL reaction flask, then NaOH (5g) and DMSO (50mL) were added and heated to 100 °C. After the reaction was completed, the mixture was poured into ice water and extracted three times with DCM. The combined organic layer was washed with brine, then dried and concentrated. After purified by flash column, the desired product **1-2** (9.4g) was obtained, yield 71%. ESI-MS ($M+H^+$): m/z calculated 268.1, founded 268.2.

The product of **2-1** (5.0g) was dissolved in ethanol, Pd / C (0.5g) was added with hydrogen pressure (0.6MPa). When the reaction was completed, the mixture was filtered and washed with ethanol, the filtrate was concentrated to give crude product (3.0g). After purified by flash column, the desired product **VIb** (2.9g) was obtained. Total yield for two steps: 61%.

¹H-NMR for the product **VIb** (CDCl₃, 500MHz): δ 6.77-6.75 (d, *J* = 8.0 Hz, 1H), 6.72-6.70 (d, *J* = 8.0 Hz, 1H), 4.29-4.28 (m, 2H), 4.27-4.26 (m, 2H), 4.19 (s, 2H), 4.17 (s, 2H), 2.27 (s, 1H, NH). ESI-MS (M+H⁺): *m/z* calculated 178.1, founded 178.2.

5

Example 3

Synthesis of Ru complex **VIc**:

SM-1 (12g, 0.5mol) and Br(CH₂)₃Br (20mL) were added to a 250mL reaction flask, then NaOH (5g) and DMSO (50mL) were added and heated to 100 °C. The reaction condition was the same as done in Example 2. After the cyclization and purification, the desired product **VIc** was
10 obtained. Total yield for two steps: 47%.

¹H-NMR for the product **VIc** (CDCl₃, 500MHz): δ 10.09 (s, 2H), 6.96-6.94 (d, *J* = 8.0 Hz, 1H), 6.92-6.90 (d, *J* = 7.5 Hz, 1H), 4.40-4.39 (m, 4H), 4.20-4.17 (t, *J* = 5.0 Hz, 2H), 4.13-4.11 (t, *J* = 5.0 Hz, 2H), 2.19-2.09 (m, 2H). ESI-MS [(M+H)⁺]: *m/z* calculated 192.1, founded 192.1.

15

Example 4

Synthesis of Ru complex **VIId**:

SM-2 (12g, 0.5mol) and Br(CH₂)₃Br (20mL) were added to a 250mL reaction flask, then NaOH (5g) and DMSO (50mL) were added and heated to 100 °C. The reaction condition was the same as done in Example 2. After the cyclization and purification, the desired product **VIc** was
20 obtained. Total yield for two steps: 41%.

¹H-NMR for the product **VIId** (CDCl₃, 500MHz): δ 6.86 (s, 2H), 4.30 (brs, 1H), 4.20 (s, 4H), 4.15-4.17 (t, *J* = 5.8 Hz, 4H), 2.16-2.18 (m, 2H).. ESI-MS [(M+H)⁺]: *m/z* calculated 192.1, founded 192.1.

25

Example 5

Synthesis of compound **VIe**

SM-2 (12g, 0.5mol) and DCE (30mL) were added to a 250mL reaction flask, then NaOH (5g) and DMSO (50mL) were added and heated to 100 °C. The reaction condition was the same as done in Example 2. After the cyclization and purification by flash column, the desired product

VIe was obtained. Total yield for two steps: 56%.

¹H-NMR for the product **VIe** (CDCl₃, 500MHz): δ 6.74 (s, 2H), 4.23 (s, 4H), 4.13 (s, 4H). ESI-MS (M+H⁺): m/z calculated 178.1, founded 178.2.

5

Example 6

Synthesis of compound **VI f**

SM-2 (12g, 0.5mol) and DCM (100mL) were added to a 250mL reaction flask, then NaOH (5g) and DMSO (50mL) were added and heated to 100 °C. The reaction condition was the same as done in Example 1. After the cyclization and purification by flash column, the desired product **VI f** was obtained. Total yield for two steps: 51%.

¹H-NMR for the product **VI f** (CDCl₃, 500MHz): δ 6.69 (s, 2H), 5.95 (s, 2H), 4.14 (s, 4H). ESI-MS (M+H⁺): m/z calculated 164.1, founded 164.2.

Example 7

15 Synthesis of compound **4a**

SM-4 (5.37g, 21.9mmol) and CDI (14.2g, 87.5mmol, 4eq.) were dissolved in 100mL anhydrous dichloromethane (DCM) and stirred overnight, followed by adding another compound **VIa** (43.7mmol, 2eq.) until completed. The reaction mixture was worked out and purified by flash column to obtain the product **4a** (5.2g) was obtained, yield 71%.

20 ¹H-NMR for the product **4a** (CDCl₃, 500MHz): δ 6.78-6.80 (m, 1H), 6.69-6.75 (m, 1H), 6.00 (s, 2H), 5.34 (m, 1H), 4.67-4.70 (d, *J* = 13.5 Hz, 2H), 4.60-4.63 (d, *J* = 15 Hz, 2H), 4.40-4.48 (m, 1H), 3.66-3.78 (m, 5H), 2.48 (m, 1H), 2.24-2.26 (m, 1H), 1.48 (s, 4H), 1.45 (s, 5H). ESI-MS (M+H⁺): m/z calculated 435.2, founded 435.3.

25

Example 8

Synthesis of compound **4b**:

SM-4 (5.37g, 21.9mmol) and CDI (14.2g, 87.5mmol, 4eq.) were dissolved in 100mL anhydrous dichloromethane and stirred at room temperature overnight, followed by adding another

compound **VIb** (43.7mmol, 2eq.) until completed. The reaction mixture was worked out and purified by flash column to obtain the product **4b** (6.1g), yield 82%.

¹H-NMR for the product **4b** (CDCl₃, 500MHz): δ 6.81-6.84 (m, 1H), 6.68-6.75 (m, 1H), 5.33 (m, 1H), 4.67 (s, 2H), 4.60 (s, 2H), 4.39-4.48 (m, 1H), 4.30 (m, 2H), 4.28 (m, 2H), 3.63-3.79 (m, 5H), 2.47-2.49 (m, 1H), 2.22-2.26 (m, 1H), 1.48 (s, 4H), 1.45 (s, 5H).

ESI-MS (M+H⁺): m/z calculated 449.2, founded 449.3.

Example 9

Synthesis of compound **4c**:

SM-4 (5.37g, 21.9mmol) and CDI (14.2g, 87.5mmol, 4eq.) were dissolved in 100mL anhydrous dichloromethane and stirred at room temperature overnight, followed by adding another compound **VIc** (43.7mmol, 2eq.) until completed. The reaction mixture was worked out and purified by flash column to obtain the product **4c** (6.1g), yield 82%.

The product **4c** was confirmed by ESI-MS (M+H⁺): m/z calculated 449.2, founded 449.3.

Example 10

Synthesis of compound **4d**:

SM-4 (5.37g, 21.9mmol) and CDI (14.2g, 87.5mmol, 4eq.) were dissolved in 100mL anhydrous dichloromethane and stirred at room temperature overnight, followed by adding another compound **VIId** (43.7mmol, 2eq.) until completed. The reaction mixture was worked out and purified by flash column to obtain the product **4d** (6.1g), yield 82%.

The product **4d** was confirmed by ESI-MS (M+H⁺): m/z calculated 449.2, founded 449.3.

Example 11

Synthesis of compound **4e**

SM-4 (5.37g, 21.9mmol) and CDI (14.2g, 87.5mmol, 4eq.) were dissolved in 100mL anhydrous dichloromethane and stirred at room temperature overnight, followed by adding another compound **VIe** (43.7mmol, 2eq.) until completed. The reaction mixture was worked out and

purified by flash column to obtain the product **4e** (5.7g), yield 75%.

¹H-NMR for the product **4e** (CDCl₃, 500MHz): ¹H-NMR (CDCl₃, 500MHz): δ 6.77 (s, 1H), 6.73 (s, 1H), 5.32 (m, 1H), 4.63 (s, 2H), 4.56 (s, 2H), 4.37-4.48 (m, 1H), 4.26 (s, 4H), 3.64-3.79 (m, 5H), 2.47 (m, 1H), 2.21-2.26 (m, 1H), 1.48 (s, 4H), 1.44 (s, 5H). ESI-MS (M+H⁺): m/z calculated 449.2, founded 449.3.

Example 12

Synthesis of compound **4f**

SM-4 (5.37g, 21.9mmol) and CDI (14.2g, 87.5mmol, 4eq.) were dissolved in 100mL anhydrous dichloromethane and stirred at room temperature overnight, followed by adding another compound **VIf** (43.7mmol, 2eq.) until completed. The reaction mixture was worked out and purified by flash column to obtain the product **4f** (5.9g), yield 74%.

¹H-NMR for the product **4f** (CDCl₃, 500MHz): ¹H-NMR (CDCl₃, 500MHz): δ 6.71 (s, 1H), 6.67 (s, 1H), 5.97 (s, 2H), 5.32 (m, 1H), 4.63 (s, 2H), 4.57 (s, 2H), 4.38-4.47 (m, 1H), 3.64-3.76 (m, 5H), 2.47 (m, 1H), 2.23-2.25 (m, 1H), 1.47 (s, 4H), 1.44 (s, 5H)

ESI-MS (M+H⁺): m/z calculated 435.2, founded 435.3.

Example 13

Synthesis of compound **6a**

The product of **4a** (2g, 4.9mmol) was dissolved in 40mL 4N HCl/Et₂O solvent and stirred at 30 °C until the completely deprotecting of Boc to give product **5a**.

The concentrated **5a** was dissolved in 50 mL DMF, compound **SM-5** (1.40g, 5.14mmol, 1.05eq.) and HATU (2.05g, 5.39mmol, 1.1eq.) were added. After cooled in ice bath for 15 minute, DIEA (2.53g, 19.6mmol, 4eq.) was added dropwise, the mixture was warmed to room temperature and stirred overnight until completed (monitored by HPLC-ELSD). The organic layer was separated and the water phase was extracted twice with ethyl acetate (2x100mL). The combined organic layer as was washed with 1N hydrochloric acid, water, saturated sodium bicarbonate, and brine, dried and evaporated, finally purified by flash column to obtain desired product **6a** (2.5g),

yield 87%, confirmed by ESI-MS ($M+H^+$): m/z calculated 588.3, founded 588.3.

Example 14

Synthesis of compound 7a

5 The product of **6a** (2.3g, 4.2mmol) was dissolved in 30mL THF, 15mL methanol and 15mL water. Lithium hydroxide monohydrate (0.54g, 12.8mmol, 3eq.) was added and stirred overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **7a** (2.1g), yield >95%, confirmed by ESI-MS ($M+H^+$): m/z calculated 574.3, founded 574.4.

10

Example 15

Synthesis of compound 8

The raw material **SM-7** (6.5g, 18mmol) was dissolved in HCl/Et₂O solution (4M, 80mL) and stirred at 30 °C until completed.

15 The above de-Boc product was concentrated and dissolved in 150mL DMF. Compound (L)-N-Boc-2-amino-8-azelaic acid (**SM-5**, 5.2g, 19mmol, 1.05 eq.) and HATU (7.6g, 20mmol, 1.1eq.) were added. After cooled in ice bathed for 15 minute, DIEA (9.5g, 76mmol, 4eq.) was added dropwise, the mixture was warmed to room temperature and stirred overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the
20 product **8** (2.5g), yield 87%.

¹H-NMR for the product **8** (CDCl₃, 500MHz): δ 7.73 (s, 1H), 5.70-5.79 (m, 2H), 5.27-5.31 (d, 1H, J = 17 Hz), 5.22-5.24 δ (d, 1H, J = 8 Hz), 5.11-5.13 (m, 1H), 4.93-5.01 (m, 2H), 4.68-4.71 (t, 1H, J = 7.5 Hz), 4.54 (br, 1H), 4.36-4.37 (m, 1H), 3.94-3.97 (d, 1H, J = 11.5 Hz), 3.65 (s, 3H), 3.55-3.58 (m, 1H), 3.39 (br, 1H), 2.97 (s, 1H), 2.89 (s, 1H), 2.49-2.52 (m, 1H), 2.12-2.16 (m, 1H),
25 2.02-2.04 (m, 4H), 1.83-1.85 (m, 1H), 1.74-1.78 (m, 1H), 1.59-1.61 (m, 1H), 1.43 (s, 9H), 1.31-1.40 (m, 4H), confirmed by ESI-MS ($M+H^+$): m/z calculated 508.3, founded 508.5.

Example 16

Synthesis of compound 9a

The two methods of synthesis of compounds **9a-9d** as showed in Schemes 4 and 5.

Method I: The product **7a** (2.0g, 4mmol) and vinyl substituted cyclopropyl amino acid methyl ester reagents **SM-6** (1.3g, 4.2mmol, 1.05eq.) and the coupling reagent HATU (1.83g, 4.82mmol, 1.1eq.) were dissolved in 80mL DMF. After cooled in ice bathed for 15 minute, DIEA (2.27g, 17.5mmol, 4eq.) was added dropwise, the mixture was warmed to room temperature and stirred overnight, followed by adding the product **VIa** (5.12mmol, 2eq.) until completed. The reaction mixture was worked out and purified by flash column to obtain the product **9a** (2.4g), yield 81%, confirmed by ESI-MS ($M+H^+$): m/z calculated 699.3, founded 699.4.

Method II: The product of the above Experiment 15 **8** (1.3g, 2.56mmol) and CDI (1.66g, 10.2mmol, 4eq.) were dissolved in 50mL anhydrous dichloromethane and stirred at room temperature overnight. When HPLC-ELSD shows the reaction was completed, the product of Experiment 1 **VIa** (5.12mmol, 2eq.) was added and stirred at room temperature until completed. The reaction mixture was worked out and purified by flash column to obtain the product **9a** (1.4g), yield 86%, confirmed by ESI-MS ($M+H^+$): m/z calculated 699.3, founded 699.4.

Example 17

Synthesis of compound **9b**

The synthesis of compounds **9b** adopted method II of Scheme 5: the product **8** (1.3g, 2.56mmol) and CDI (1.66g, 10.2mmol, 4eq.) were dissolved in 50mL of anhydrous dichloromethane at room temperature overnight, followed by adding the product **VIb** (5.12mmol, 2eq.) until completed. The reaction mixture was worked out and purified by flash column to obtain the product **9b** (1.6g), yield 94%, confirmed by ESI-MS ($M+H^+$): m/z calculated 711.4, founded 711.5.

Example 18

Synthesis of compound **9c**

The synthesis of compounds **9c** adopted method II of Scheme 5: the product **8** (1.3g, 2.56mmol) and CDI (1.66g, 10.2mmol, 4eq.) were dissolved in 50mL of anhydrous dichloromethane at room temperature overnight, followed by adding the product **VIc** (5.12mmol, 2eq.) until completed. The reaction mixture was worked out and purified by flash column to obtain the product **9c** (1.3g),

yield 77%, confirmed by ESI-MS ($M+H^+$): m/z calculated 711.4, founded 711.5.

Example 19

Synthesis of compound **9d**

5 The synthesis of compounds **9d** adopted method II of Scheme 5: the product **8** (1.3g, 2.56mmol) and CDI (1.66g, 10.2mmol, 4eq.) were dissolved in 50mL of anhydrous dichloromethane at room temperature overnight, followed by adding the product **VId** (5.12mmol, 2eq.) until completed. The reaction mixture was worked out and purified by flash column to obtain the product **9d** (1.3g), yield 77%, confirmed by ESI-MS ($M+H^+$): m/z
10 calculated 711.4, founded 711.5.

Example 20

Synthesis of compound **9e**

15 The synthesis of compounds **9e** adopted method II of Scheme 5: the product of the above mentioned Experiment 9 **8** (1.3g, 2.56mmol) and CDI (1.66g, 10.2mmol, 4eq.) were dissolved in 50mL of anhydrous dichloromethane at room temperature overnight, followed by adding the product **VIe** (5.12mmol, 2eq.) until completed. The reaction mixture was worked out and purified by flash column to obtain the product **9e** (1.4g), yield 83%, and confirmed by ESI-MS ($M+H^+$): m/z calculated 711.4, founded 711.5.

20

Example 21

Synthesis of compound **9f**

25 The synthesis of compounds **9f** adopted method II of Scheme 5: the product **8** (1.3g, 2.56mmol) and CDI (1.66g, 10.2mmol, 4eq.) were dissolved in 50mL of anhydrous dichloromethane at room temperature overnight, followed by adding the product **VI f** (5.12mmol, 2eq.) until completed. The reaction mixture was worked out and purified by flash column to obtain the product **9f** (1.3g), yield 78%, and confirmed by ESI-MS ($M+H^+$): m/z calculated 697.3, founded 697.4.

30

Example 22

Synthesis of compound **9-Ref**

Synthesis of compounds **9-Ref** adopted method II of Scheme 5: the product **8** (1.3g, 2.56mmol) and CDI (1.66g, 10.2mmol, 4eq.) were dissolved in 50mL of anhydrous DCE at room temperature overnight, followed by adding another compound **SM-8** (43.7mmol, 2eq.) until completed. The reaction mixture was worked out and purified by flash column to obtain the product **9-Ref** (1.4g), yield 81%.

¹H-NMR for the product **9-Ref** (CDCl₃, 500MHz): δ 7.65-7.70 (d, 1H, J = 9 Hz), 6.96-7.07 (m, 2H), 5.72-5.78 (m, 2H), 5.40 (br, 1H), 5.28-5.31 (d, 1H, J = 16.5 Hz), 5.12-5.14 (d, 1H, J = 10.5 Hz), 5.07-5.09 (d, 1H, J = 7.5 Hz), 4.93-5.00 (m, 2H), 4.64-4.79 (m, 5H), 4.36-4.37 (m, 1H), 4.06 (m, 1H), 3.72-3.75 (m, 1H), 3.67 (s, 3H), 2.78 (m, 1H), 2.26 (m, 1H), 2.14-2.16 (m, 1H), 2.01-2.03 (m, 2H), 1.86-1.88 (m, 1H), 1.70-1.73 (m, 1H), 1.57-1.60 (m, 1H), 1.45-1.49 (m, 2H), 1.37-1.40 (m, 4H), 1.32 (s, 4H), 1.29 (s, 5H), and confirmed by Mass spectrometry, ESI-MS (M+H⁺): m/z calculated 691.3, founded 691.4.

Example 23

Synthesis of compound **10a**

Under argon protection atmosphere, compound **9a** (2.25mmol) was dissolved in 450mL of anhydrous dichloromethane, and Zhan Catalyst-1B (RC-303, 74.4mg, 0.113mmol, 0.05eq.) was added. The reaction flask was stirred in a preheated oil bath at 80 °C overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **10a** (1.2g), yield 64%, and confirmed by ESI-MS (M+H⁺): m/z calculated 669.3, founded 669.4.

Example 24

Synthesis of compound **10b**

Under argon protection atmosphere, compound **9b** (2.25mmol) was dissolved in 450mL of anhydrous dichloromethane, and Zhan Catalyst-1B (RC-303, 74.4mg, 0.113mmol, 0.05eq.) was added. The reaction flask was stirred in a preheated oil bath at 80 °C overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **10b** (1.3g), yield 67%, and confirmed by ESI-MS (M+H⁺): m/z calculated 683.3, founded 683.5.

Example 25Synthesis of compound **10c**

Under argon protection atmosphere, compound **9c** (2.25mmol) was dissolved in 450mL of anhydrous dichloromethane, and Zhan Catalyst-1B (RC-303, 74.4mg, 0.113mmol, 0.05eq.) was added. The reaction flask was stirred in a preheated oil bath at 80 °C overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **10c** (1.2g), yield 56%, and confirmed by ESI-MS ($M+H^+$): m/z calculated 683.3, founded 683.5.

Example 2610 Synthesis of compound **10d**

Under argon protection atmosphere, compound **9d** (2.25mmol) was dissolved in 450mL of anhydrous dichloromethane, and Zhan Catalyst-1B (RC-303, 74.4mg, 0.113mmol, 0.05eq.) was added. The reaction flask was stirred in a preheated oil bath at 80 °C overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **10d** (1.3g), yield 61%, and confirmed by ESI-MS ($M+H^+$): m/z calculated 683.3, founded 683.5.

Example 27Synthesis of compound **10e**

Under argon protection atmosphere, compound **9e** (2.25mmol) was dissolved in 450mL of anhydrous dichloromethane, and Zhan Catalyst-1B (RC-303, 74.4mg, 0.113mmol, 0.05eq.) was added. The reaction flask was stirred in a preheated oil bath at 80 °C overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **10e** (1.1g), yield 51%, and confirmed by ESI-MS ($M+H^+$): m/z calculated 683.3, founded 683.5.

25

Example 28Synthesis of compound **10f**

Under argon protection atmosphere, compound **9f** (2.25mmol) was dissolved in 450mL of anhydrous dichloromethane, and Zhan Catalyst-1B (RC-303, 74.4mg, 0.113mmol, 0.05eq.) was

added. The reaction flask was stirred in a preheated oil bath at 80 °C overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **10f** (0.9g), yield 47%, and confirmed by ESI-MS ($M+H^+$): m/z calculated 669.3, founded 669.4.

5

Example 29

Synthesis of compound **10-Ref**

Under argon protection atmosphere, compound **9-Ref** (2.25mmol) was dissolved in 450mL of anhydrous dichloromethane, and Zhan Catalyst-1B (RC-303, 74.4mg, 0.113mmol, 0.05eq.) was added. The reaction flask was stirred in a preheated oil bath at 80 °C overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **10-Ref** (1.4g), yield 71%.

^1H -NMR for the product **10-Ref** ($CDCl_3$, 500MHz): δ 6.96-7.07 (m, 3H), 5.53-5.55 (m, 1H), 5.39 (m, 1H), 5.23-5.28 (m, 2H), 4.69-4.84 (m, 5H), 4.49 (m, 1H), 4.05-4.07 (m, 1H), 3.86-3.89 (m, 1H), 3.67 (s, 3H), 2.82-2.85 (m, 1H), 2.25-2.27 (m, 1H), 2.16-2.19 (m, 3H), 1.85-1.88 (m, 2H), 1.56-1.73 (m, 3H), 1.38-1.43 (m, 4H), 1.35 (s, 4H), 1.34 (s, 5H), and confirmed by ESI-MS ($M+H^+$): m/z calculated 643.3, founded 643.5.

Example 30

Synthesis of compound **11a**

The compound **10a** (0.6mmol) was dissolved in 30mL THF, 15mL methanol and 15mL water. Lithium hydroxide monohydrate (122.9mg, 2.93mmol, 5eq.) was added and stirred overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **11a** (466mg), yield >95%, and confirmed by ESI-MS ($M+H^+$): m/z calculated 655.3, founded 655.3.

25

Example 31

Synthesis of compound **11b**

The compound **10b** (0.6mmol) was dissolved in 30mL THF, 15mL methanol and 15mL water.

Lithium hydroxide monohydrate (122.9mg, 2.93mmol, 5eq.) was added and stirred overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **11b** (439mg), yield >95%, and confirmed by ESI-MS ($M+H^+$): m/z calculated 669.3, founded 669.3.

5

Example 32

Synthesis of compound **11c**

The compound **10c** (0.6mmol) was dissolved in 30mL THF, 15mL methanol and 15mL water. Lithium hydroxide monohydrate (122.9mg, 2.93mmol, 5eq.) was added and stirred overnight until
10 completed. The reaction mixture was worked out and purified by flash column to obtain the product **11c** (453mg), yield >95%, and confirmed by ESI-MS ($M+H^+$): m/z calculated 673.3, founded 673.3.

Example 33

15 Synthesis of compound **11d**

The compound **10d** (0.6mmol) was dissolved in 30mL THF, 15mL methanol and 15mL water. Lithium hydroxide monohydrate (122.9mg, 2.93mmol, 5eq.) was added and stirred overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **11d** (457mg), yield >95%, and confirmed by ESI-MS ($M+H^+$): m/z calculated 673.3,
20 founded 673.3.

Example 34

Synthesis of compound **11e**

The compound **10e** (0.6mmol) was dissolved in 30mL THF, 15mL methanol and 15mL water.
25 Lithium hydroxide monohydrate (122.9mg, 2.93mmol, 5eq.) was added and stirred overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **11e** (418mg), yield 85%, and confirmed by ESI-MS ($M+H^+$): m/z calculated 669.3, founded 669.3.

Example 35Synthesis of compound **11f**

The compound **10f** (0.6mmol) was dissolved in 30mL THF, 15mL methanol and 15mL water. Lithium hydroxide monohydrate (122.9mg, 2.93mmol, 5eq.) was added and stirred overnight until
5 completed. The reaction mixture was worked out and purified by flash column to obtain the product **11f** (453mg), yield >95%, and confirmed by ESI-MS ($M+H^+$): m/z calculated 655.3, founded 655.4.

Example 3610 Synthesis of compound **11j**

Compound **10e** (0.55g, 0.81mmol) was suspended in 10mL 4N HCl/ ether solvent, stirred for 2 h and concentrated. 10mL DCM and triethylamine (0.82g, 8mmol) were added and cooled to 0-5 °C. The raw material sulfonyl chloride (0.29g, 1.6mmol) was added slowly and the reaction was stirred at room temperature overnight until completed. The reaction mixture was worked out and
15 purified by flash column, and the product **13j** (0.43g, yield: 73%).

Compound **13j** (0.4g) was to added to the mixture solvent of NaOH (120mg, 3 mmol) , 10mL methanol and 0.5mL of water. The reaction mixture was stirred at 60 °C for 5 hr until completed. The reaction mixture was worked out and purified by flash column to obtain the product **11j** (0.31g, yield: 80%).

20 ^1H -NMR for the product **11j** ($CDCl_3$, 500MHz): δ 7.30 (s, 1H); 6.76 (s, 1H); 6.68 (s, 1H); 5.69 (q, J = 8.0Hz, 1H); 5.48 (s, 1H); 5.15 (t, J = 8.0Hz, 1H); 4.63-4.48 (m, 5H); 4.24 (s, 4H); 4.23-4.14 (m, 2H); 3.86 (m, 1H); 3.71 (m, 1H); 3.39 (m, 1H); 3.07-2.91 (m, 2H); 2.57 (m, 1H); 2.44 (m, 1H); 2.36-2.22 (br, 4H); 2.04 (m, 1H); 1.93 (m, 1H); 1.81 (m, 1H); 1.64-1.55 (br, 3H); 1.46-1.29 (br, 4H); 1.24-1.20 (br, 2H), and confirmed by ESI-MS ($M+H^+$): m/z calculated 673.2,
25 founded 673.3.

Example 37Synthesis of compound **11k**

The synthesis of compound **11k** was the same as **11j**.

Compound **10f** (0.55g, 0.81mmol) was suspended in 10mL 4N HCl/ ether solvent, stirred for 2 h and concentrated. 10mL DCM and triethylamine (0.82g, 8mmol) were added and cooled to 0-5 °C. The raw material sulfonyl chloride (0.29g, 1.6mmol) was added slowly and the reaction was stirred at room temperature overnight until completed. The reaction mixture was worked out and purified by flash column, and the product **13k** (0.48g, yield: 91%).

Compound **13k** (0.4g) was added to the mixture solvent of NaOH (120mg, 3mmol) , 10mL methanol and 0.5mL of water. The reaction mixture was stirred at 60 °C for 5 hr until completed. The reaction mixture was worked out and purified by flash column to obtain the product **11k** (0.30g, yield: 78%).

¹H-NMR for the product **11k** (CDCl₃, 500MHz): δ 7.32 (s, 1H); 6.71 (s, 1H); 6.63 (s, 1H); 5.96 (s, 2H); 5.69 (q, J = 8.0Hz, 1H); 5.48 (s, 1H); 5.15 (t, J = 8.0Hz, 1H); 4.64-4.49 (m, 5H); 4.23-4.15 (m, 2H); 3.89 (m, 1H); 3.72 (m, 1H); 3.40 (m, 1H); 3.09-2.89 (m, 2H); 2.58 (m, 1H); 2.48 (m, 1H); 2.39-2.26 (br, 4H); 2.08 (m, 1H); 1.96 (m, 1H); 1.82 (m, 1H); 1.69-1.54 (br, 3H); 1.46-1.29 (br, 4H); 1.26-1.20 (br, 2H) and confirmed by ESI-MS (M+H⁺): m/z calculated 659.2, founded 659.3.

Example 38

Synthesis of compound **11m**

The synthesis of compound **11m** was the same as **11j**.

Compound **10-Ref** (0.55g, 0.81mmol) was suspended in 10mL 4N HCl/ ether solvent, stirred for 2 h and concentrated. 10mL DCM and triethylamine (0.82g, 8mmol) were added and cooled to 0-5 °C. The raw material sulfonyl chloride (0.29g, 1.6mmol) was added slowly and the reaction was stirred at room temperature overnight until completed. The reaction mixture was worked out and purified by flash column, and the product **13m** (0.35g, yield: 65%).

Compound **13m** (0.3g) was added to the mixture solvent of NaOH (120mg, 3mmol) , 10mL methanol and 0.5mL of water. The reaction mixture was stirred at 60 °C for 5 hr until completed. The reaction mixture was worked out and purified by flash column to obtain the product **11m** (0.21g, yield: 76%).

¹H-NMR for the product **11m** (CDCl₃, 500MHz): δ 7.25 (m, 1H); 7.06-6.95 (m, 2H); 5.71 (q,

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J = 8.0Hz, 1H); 5.49 (s, 1H); 5.32 (s, 1H); 5.14 (t, J = 8.0Hz, 1H); 4.80-4.4.61 (m, 5H); 4.31 (m, 1H); 4.16 (m, 1H); 3.86 (m, 1H); 3.72 (q, J = 5.6Hz, 1H); 3.40 (q, J = 5.6Hz, 1H); 3.02 (m, 1H); 2.92 (m, 1H); 2.61 (br, 1H); 2.52 -2.41 (br, 2H); 2.33-2.24 (br, 3H); 2.06 (br, 1H); 1.93 (br, 1H); 1.83 (br, 1H); 1.63-1.54 (br, 3H); 1.42-1.22 (br, 6H) and confirmed by ESI-MS ($M+H^+$): m/z

5 calculated 633.2, founded 633.3.

Example 39

Synthesis of compound **11-Ref**

Synthesis of compound **11-Ref** was the same as **11a**.

10 The compound **10-Ref** (0.6mmol) was dissolved in 30mL THF, 15mL methanol and 15mL water. Lithium hydroxide monohydrate (122.9mg, 2.93mmol, 5eq.) was added and stirred overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **11-Ref** (438mg), yield >95%.

^1H -NMR for the product **11-Ref** ($CDCl_3$, 500MHz): δ 7.16 (m, 1H), 6.96-7.07 (m, 2H),
 15 5.63-5.64 (m, 1H), 5.32 (m, 1H), 5.20-5.28 (m, 2H), 4.68-4.78 (m, 5H), 4.34-4.40 (m, 1H), 4.19 (m, 1H), 3.89 (m, 1H), 2.68-2.78 (m, 1H), 2.32 (m, 2H), 2.21 (m, 1H), 2.10 (m, 1H), 1.84-1.87 (m, 2H), 1.59-1.62 (m, 2H), 1.40-1.45 (m, 5H), 1.32 (s, 4H), 1.30 (s, 5H) and confirmed by ESI-MS ($M+H^+$): m/z calculated 629.3, founded 629.4.

Example 40

20 Synthesis of compound **12a**

Compound **11a** (0.18mmol) was dissolved in 10mL anhydrous dichloromethane, EDCI (69.8mg, 0.36mmol, 2eq.) was added and stirred at room temperature overnight until completed. The reaction mixture was worked out and concentrated.

The obtained solid mixture above was dissolved in 10mL of anhydrous DCE, DBU (61.0mg,
 25 0.40mmol) and RSO_2NH_2 (0.36mmol, **R** = **cyclopropyl**) were added and stirred at room temperature overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **12a** (56mg; Yield: 58%).

^1H -NMR for the product **12a** ($CDCl_3$, 500MHz): δ 10.29-10.30 (d, 1H), 6.97-7.02 (d, 2H),

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6.60-6.78 (m, 2H), 5.98-5.99 (m, 2H), 5.70-5.73 (m, 1H), 5.47 (m, 1H), 4.98-5.08 (m, 2H),
 4.56-4.70 (m, 5H), 4.37-4.40 (m, 1H), 4.21-4.23 (m, 1H), 3.84-3.86 (m, 1H), 2.90-2.93 (m, 1H),
 2.50-2.56 (m, 2H), 2.46-2.48 (m, 1H), 2.25-2.28 (m, 1H), 1.89-1.95 (m, 2H), 1.74-1.79 (m, 2H),
 1.46-1.58 (m, 6H), 1.36-1.39 (m, 2H), 1.29 (s, 4H), 1.25 (s, 5H), 1.08-1.16 (m, 2H), 0.90-0.95 (m,
 5 1H); and confirmed by ESI-MS ($M+H^+$): m/z calculated 758.3, founded 758.4.

Example 41

Synthesis of compound **12b**

Compound **11b** (0.18mmol) was dissolved in 10mL anhydrous dichloromethane, EDCI
 10 (69.8mg, 0.36mmol, 2eq.) was added and stirred at room temperature overnight until completed.
 The reaction mixture was worked out and concentrated.

The obtained solid mixture was dissolved in 10mL of anhydrous dichloromethane, DBU
 (61.0mg, 0.40mmol) and RSO_2NH_2 (0.36mmol, **R** = **cyclopropyl**) were added and stirred at room
 temperature overnight until completed. The reaction mixture was worked out and purified by flash
 15 column to obtain the product **12b** (53mg; Yield: 51%).

^1H -NMR for the product **12b** ($CDCl_3$, 500MHz): δ 10.25-10.25 (d, 1H), 6.88-6.91 (m, 1H),
 6.77-6.80 (m, 1H), 6.58-6.60 (m, 1H), 5.68-5.74 (m, 1H), 5.45 (m, 1H), 4.98-5.06 (m, 2H),
 4.64-4.68 (m, 2H), 4.52-4.60 (m, 3H), 4.35-4.39 (m, 1H), 4.22-4.29 (m, 5H), 3.82-3.84 (m, 1H),
 2.88-2.91 (m, 1H), 2.45-2.56 (m, 2H), 2.41-2.45 (m, 1H), 2.23-2.29 (m, 1H), 1.82-1.93 (m, 1H),
 20 1.60-1.79 (m, 3H), 1.36-1.56 (m, 8H), 1.23-1.29 (m, 9H), 0.93-1.06 (m, 2H), 0.89-0.93 (m, 1H);
 and confirmed by ESI-MS ($M+H^+$): m/z calculated 772.3, founded 773.4.

Example 42

Synthesis of compound **12c**

Compound **11e** (0.18mmol) was dissolved in 10mL anhydrous dichloromethane, EDCI
 25 (69.8mg, 0.36mmol, 2eq.) was added and stirred at room temperature overnight until completed.
 The reaction mixture was worked out and concentrated.

The obtained solid mixture was dissolved in 10mL of anhydrous dichloromethane, DBU

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(61.0mg, 0.40mmol) and RSO₂NH₂ (0.36mmol, **R = cyclopropyl**) were added and stirred at room temperature overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **12c** (47mg; Yield: 42%).

¹H-NMR for the product **12c** (CDCl₃, 500MHz): δ 10.27 (s, 1H), 6.92 (s, 1H), 6.77 (s, 1H), 6.65 (s, 1H), 5.72-5.73 (m, 1H), 5.46 (m, 1H), 5.09 (m, 1H), 5.00 (m, 1H), 4.64 (m, 2H), 4.53-4.56 (m, 3H), 4.37-4.40 (m, 1H), 4.25 (m, 5H), 3.84-3.86 (m, 1H), 2.90 (m, 1H), 2.46-2.53 (m, 3H), 2.27-2.29 (m, 1H), 1.87-1.94 (m, 2H), 1.72 (m, 2H), 1.58 (m, 1H), 1.47 (m, 5H), 1.38 (m, 2H), 1.31 (s, 9H), 1.11 (m, 2H), 0.91 (m, 1H); and confirmed by ESI-MS (M+H⁺): m/z calculated 772.3, founded 773.4.

10

Example 43

Synthesis of compound **12d**

Compound **11f** (0.18mmol) was dissolved in 10mL anhydrous dichloromethane, EDCI (69.8mg, 0.36mmol, 2eq.) was added and stirred at room temperature overnight until completed. The reaction mixture was worked out and concentrated.

The obtained solid mixture was dissolved in 10mL of anhydrous dichloromethane, DBU (61.0mg, 0.40mmol) and RSO₂NH₂ (0.36mmol, **R = cyclopropyl**) were added and stirred at room temperature overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **12d** (65mg; Yield: 67%).

¹H-NMR for the product **12d** (CDCl₃, 500MHz): δ 10.24 (s, 1H), 6.80 (s, 1H), 6.72 (s, 1H), 6.59 (s, 1H), 5.98 (s, 2H), 5.70-5.76 (m, 1H), 5.47 (m, 1H), 5.03 (m, 2H), 4.65 (m, 2H), 4.53-4.57 (m, 3H), 4.38-4.41 (m, 1H), 4.23 (m, 1H), 3.85 (d, 1H), 2.92 (m, 1H), 2.51-2.57 (m, 2H), 2.45 (m, 1H), 2.28 (m, 1H), 1.95 (m, 2H), 1.59 (m, 1H), 1.59-1.65 (m, 2H), 1.48 (m, 5H), 1.38 (m, 2H), 1.30 (s, 9H), 1.12 (m, 2H), 0.92 (m, 1H).

ESI-MS (M+H⁺): m/z calculated 758.3, founded 758.5.

25

Example 44

Synthesis of compound **12e**

Compound **11a** (0.18mmol) was dissolved in 10mL anhydrous dichloromethane, EDCI (69.8mg, 0.36mmol, 2eq.) was added and stirred at room temperature overnight until completed. The reaction mixture was worked out and concentrated.

The obtained solid mixture was dissolved in 10mL of anhydrous dichloromethane, DBU (61.0mg, 0.40mmol) and RSO₂NH₂ (0.363mmol, **R = isopropyl**) were added and stirred at room temperature overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **12e** (53mg; Yield: 49%).

¹H-NMR for the product **12e** (CDCl₃, 500MHz): δ 9.91-9.93 (d, 1H), 6.72-6.83 (m, 3H), 5.95-5.99 (m, 2H), 5.72-5.73 (m, 1H), 5.47 (m, 1H), 4.99-5.05 (m, 2H), 4.57-4.71 (m, 5H), 4.40-4.42 (m, 1H), 4.22 (m, 1H), 3.83-3.85 (d, 1H), 3.70-3.72 (m, 1H), 2.55-2.57 (m, 2H), 2.46-2.48 (m, 1H), 2.27-2.30 (m, 1H), 1.97 (m, 1H), 1.76-1.86 (m, 3H), 1.42-1.46 (m, 6H), 1.32-1.37 (m, 4H), 1.24-1.28 (d, 9H), 0.89-0.91 (m, 3H).

ESI-MS (M+H⁺): m/z calculated 760.3, founded 760.4.

15

Example 45

Synthesis of compound **12f**

Compound **11b** (0.18mmol) was dissolved in 10mL anhydrous dichloromethane, EDCI (69.8mg, 0.36mmol, 2eq.) was added and stirred at room temperature overnight until completed. The reaction mixture was worked out and concentrated.

The obtained solid mixture was dissolved in 10mL of anhydrous dichloromethane, DBU (61.0mg, 0.40mmol) and RSO₂NH₂ (0.363mmol, **R = isopropyl**) were added and stirred at room temperature overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **12f** (50mg; Yield: 46%).

¹H-NMR for the product **12f** (CDCl₃, 500MHz): δ 9.94 (s, 1H), 6.73-6.78 (m, 2H), 6.59-6.73 (m, 1H), 5.69-5.75 (m, 1H), 5.47 (m, 1H), 4.99-5.05 (m, 2H), 4.63-4.67 (m, 2H), 4.42-4.53 (m, 3H), 4.29-4.38 (m, 1H), 4.25-4.29 (m, 5H), 3.83-3.86 (m, 1H), 3.68-3.75 (m, 1H), 2.53-2.58 (m, 2H), 2.43-2.48 (m, 1H), 2.28-2.30 (m, 1H), 1.96-2.00 (m, 1H), 1.69-1.93 (m, 3H), 1.42-1.47 (m, 6H), 1.32-1.44 (m, 4H), 1.24-1.29 (m, 9H), 0.86-0.93 (m, 3H); and confirmed by

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ESI-MS ($M+H^+$): m/z calculated 774.3, founded 774.4.

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Example 46

Synthesis of compound **12g**

5 Compound **11c** (0.18mmol) was dissolved in 10mL anhydrous dichloromethane, EDCI (69.8mg, 0.36mmol, 2eq.) was added and stirred at room temperature overnight until completed. The reaction mixture was worked out and concentrated.

The obtained solid mixture was dissolved in 10mL of anhydrous dichloromethane, DBU (61.0mg, 0.40mmol) and RSO_2NH_2 (0.363mmol, **R** = **isopropyl**) were added and stirred at room
10 temperature overnight until completed. The reaction mixture was worked out to obtain the white solid product **12g** (45mg; Yield: 38%).

^1H -NMR for the product **12g** ($CDCl_3$, 500MHz): δ 9.91 (s, 1H), 6.77-6.78 (m, 2H), 6.65 (s, 1H), 5.69-5.75 (m, 1H), 5.47 (m, 1H), 5.01-5.03 (m, 2H), 4.60-4.64 (m, 2H), 4.53-4.60 (m, 3H), 4.39-4.42 (m, 1H), 4.26 (m, 5H), 3.84-3.85 (m, 1H), 3.69-3.72 (m, 1H), 2.54-2.56 (m, 2H),
15 2.43-2.48 (m, 1H), 2.28-2.29 (m, 1H), 1.96 (m, 1H), 1.74-1.86 (m, 2H), 1.59 (m, 1H), 1.37-1.43 (m, 7H), 1.32-1.33 (m, 15H); and confirmed by ESI-MS ($M+H^+$): m/z calculated 774.3, founded 774.4.

Example 47

20 Synthesis of compound **12h**

Compound **11d** (0.18mmol) was dissolved in 10mL anhydrous dichloromethane, EDCI (69.8mg, 0.36mmol, 2eq.) was added and stirred at room temperature overnight until completed. The reaction mixture was worked out and concentrated.

The obtained solid mixture was dissolved in 10mL of anhydrous dichloromethane, DBU
25 (61.0mg, 0.40mmol) and RSO_2NH_2 (0.363mmol, **R** = **isopropyl**) were added and stirred at room temperature overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **12h** (53mg; Yield: 48%).

^1H -NMR for the product **12h** ($CDCl_3$, 500MHz): δ 9.95 (s, 1H), 6.90 (s, 1H), 6.71 (s, 1H),

6.59 (s, 1H), 5.98 (s, 2H), 5.73 (m, 1H), 5.47 (m, 1H), 5.04 (m, 2H), 4.65 (m, 2H), 4.53-4.57 (m, 3H), 4.39-4.41 (m, 1H), 4.23 (m, 1H), 3.84-3.85 (d, 1H), 3.70 (m, 1H), 2.53 (m, 2H), 2.48 (m, 1H), 2.28 (m, 1H), 1.95 (m, 1H), 1.76-1.86 (m, 3H), 1.57 (m, 1H), 1.41-1.46 (m, 7H), 1.30 (m, 15H); and confirmed by ESI-MS ($M+H^+$): m/z calculated 760.3, founded 760.4.

5

Example 48

Synthesis of compound **12j**

Compound **11j** (0.18mmol) was dissolved in 10mL anhydrous dichloromethane, EDCI (69.8mg, 0.36mmol, 2eq.) was added and stirred at room temperature overnight until completed.

10 The reaction mixture was worked out and concentrated.

The obtained solid mixture was dissolved in 10mL of anhydrous dichloromethane, DBU (61.0mg, 0.40mmol) and RSO_2NH_2 (0.363mmol, R = cyclopropyl) were added and stirred at room temperature overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **12j** (73mg; Yield: 61%).

15 ^1H -NMR for the product **12j** ($CDCl_3$, 500MHz): δ 10.35 (s, 1H), 7.35 (s, 1H), 6.74 (s, 1H), 6.67 (s, 1H), 5.72-5.77 (q, 1H, $J = 8.5$ Hz), 5.52 (m, 1H), 5.00-5.04 (t, 1H, $J = 9.5$ Hz), 4.57-4.64 (m, 2H), 4.46-4.57 (m, 3H), 4.23 -4.25 (m, 5H), 4.08-4.11 (d, 1H), 3.88-3.90 (m, 1H), 3.65-3.69 (m, 1H), 3.32-3.37 (m, 1H), 2.92-3.05 (m, 2H), 2.88-2.92 (m, 1H), 2.66-2.74 (m, 1H), 2.40-2.53 (m, 2H), 2.26-2.35 (m, 3H), 1.80-2.05 (m, 3H), 1.48- 1.68 (m, 3H), 1.26-1.48 (m, 6H), 1.08-1.13
20 (m, 2H), 0.90-0.94 (m, 1H). ESI-MS ($M+H^+$): m/z calculated 776.3, founded 776.4.

Example 49

Synthesis of compound **12k**

Compound **11k** (0.18mmol) was dissolved in 10mL anhydrous dichloromethane, EDCI
25 (69.8mg, 0.36mmol, 2eq.) was added and stirred at room temperature overnight until completed. The reaction mixture was worked out and concentrated.

The obtained solid was dissolved in 10mL of anhydrous dichloromethane, DBU (61.0mg, 0.40mmol) and RSO_2NH_2 (0.363mmol, **R = cyclopropyl**) were added and stirred at room

temperature overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **12k** (54mg; Yield: 38%).

¹H-NMR for the product **12k** (CDCl₃, 500MHz): δ 10.36 (s, 1H), 7.39 (s, 1H), 6.70 (s, 1H), 6.64 (s, 1H), 5.97 (s, 2H), 5.74-5.76 (m, 2H), 5.53 (m, 1H), 5.01-5.05 (t, 1H, J = 9.5 Hz), 4.46-4.64 (m, 5H), 4.24-4.26 (d, 1H), 4.10-4.13 (m, 1H), 3.88-3.91 (m, 1H), 3.66-3.68 (m, 1H), 3.33-3.38 (m, 1H), 2.90-3.03 (m, 3H), 2.71 (m, 1H), 2.49-2.51 (m, 1H), 2.42-2.45 (m, 1H), 2.28-2.34 (m, 3H), 1.81-2.02 (m, 4H), 1.62-1.69 (m, 4H), 1.44-1.49 (m, 4H), 1.08-1.14 (m, 2H), 0.86-0.96 (m, 1H). ESI-MS (M+H⁺): m/z calculated 762.2, founded 762.3.

10

Example 50

Synthesis of compound **12m**

Compound **11m** (0.18mmol) was dissolved in 10mL anhydrous dichloromethane, EDCI (69.8mg, 0.36mmol, 2eq.) was added and stirred at room temperature overnight until completed. The reaction mixture was worked out and concentrated.

15

The obtained solid was dissolved in 10mL of anhydrous dichloromethane, DBU (61.0mg, 0.40mmol) and RSO₂NH₂ (0.363mmol, **R = cyclopropyl**) were added and stirred at room temperature overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **12m** (61mg; Yield: 52%).

20

¹H-NMR for the product **12m** (CDCl₃, 500MHz): δ 10.38-10.41 (d, 1H), 7.51-7.55 (d, 1H, J = 20 Hz), 6.94-7.05 (m, 2H), 5.73-5.79 (m, 2H), 5.54 (m, 1H), 5.02-5.06 (t, 1H, J = 9.5 Hz), 4.75-4.85 (m, 2H), 4.54-4.64 (m, 3H), 4.29-4.33 (t, 1H, J = 11 Hz), 4.08-4.10 (d, 1H), 3.85-3.89 (m, 1H), 3.65-3.68 (m, 1H), 3.31-3.36 (m, 3H), 2.73-2.74 (m, 1H), 2.51-2.52 (m, 2H), 2.27-2.36 (m, 3H), 1.72-2.02 (m, 4H), 1.27-1.66 (m, 9H), 1.09-1.13 (m, 2H), 0.91-0.95 (m, 1H). ESI-MS (M+H⁺): m/z calculated 736.2, founded 736.4.

25

Example 51

Synthesis of compound **12n**

Compound **11c** (0.18mmol) was dissolved in 10mL anhydrous dichloromethane, EDCI

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(69.8mg, 0.36mmol, 2eq.) was added and stirred at room temperature overnight until completed.

The reaction mixture was worked out and concentrated.

The obtained solid mixture was dissolved in 10mL of anhydrous dichloromethane, DBU (61.0mg, 0.40mmol) and RSO₂NH₂ (0.36mmol, **R = cyclopropyl**) were added and stirred at room temperature overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **12n** (47mg; Yield: 42%).

¹H-NMR for the product **12n** (CDCl₃, 500MHz): δ 10.27 (s, 1H), 6.89-6.92 (m, 2H), 6.67-6.79 (m, 1H), 5.72-5.74 (m, 1H), 5.46-5.47 (m, 1H), 4.99-5.07 (m, 2H), 4.55-4.69 (m, 5H), 4.39 (m, 1H), 4.21-4.25 (m, 5H), 3.84-3.86 (m, 1H), 2.90-2.93 (m, 1H), 2.45-2.56 (m, 3H), 2.19-2.29 (m, 3H), 1.89-1.95 (m, 2H), 1.71-1.79 (m, 2H), 1.58 (m, 1H), 1.34-1.50 (m, 7H), 1.29 (s, 5H), 1.25 (s, 4H), 1.08-1.16 (m, 2H), 0.92-0.94 (m, 1H). ESI-MS (M+H⁺): m/z calculated 786.3, founded 786.4.

Example 52

Synthesis of compound **12p**

Compound **11d** (0.18mmol) was dissolved in 10mL anhydrous dichloromethane, EDCI (69.8mg, 0.36mmol, 2eq.) was added and stirred at room temperature overnight until completed. The reaction mixture was worked out and concentrated.

The obtained solid mixture was dissolved in 10mL of anhydrous dichloromethane, DBU (61.0mg, 0.40mmol) and RSO₂NH₂ (0.36mmol, **R = cyclopropyl**) were added and stirred at room temperature overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **12p** (65mg; Yield: 67%).

¹H-NMR for the product **12p** (CDCl₃, 500MHz): δ 10.28 (s, 1H), 7.00 (s, 1H), 6.87 (s, 1H), 6.75 (s, 1H), 5.70-5.72 (m, 1H), 5.45 (m, 1H), 4.97-5.09 (m, 2H), 4.52-4.63 (m, 5H), 4.35-4.38 (m, 1H), 4.14-4.22 (m, 5H), 3.83-3.84 (m, 1H), 2.88-2.91 (m, 1H), 2.44-2.53 (m, 3H), 2.17-2.27 (m, 3H), 1.76-1.91 (m, 4H), 1.57 (m, 1H), 1.37-1.51 (m, 7H), 1.28 (s, 9H), 1.06-1.13 (m, 2H), 0.89-0.93 (m, 1H). ESI-MS (M+H⁺): m/z calculated 786.3, founded 786.4.

Example 53

Synthesis of compound **12q**

Compound **12d** (0.18mmol) was dissolved in 20mL HCl-Et₂O (2N) and stirred at 30 °C until completed to obtain de-Boc product, followed by reacting with another reagent iPrOC(O)Cl (1.2eq) to obtain the product **12q**. yield: 72%.

5 ¹H-NMR for the product **12q** (CDCl₃, 500MHz): δ 10.27 (s, 1H), 6.97 (br, 1H), 6.70 (s, 1H), 6.59 (s, 1H), 5.95 (s, 2H), 5.70 (q, *J* = 8.1 Hz, 1H), 5.44 (s, 1H), 5.14 (s, 1H), 4.99 (t, *J* = 8.1 Hz, 1H), 4.65-4.47 (m, 5H), 4.35 (m, 2H), 4.24 (br, 1H), 3.82 (m, 1H), 2.91 (m, 1H), 2.45 (m, 3H), 2.23 (m, 1H), 1.92 (br, 2H), 1.74 (br, 2H), 1.59 (m, 1H), 1.47-1.27 (br, 8H), 1.11-1.06 (br, 5H), 1.01 (d, *J* = 4.7 Hz, 3H), 0.96 (m, 1H). ESI-MS (M+H⁺): *m/z* calculated 744.3, founded 744.3.

10

Example 54Synthesis of compound **12r**

Compound **12d** (0.18mmol) was dissolved in 20mL HCl-Et₂O (2N) and stirred at 30 °C until completed to obtain de-Boc product, followed by reacting with another reagent iPrOC(O)Cl
15 (1.2eq) to obtain the product **12r**. yield: 76%.

¹H-NMR for the product **12r** (CDCl₃, 500MHz): δ 10.35 (s, 1H), 7.26 (s, 1H), 6.68 (s, 1H), 6.57 (s, 1H), 5.92 (s, 2H), 5.67 (q, *J* = 8.1 Hz, 1H), 5.42 (s, 1H), 4.95 (t, *J* = 8.1 Hz, 1H), 4.58 (m, 5H), 4.29 (m, 2H), 3.81 (m, 1H), 2.86 (m, 1H), 2.42 (br, 3H), 2.24 (m, 1H), 1.77 (m, 4H), 1.58-1.25 (m, 18H), 1.07 (m, 2H), 0.90 (m, 1H). ESI-MS (M+H⁺): *m/z* calculated 770.3, founded 770.4.

20

Example 55Synthesis of compound **12s**

The synthetic procedure is the same as in Examples 48-50 starting **10f** with in 0.3 mmol scale. Finally, 32 mg of product **12s** was obtained, and confirmed by ESI-MS (M+H⁺): *m/z*
25 calculated 770.3, founded 770.4.

Example 56

The synthetic procedure is the same as in Examples 48-50 starting **10f** with in 0.3 mmol scale. Finally, 41 mg of product **12s** was obtained, and confirmed by ESI-MS ($M+H^+$): m/z calculated 770.3, founded 770.4.

5

Example 57Synthesis of compound **12u**

The synthetic procedure is the same as in Examples 48-50 starting **10-Ref** with in 0.3 mmol scale. Finally, 52 mg of product **12u** was obtained, and confirmed by ESI- MS ($M+H^+$): m/z calculated 810.3, founded 810.4.

10

Example 58Synthesis of compound **12-Ref**

Compound **11-Ref** (0.18mmol) was dissolved in 10mL anhydrous dichloromethane, EDCI (69.8mg, 0.36mmol, 2eq.) was added and stirred at room temperature overnight until completed. The reaction mixture was worked out and concentrated.

15

The obtained solid was dissolved in 10mL of anhydrous dichloromethane, DBU (61.0mg, 0.40mmol) and RSO_2NH_2 (0.363mmol, R = cyclopropyl) were added and stirred at room temperature overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **12-Ref** (62mg; Yield: 53%).

20

^1H -NMR for the product **12-Ref** ($CDCl_3$, 500MHz): δ 10.28-10.29 (d, 1H), 6.87-7.07 (m, 3H), 5.72-5.74 (m, 1H), 5.48 (br , 1H), 4.99-5.03 (m, 2H), 4.58-4.79 (m, 5H), 4.42 (m, 1H), 4.21 (m, 1H), 3.83-3.85 (m, 1H), 2.90-2.93 (m , 1H), 2.48-2.57 (m, 3H), 2.27-2.30 (m, 1H), 1.88-1.97 (m, 2H), 1.67-1.79 (m, 2H), 1.45-1.58 (m, 6H), 1.34 -1.40 (m, 2H), 1.27 (s, 4H), 1.24 (s, 5H), 1.08-1.15 (m, 2H), 0.91-0.94 (m, 1H). ESI-MS ($M+H^+$): m/z calculated 732.3, founded 732.5.

25

Example 59

Compound **12d** (3.0mmol) was dissolved in 30mL HCl-Et₂O (4N) to remove Boc group, followed by adding phenyl borate and Cu(AcO)₂ (2eq/each.) in DCE (30mL) to obtain the product **15a** (Yield: 62%). ESI-MS (M+H⁺): m/z calculated 734.3, founded 734.4.

5

Example 60Synthesis of compound **15b**

Compound **12d** (3.0mmol) was dissolved in 30mL HCl-Et₂O (4N) to remove Boc group, followed by adding m-fluorophenyl borate and Cu(AcO)₂ (2eq/each.) in DCE (30mL) to obtain the product **15b** (Yield: 53%). ESI-MS (M+H⁺): m/z calculated 752.3, founded 752.3.

10

Example 61Synthesis of compound **16a**

Compound **12d** (3.0mmol) was dissolved in 30mL HCl-Et₂O (4N) to remove Boc group, followed by adding p-chlorophenylsulfonyl chloride (1.3eq) in DCE (30mL) to obtain the product **16a** (Yield: 81%). ESI-MS (M+H⁺): m/z calculated 832.2, founded 832.2.

15

Example 62Synthesis of compound **16b**

Compound **12d** (3.0mmol) was dissolved in 30mL HCl-Et₂O (4N) to remove Boc group, followed by adding phenylsulfonyl chloride (1.3eq)) in DCE (30mL) to obtain the product **16b** (Yield: 74%). ESI-MS (M+H⁺): m/z calculated 798.2, founded 798.3.

20

Example 6325 Synthesis of compound **16c**

Compound **12d** (3.0mmol) was dissolved in 30mL HCl-Et₂O (4N) to remove Boc group, followed by adding p-methoxyphenylsulfonyl chloride (1.3eq) in DCE (30mL) to obtain the

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product **16c** (Yield: 79%). ESI-MS ($M+H^+$): m/z calculated 828.2, founded 828.3.

Example 64

Synthesis of compound **17**

5 **SM-11** (35g), DMF (350mL) were added to a flask, followed by adding **SM-12** (17g) and HATU (10.4g) into the reaction mixture in ice-water bath. After stirred for 10 minutes, DIEA (125mL) was added, the mixture was allowed to room temperature. The mixture was stirred overnight and concentrated under reduced pressure. The reaction mixture was worked out and purified by flash column to obtain the foamy solid product **17** (18.6g). Confirmed by ESI-MS
10 ($M+H^+$): m/z calculated 407.3, founded 407.5.

Example 65

Synthesis of compound **21a**

 The synthetic procedure starting with intermediate **17** is the same as in Examples 16-47 for
15 preparation of **12a-12h** in 1.0 mmol scale to prepare **21a**. After purification, 59 mg of product **21a** was obtained. Confirmed by ESI-MS ($M+H^+$): m/z calculated 669.3, founded 669.4.

Example 66

Synthesis of compound **21b**

20 The synthetic procedure starting with intermediate **17** is the same as in Examples 16-47 for preparation of **12a-12h** in 1.0 mmol scale to prepare **21b**. After purification, 46 mg of product **21b** was obtained. Confirmed by ESI-MS ($M+H^+$): m/z calculated 683.3, founded 683.4.

Example 67

25 Synthesis of compound **21c**

 The synthetic procedure starting with intermediate **17** is the same as in Examples 16-47 for preparation of **12a-12h** in 1.0 mmol scale to prepare **21c**. After purification, 49 mg of product **21c**

was obtained. Confirmed by ESI-MS ($M+H^+$): m/z calculated 643.3, founded 643.4.

Example 68

Synthesis of compound **21d**

5 The synthetic procedure starting with intermediate **17** is the same as in Examples 16-47 for preparation of **12a-12h** in 1.0 mmol scale to prepare **21d**. After purification, 63 mg of product **21d** was obtained. Confirmed by ESI-MS ($M+H^+$): m/z calculated 683.3, founded 683.4.

Example 69

10 Synthesis of compound **21e**

 The synthetic procedure starting with intermediate **17** is the same as in Examples 16-47 for preparation of **12a-12h** in 1.0 mmol scale to prepare **21e**. After purification, 63 mg of product **21e** was obtained.

^1H -NMR for the product **21e** ($CDCl_3$, 500MHz): δ 10.60 (s, 1H), 7.10 (s, 1H), 6.61-6.74
15 (m,3H), 5.95 (s, 2H), 5.65-5.69 (m, 1H), 5.26-5.29 (m, 1H), 4.98-5.09 (m, 1H), 4.65-4.68 (m, 1H),
4.41-4.56 (m, 4H), 3.88-3.91 (m,1H), 3.47-3.53 (m, 2H), 3.19-3.26 (m, 1H), 3.07 (s, 1H),
2.96-3.01 (m, 1H), 2.90 (s, 3H), 2.50-2.64 (m, 1H), 2.24-2.28 (m, 1H), 2.04-2.16 (m, 3H),
1.67-1.99 (m, 4H), 1.08-1.49 (m, 8H), 0.86-0.96 (m, 2H). ESI-MS ($M+H^+$): m/z calculated 657.3,
founded 657.4

20

Example 70

Synthesis of compound **21f**

 The synthetic procedure starting with intermediate **17** is the same as in Examples 16-47 for preparation of **12a-12h** in 1.0 mmol scale to prepare **21f**. After purification, 63 mg of product **21f**
25 was obtained. Confirmed by ESI-MS ($M+H^+$): m/z calculated 669.3, founded 669.5.

Example 71**Synthesis of compound 27a**

The synthetic procedure starting with **SM-7** in 5.0 mmol scale is the same as in Examples 7-47 for preparation of **12a-12h** to prepare **27a**. After purification, 69mg of product **27a** was
5 obtained.

¹H-NMR for the product **27a** (CDCl₃, 500MHz): δ 6.71 (s, 1H), 6.66 (s, 1H), 5.97-5.98 (s, 2H),
5.70-5.73 (m, 1H), 5.31-5.37 (m, 1H), 5.13-5.17 (m, 1H), 4.83-4.86 (m, 1H), 4.51-4.62 (m, 4H),
3.80-3.83 (m, 1H), 3.78-3.79 (m, 1H), 3.52-3.54 (m, 1H), 3.06-3.09 (m, 1H), 2.90 (s, 3H),
2.48-2.49 (m, 1H), 2.23-2.35 (m, 2H), 2.00-2.08 (m, 4H), 1.63-1.72 (m, 2H), 1.38-1.51 (m, 8H),
10 1.80-1.82 (m, 3H). ESI-MS (M+H⁺): m/z calculated 658.3, founded 658.4.

Example 72**Synthesis of compound 27b**

The synthetic procedure starting with **SM-7** in 5.0 mmol scale is the same as in Examples
15 7-47 for preparation of **12a-12h** to prepare **27b**. After purification, 83mg of product **27b** was
obtained.

¹H-NMR for the product **27b** (CDCl₃, 500MHz): δ 6.72-6.76 (m, 2H), 5.71-5.72 (m, 1H),
5.36-5.37 (m, 1H), 5.15-5.17 (m, 1H), 4.84-4.85 (m, 1H), 4.53-4.61 (m, 4H), 4.25 (s, 4H),
3.79-3.82 (m, 2H), 3.51-3.53 (m, 1H), 2.93-3.04 (m, 2H), 2.89 (s, 3H), 2.48-2.49 (m, 1H),
20 2.24-2.35 (m, 2H), 1.93-2.03 (m, 3H), 1.69-1.73 (m, 1H), 1.49-1.51 (m, 2H), 1.27-1.38 (m, 3H),
1.06-1.14 (m, 2H), 0.80-0.88 (m, 3H). ESI-MS (M+H⁺): m/z calculated 672.3, founded 672.4.

Example 73**Synthesis of compound 27c**

The synthetic procedure starting with **SM-7** in 5.0 mmol scale is the same as in Examples
25 7-47 for preparation of **12a-12h** to prepare **27c**. After purification, 57mg of product **27c** was
obtained. Confirmed by ESI-MS (M+H⁺): m/z calculated 630.3, founded 630.5

Example 74Synthesis of compound **27-Ref**

The synthetic procedure starting with **SM-7** in 5.0 mmol scale is the same as in Examples 7-47 for preparation of **12a-12h** to prepare **27-Ref**. After purification, 89mg of product **27-Ref** was obtained.

¹H-NMR for the product **21e** (CDCl₃, 500MHz): δ 7.41-7.43 (m, 1H), 6.96-7.07 (m, 2H), 5.71-5.73 (m, 1H), 5.38-5.39 (m, 1H), 5.13-5.18 (m, 1H), 4.84-4.88 (m, 1H), 4.73-4.77 (m, 2H), 4.67-4.70 (m, 2H), 3.80-3.84 (m, 1H), 3.65-3.68 (m, 1H), 3.52-3.56 (m, 1H), 3.06-3.09 (m, 1H), 2.93-2.96 (m, 1H), 2.89 (s, 3H), 2.49-2.52 (m, 2H), 2.24-2.36 (m, 2H), 2.00-2.10 (m, 2H), 1.68-1.69 (m, 2H), 1.48-1.51 (m, 2H), 1.27-1.38 (m, 5H), 1.07-1.31 (m, 2H). ESI-MS (M+H⁺): m/z calculated 632.3, founded 632.4.

Example 75Synthesis of compound **27-Ref-2**

The synthetic procedure starting with **SM-7** in 5.0 mmol scale is the same as in Examples 7-47 for preparation of **12a-12h** to prepare **27-Ref-2**. After purification, 61mg of product **27-Ref-2** was obtained. Confirmed by ESI-MS (M+H⁺): m/z calculated 658.3, founded 658.4.

Example 7620 Synthesis of compound **30a**

Chemical **SM-13a** (5.4g, 10mmol), sulfonamide (**SM-8a**, 1.1eq) and DMF (80mL) were added into 250mL flask reactor, followed by adding coupling reagent EDCI (1.3eq) to keep the amidation at 55°C until completed. The reaction mixture was worked out to obtain crude product **28a**, followed by removing Boc group with HCl-THF solution to obtain **29a** (3.7g, yield: 83%), which was purified by precipitation in hexane-EtOAc and dried directly for next step. ESI-MS (M+H⁺): m/z calculated 533.2, founded 533.2.

In the presence of coupling reagent HATU (1.3eq) in DMF (1.0mL), compound **29a** (60mg, 0.1mmol) was reacted with another acid derivative **SM-14a** to obtain product **30a**. After

purification by falsh column, 39mg of **30a** was obtained.

¹H-NMR for the product **30a** (CDCl₃, 500MHz): δ 9.98 (s, 1H), 9.39 (m, 1H), 8.77 (m, 1H), 8.56 (m, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 7.32 (s, 1H), 6.89 (m, 1H), 6.71 (s, 1H), 6.67 (s, 1H), 5.95-5.96 (d, *J* = 5.1 Hz, 2H), 5.72-5.81 (m, 1H), 5.26-5.30 (m, 1H), 5.13-5.16 (m, 1H), 5.40 (s, 1H), 4.63-4.70 (m, 2H), 4.52-4.60 (m, 3H), 4.43-4.48 (m, 2H), 4.20-4.22 (d, *J* = 1.8 Hz, 1H), 3.88-3.91 (m, 1H), 2.81-2.86 (m, 1H), 2.35-2.38 (m, 1H), 2.06-2.13 (m, 1H), 2.04 (s, 1H), 1.95 (m, 2H), 1.87 (m, 1H), 1.61-1.73 (m, 6H), 1.46-1.50 (m, 1H), 1.24-1.31 (m, 4H), 0.99-1.06 (m, 12H). ESI-MS [(M+H)⁺]: m/z calculated 891.4, founded 891.5

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Example 77

Synthesis of compound **30b**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30b**. After purification, 46mg of product **30b** was obtained.

¹H-NMR for the product **30b** (CDCl₃, 500MHz): δ 9.99 (s, 1H), 9.39 (m, 1H), 8.76 (m, 1H), 8.55 (m, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 7.24 (s, 1H), 6.87-6.89 (d, *J* = 8.6 Hz, 1H), 6.72 (s, 1H), 6.67 (s, 1H), 5.95-5.96 (d, *J* = 5.1 Hz, 2H), 5.40 (s, 1H), 4.64-4.70 (m, 2H), 4.53-4.59 (m, 3H), 4.44-4.49 (m, 2H), 4.18-4.20 (d, *J* = 1.8 Hz, 1H), 3.86-3.89 (m, 1H), 2.96 (s, 1H), 2.88 (m, 1H), 2.04 (s, 1H), 1.95 (m, 2H), 1.85 (m, 1H), 1.53-1.73 (m, 9H), 1.17-1.35 (m, 6H), 0.96-1.03 (m, 12H). ESI-MS [(M+H)⁺]: m/z calculated 893.4, founded 893.4

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Example 78

Synthesis of compound **30c**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30c**. After purification, 41mg of product **30c** was obtained.

¹H-NMR for the product **30c** (CDCl₃, 500MHz): δ 10.37 (s, 1H), 9.26 (s, 1H), 8.74 (m, 1H), 8.57 (m, 1H), 8.34-8.36 (m, 1H), 7.31-7.32 (m, 1H), 6.76 (m, 1H), 6.79 (m, 1H), 5.92 (m, 1H), 5.39 (s, 1H), 5.30-5.33 (m, 1H), 5.13-5.15 (m, 2H), 4.72-4.74 (m, 1H), 4.61 (m, 2H), 4.49 (m, 2H), 4.40-4.43 (m, 2H), 4.25 (m, 4H), 2.87 (m, 1H), 2.47 (m, 1H), 2.25 (m, 2H), 1.89 (m, 4H),

1.78-1.80 (m, 4H), 1.65-1.67 (m, 1H), 1.44-1.48 (m, 2H), 1.13-1.21 (m, 8H), 1.02 (s, 9H). ESI-MS [(M+H)⁺]: m/z calculated 905.4, founded 905.4

Example 79

5 Synthesis of compound 30d

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30d**. After purification, 38mg of product **30d** was obtained.

¹H-NMR for the product **30d** (CDCl₃, 500MHz): δ10.38 (s, 1H), 9.27 (s, 1H), 8.74 (m, 1H), 8.57 (m, 1H), 8.34-8.36 (m, 1H), 7.30-7.32 (m, 1H), 6.82 (m, 1H), 6.64-6.71 (m, 1H), 5.90 (m, 1H), 5.39 (s, 1H), 5.30-5.32 (m, 1H), 5.13-5.15 (m, 2H), 4.73-4.75 (m, 1H), 4.64 (m, 2H), 4.46-4.52 (m, 2H), 4.37-4.39 (m, 2H), 4.27-4.29 (m, 4H), 2.88 (m, 1H), 2.46 (m, 1H), 2.23 (m, 2H), 1.87-1.90 (m, 6H), 1.78-1.80 (m, 4H), 1.65-1.67 (m, 1H), 1.43-1.49 (m, 2H), 1.14-1.231 (m, 6H), 1.03 (s, 9H). ESI-MS [(M+H)⁺]: m/z calculated 905.4, founded 905.4.

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Example 80

Synthesis of compound 30e

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30e**. After purification, 43mg of product **30e** was obtained.

¹H-NMR for the product **30e** (CDCl₃, 500MHz): δ10.39 (s, 1H), 9.27 (s, 1H), 8.74 (m, 1H), 8.57 (m, 1H), 8.38 (m, 1H), 7.30-7.32 (m, 1H), 6.78 (m, 1H), 6.69-6.74 (m, 1H), 5.99 (s, 2H), 5.87-5.95 (m, 1H), 5.40 (s, 1H), 5.31-5.34 (m, 1H), 5.12-5.14 (m, 2H), 4.73-4.76 (m, 1H), 4.65-4.66 (m, 2H), 4.47-4.58 (m, 3H), 4.37-4.42 (m, 1H), 2.88 (m, 1H), 2.47 (m, 1H), 2.24 (m, 2H), 1.89 (m, 3H), 1.78-1.80 (m, 4H), 1.65-1.67 (m, 1H), 1.42-1.47 (m, 2H), 1.14-1.23 (m, 6H), 1.03 (s, 9H), 0.84-0.88 (m, 3H), ESI-MS [(M+H)⁺]: m/z calculated 891.4, founded 891.4

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Example 81

Synthesis of compound 30f

The synthetic procedure was carried out as the same as in Example 76 for preparation of

compound **30f**. After purification, 43mg of product **30f** was obtained.

¹H-NMR for the product **30f** (CDCl₃, 500MHz): δ9.97-9.99 (m, 1H), 9.40 (s, 1H), 8.76 (m, 1H), 8.55 (m, 1H), 8.19 (m, 1H), 7.32-7.35 (m, 1H), 7.00 (m, 1H), 6.65-6.77 (m, 2H), 5.92-5.97 (m, 2H), 5.41 (s, 1H), 4.47-4.76 (m, 7H), 4.21-4.26 (m, 1H), 3.88-3.90 (m, 1H), 2.84-2.91 (m, 1H),
5 2.33-2.40 (m, 2H), 2.21 (m, 3H), 1.83 (m, 1H), 1.55-1.65 (m, 9H), 1.12-1.42 (m, 6H), 0.96-1.03 (m, 13H). ESI-MS [(M+H)⁺]: m/z calculated 893.4, founded 893.5

Example 82

Synthesis of compound **30g**

10 The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30g**. After purification, 26mg of product **30g** was obtained. Confirmed by ESI-MS [(M+H)⁺]: m/z calculated 919.4, founded 919.4.

Example 83

15 Synthesis of compound **30h**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30h**. After purification, 43mg of product **30h** was obtained.

¹H-NMR for the product **30h** (CDCl₃, 500MHz): δ9.99 (s, 1H), 9.38 (m, 1H), 8.76 (m, 1H), 8.56 (m, 1H), 8.15-8.17 (m, 1H), 7.10 (s, 1H), 6.89 (s, 1H), 6.84 (s, 1H), 6.73-6.75 (m, 2H), 5.40 (s,
20 1H), 4.62-4.72 (m, 2H), 4.52-4.60 (m, 3H), 4.41-4.46 (m, 2H), 4.16-4.21 (m, 5H), 3.85-3.88 (m, 1H), 2.84-2.91 (m, 1H), 2.36-2.45 (m, 1H), 2.32-2.36 (m, 1H), 2.16-2.21 (m, 2H), 1.87 (m, 1H), 1.72-1.75 (m, 6H), 1.65-1.68 (m, 3H), 1.57-1.59 (m, 2H), 1.49-1.5 (m, 2H), 1.31-1.33 (m, 2H), 1.27 (m, 1H), 1.21-1.23 (m, 2H), 1.08-1.09 (m, 3H), 1.01 (s, 9H), 0.97-0.99 (m, 3H). ESI-MS [(M+H)⁺]: m/z calculated 921.4, founded 921.4.

25

Example 84

Synthesis of compound **30j**

The synthetic procedure was carried out as the same as in Example 76 for preparation of

compound **30j**. After purification, 43mg of product **30j** was obtained.

¹H-NMR for the product **30j** (CDCl₃, 500MHz): δ 9.98-10.02 (m, 1H), 9.40-9.41 (m, 1H), 8.75 (m, 1H), 8.52-8.55 (m, 1H), 8.18-8.21 (m, 1H), 7.09 (s, 1H), 6.89-6.92 (m, 1H), 6.79-6.81 (d, *J* = 8.0 Hz, 1H), 6.74-6.75 (d, *J* = 8.0 Hz, 1H), 5.42 (s, 1H), 4.67-4.76 (m, 2H), 4.54-4.61 (m, 3H), 4.42-4.49 (m, 2H), 4.24-4.26 (t, *J* = 5.5Hz, 2H), 4.16-4.20 (m, 3H), 3.87-3.93 (m, 1H), 2.84-2.91 (m, 1H), 2.40- 2.46 (m, 1H), 2.30-2.36 (m, 1H), 2.18-2.23 (m, 2H), 1.88 (m, 1H), 1.80 (m, 3H), 1.63-1.71 (m, 5H), 1.57-1.61 (m, 3H), 1.36-1.41 (m, 1H), 1.30 (m, 2H), 1.18-1.26 (m, 2H), 1.08-1.10 (m, 2H), 1.02-1.04 (m, 2H), 0.99 (s, 9H), 0.96-0.98 (m, 3H). ESI-MS [(M+H)⁺]: m/z calculated 921.4, founded 921.4.

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Example 85

Synthesis of compound **30k**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30k**. After purification, 42mg of product **30k** was obtained.

¹H-NMR for the product **30k** (CDCl₃, 500MHz): δ 10.36 (s, 1H), 9.27 (m, 1H), 8.74 (m, 1H), 8.57 (m, 1H), 8.34-8.37 (m, 1H), 7.30 (m, 1H), 7.08 (m, 1H), 6.98 (m, 2H), 5.92 (m, 1H), 5.41 (s, 1H), 5.30-5.33 (m, 1H), 5.13-5.15 (m, 2H), 4.75 (m, 3H), 4.65-4.68 (m, 1H), 4.59 (m, 1H), 4.47-4.51 (m, 1H), 4.38-4.42 (m, 1H), 2.87 (m, 1H), 2.49 (m, 1H), 2.37 (m, 1H), 2.23-2.26 (m, 1H), 1.89 (m, 1H), 1.79 (m, 4H), 1.67 (m, 2H), 1.42-1.45 (m, 2H), 1.26-1.31 (m, 4H), 1.14-1.19 (m, 4H), 1.01-1.06 (m, 12H). ESI-MS [(M+H)⁺]: m/z calculated 865.4, founded 865.6

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Example 86

Synthesis of compound **30m**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30m**. After purification, 43mg of product **30m** was obtained.

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¹H-NMR for the product **30m** (CDCl₃, 500MHz): δ 10.02 (m, 1H), 7.20 (s, 1H), 6.71 (s, 1H), 6.64 (m, 2H), 5.95-5.97 (m, 2H), 5.38 (s, 1H), 4.82-4.83 (m, 1H), 4.62-4.69 (m, 2H), 4.45-4.51 (m, 4H), 4.17-4.20 (m, 1H), 3.83-3.85 (m, 2H), 2.93 (m, 1H), 2.48 (m, 1H), 2.29 (m, 1H), 1.89 (m, 1H), 1.63-1.72 (m, 5H), 1.53-1.60 (m, 5H), 1.49 (s, 9H), 1.34-1.37 (m, 3H), 1.16-1.21 (m,

2H), 1.04-1.06 (m, 4H), 1.00 (s, 9H), 0.97-0.99 (m, 3H). ESI-MS $[(M+H)^+]$: m/z calculated 887.4, founded 887.4.

Example 87

Synthesis of compound **30n**

5 The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30n**. After purification, 43mg of product **30n** was obtained.

$^1\text{H-NMR}$ for the product **30n** (CDCl_3 , 500MHz): δ 10.10 (s, 1H), 7.39 (s, 1H), 6.94 (m, 1H), 6.68 (s, 1H), 6.61 (m, 1H), 5.96 (s, 2H), 5.42 (s, 1H), 5.25 (br, 1H), 4.52-4.64 (m, 4H), 4.42-4.49 (m, 2H), 4.17-4.19 (m, 1H), 3.88-3.89 (m, 1H), 3.65 (m, 1H), 2.94 (m, 1H), 2.90 (s, 1H), 2.36-2.41 (m, 2H), 1.93 (m, 1H), 1.73 (m, 3H), 1.58-1.64 (m, 6H), 1.35 (m, 2H), 1.19-1.26 (m, 5H), 1.03-1.06 (m, 3H), 1.03 (s, 9H), 0.98-0.99 (m, 3H). ESI-MS $[(M+H)^+]$: m/z calculated 865.3, founded 865.4

Example 88

Synthesis of compound **30p**

15 The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30p**. After purification, 33mg of product **30p** was obtained.

$^1\text{H-NMR}$ for the product **30p** (CDCl_3 , 500MHz): δ 10.24 (s, 1H), 8.65 (m, 1H), 8.08 (m, 1H), 8.01 (m, 1H), 7.9 (m, 1H), 7.67 (m, 1H), 7.58 (m, 1H), 7.48 (m, 1H), 7.40 (m, 1H), 6.68 (m, 1H), 6.62 (s, 1H), 6.44 (s, 1H), 5.86-5.91 (m, 2H), 5.63 (s, 1H), 5.40 (s, 1H), 4.44-4.62 (m, 4H), 4.37-4.40 (m, 2H), 3.99-4.01 (m, 1H), 3.83 (m, 1H), 3.26 (m, 1H), 2.96 (m, 1H), 2.46 (m, 1H), 2.35 (m, 1H), 1.86 (m, 1H), 1.56-1.65 (m, 4H), 1.46-1.48 (m, 4H), 1.39-1.42 (m, 4H), 1.09 (m, 3H), 0.99-1.02 (m, 4H), 0.84 (s, 9H), 0.72 (m, 3H). ESI-MS $[(M+H)^+]$: m/z calculated 977.4, founded 977.4.

Example 89

25 Synthesis of compound **30q**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30q**. After purification, 39mg of product **30q** was obtained.

Confirmed by ESI-MS $[(M+H)^+]$: m/z calculated 891.4, founded 891.5.

Example 90

Synthesis of compound **30r**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30r**. After purification, 44mg of product **30r** was obtained.

¹H-NMR for the product **30r** (CDCl₃, 500MHz): δ 10.51 (s, 1H), 7.65-7.67 (d, *J* = 7.4 Hz, 2H), 7.47-7.51 (m, 2H), 7.34-7.37 (t, *J* = 7.8 Hz, 2H), , 6.98-6.99 (m, 1H), 6.54 (s, 1H), 6.30 (s, 1H), 5.87 (s, 1H), 5.81 (s, 2H), 5.45 (s, 1H), 4.55-4.63 (m, 3H), 4.46-4.49 (m, 1H), 4.19-4.26 (m, 2H), 4.05-4.07 (m, 1H), 3.85-3.87 (m, 1H), 3.18 (m, 1H), 2.96 (m, 1H), 2.68 (m, 1H), 2.42 (m, 1H), 1.84 (m, 1H), 1.65-1.67 (m, 2H), 1.51-1.55 (m, 9H), 1.25-1.37 (m, 5H), 1.08-1.13 (m, 5H), 0.99 (s, 9H), 0.85 (m, 3H). ESI-MS [(M+H)⁺]: m/z calculated 927.4, founded 927.4.

Example 91

Synthesis of compound **30s**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30s**. After purification, 37mg of product **30s** was obtained.

¹H-NMR for the product **30s** (CDCl₃, 500MHz): δ 10.52 (s, 1H), 8.10 (m, 1H), 7.84-7.88 (t, *J* = 9.0 Hz, 2H), 7.76-7.78 (m, 1H), 7.66-7.67 (m, 1H), 7.59-7.62 (m, 1H), 7.51-7.54 (m, 1H), 6.98 (m, 1H), 6.49 (s, 1H), 6.24 (s, 1H), 5.88-5.91 (m, 2H), 5.72 (s, 1H), 5.49 (s, 1H), 5.41 (s, 1H), 4.59-4.66 (m, 3H), 4.49-4.51 (m, 1H), 4.19-4.24 (m, 2H), 4.03-4.05 (m, 1H), 3.85-3.87 (m, 1H), 3.25 (m, 1H), 2.98 (m, 1H), 2.68 (m, 1H), 2.45 (m, 1H), 1.87 (m, 1H), 1.64-1.66 (m, 2H), 1.50-1.59 (m, 8H), 1.30-1.36 (m, 4H), 0.99-1.05 (m, 5H), 0.94 (s, 9H), 0.88 (m, 3H). ESI-MS [(M+H)⁺]: m/z calculated 977.4, founded 977.4

Example 92

Synthesis of compound **30t**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30t**. After purification, 21mg of product **30t** was obtained.

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¹H-NMR for the product **30t** (CDCl₃, 500MHz): δ 10.05 (m, 1H), 7.32 (s, 1H), 6.71 (m, 1H), 6.63 (m, 1H), 6.59 (m, 1H), 5.96 (m, 2H), 5.39(s, 1H), 4.91 (m, 1H), 4.43-4.66 (m, 7H), 4.19 (m, 1H), 3.87-3.95 (m, 1H), 3.68-3.77 (m, 1H), 2.93 (m, 1H), 2.49 (m, 1H), 2.33 (m, 1H), 1.96 (s, 1H), 1.81 (m, 1H), 1.71 (m, 3H), 1.57-1.63 (m, 6H), 1.36 (m, 3H), 1.25 (s, 3H), 1.15 (s, 2H), 1.11 (s, 3H), 0.99-1.04 (m, 18H). ESI-MS [(M+H)⁺]: m/z calculated 899.4, founded 899.4

Example 93

Synthesis of compound **30v**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30v**. After purification, 45mg of product **30v** was obtained.

¹H-NMR for the product **30v** (CDCl₃, 500MHz): δ 10.04 (s, 1H), 7.23 (s, 1H), 6.72 (s, 1H), 6.64 (m, 2H), 5.96-5.97 (m, 2H), 5.38 (s, 1H), 4.97-4.98 (m, 1H), 4.59-4.69 (m, 2H), 4.47-4.52 (m, 4H), 4.18-4.20 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 2.94 (m, 1H), 2.47 (m, 1H), 2.33 (m, 1H), 1.87 (m, 1H), 1.66-1.69 (m, 5H), 1.56-1.58 (m, 5H), 1.36 (m, 3H), 1.22-1.27 (m, 3H), 1.17-1.19 (m, 2H), 1.14-1.16 (m, 2H), 1.03-1.08 (m, 4H), 1.00 (s, 9H), 0.97-0.98 (m, 3H). ESI-MS [(M+H)⁺]: m/z calculated 859.4, founded 859.4

Example 94

Synthesis of compound **30w**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30w**. After purification, 40mg of product **30w** was obtained.

¹H-NMR for the product **30w** (CDCl₃, 500MHz): δ 10.02 (m, 1H), 7.19 (s, 1H), 6.72 (s, 1H), 6.65 (m, 2H), 5.96-5.97 (m, 2H), 5.38 (s, 1H), 4.89 (m, 2H), 4.60-4.69 (m, 2H), 4.47-4.51 (m, 4H), 4.20-4.22 (m, 1H), 3.83-3.90 (m, 2H), 2.94 (m, 1H), 2.48 (m, 1H), 2.33 (m, 1H), 1.88 (m, 1H), 1.64-1.69 (m, 5H), 1.56-1.58 (m, 5H), 1.36-1.37 (m, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.14-1.19 (m, 3H), 0.97-1.05 (m, 12H), 0.82-0.91 (m, 3H). ESI-MS [(M+H)⁺]: m/z calculated 873.4, founded 873.5

Example 95Synthesis of compound **30x**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30x**. After purification, 41mg of product **30x** was obtained.

5 ¹H-NMR for the product **30x** (CDCl₃, 500MHz): δ 10.09 (s, 1H), 7.34 (br, 1H), 6.71 (s, 1H), 6.65 (m, 2H), 5.96-5.97 (m, 2H), 5.38 (s, 1H), 5.05 (m, 1H), 4.59-4.689 (m, 2H), 4.49-4.52 (m, 4H), 4.17-4.19 (m, 1H), 3.96 (m, 1H), 3.88 (m, 1H), 3.68 (s, 3H), 2.92 (m, 1H), 2.43 (m, 1H), 2.34 (m, 1H), 1.88 (m, 1H), 1.64-1.69 (m, 5H), 1.56-1.57 (m, 5H), 1.35 (m, 3H), 1.26 (m, 4H), 1.17-1.20 (m, 2H), 1.01 (s, 9H), 0.88-0.89 (m, 3H). ESI-MS [(M+H)⁺]: m/z calculated 845.4,
10 founded 845.4

Example 96Synthesis of compound **30y**

The synthetic procedure was carried out as the same as in Example 76 for preparation of
15 compound **30y**. After purification, 43mg of product **30y** was obtained.

Confirmed by ESI-MS [(M+H)⁺]: m/z calculated 921.4, founded 921.4

Example 97Synthesis of compound **30z**

20 The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30z**. After purification, 31mg of product **30z** was obtained.

Confirmed by ESI-MS [(M+H)⁺]: m/z calculated 907.4, founded 907.5.

Example 9825 Synthesis of compound **30aa**

The synthetic procedure was carried out as the same as in Example 76 for preparation of

compound **30aa**. After purification, 31mg of product **30aa** was obtained.

¹H-NMR for the product **30aa** (CDCl₃, 500MHz): δ 10.00 (s, 1H), 7.76-7.78 (d, *J* = 7.3 Hz, 2H), 7.58-7.62 (d, *J* = 7.4 Hz, 2H), 7.38-7.42 (m, 2H), 7.30-7.34 (m, 2H), 7.03 (s, 1H), 6.69 (m, 2H), 6.65 (s, 1H), 5.93-5.96 (m, 2H), 5.38(s, 1H), 5.13-5.15 (m, 1H), 4.59-4.69 (m, 2H), 4.52 (s, 2H), 4.39-4.48 (m, 4H), 4.17-4.20 (m, 1H), 3.95 (m, 1H), 3.83-3.87 (m, 1H), 2.91 (m, 1H), 2.43 (m, 1H), 2.30 (m, 1H), 1.86 (s, 1H), 1.68-1.73 (m, 2H), 1.61-1.64 (m, 3H), 1.53-1.58 (m, 3H), 1.33-1.36 (m, 2H), 1.26-1.30 (m, 2H), 1.15-1.20 (m, 3H), 0.97-1.03 (m, 15H). ESI-MS [(M+H)⁺]: m/z calculated 1009.4, founded 1009.4

10

Example 99

Synthesis of compound **30ab**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30ab**. After purification, 46mg of product **30ab** was obtained.

¹H-NMR for the product **30ab** (CDCl₃, 500MHz): δ 10.49 (brs, 1H), 7.40 (brs, 1H), 6.68 (s, 1H), 6.64 (m, 2H), 5.92-5.95 (m, 2H), 5.81 (brs, 1H), 5.43 (m, 1H), 5.28-5.30 (m, 1H), 5.11-5.19 (m, 1H), 4.87 (m, 1H), 4.55-4.64 (m, 3H), 4.25-4.51 (m, 3H), 4.19 (m, 1H), 3.92-4.04 (m, 2H), 2.83 (m, 1H), 2.28-2.39 (m, 2H), 2.20 (m, 1H), 1.98 (m, 1H), 1.67-1.81 (m, 3H), 1.41-1.62 (m, 5H), 1.30 (s, 9H), 1.12-1.26 (m, 3H), 1.07-1.09 (m, 3H), 1.03 (s, 9H), 0.86-0.99 (m, 3H). ESI-MS [(M+H)⁺]: m/z calculated 884.4, founded 884.5

20

Example 100

Synthesis of compound **30ac**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30ac**. After purification, 42mg of product **30ac** was obtained.

¹H-NMR for the product **30ac** (CDCl₃, 500MHz): δ 7.35 (brs, 1H), 6.63-6.68 (m, 2H), 5.93-5.95 (m, 2H), 5.39 (m, 1H), 4.89 (m, 1H), 4.33-4.59 (m, 6H), 4.16 (m, 1H), 3.92-4.00 (m, 2H), 2.85 (m, 1H), 2.32-2.39 (m, 3H), 1.67-1.80 (m, 5H), 1.52-1.62 (m, 5H), 1.40-1.48 (m, 3H), 1.30 (s, 9H), 1.13-1.26 (m, 4H), 1.05-1.10 (m, 3H), 1.04 (s, 9H), 0.89-0.99 (m, 3H). ESI-MS [(M+H)⁺]:

Example 101Synthesis of compound **30ad**

5 The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30ad**. After purification, 31mg of product **30ad** was obtained.

¹H-NMR for the product **30ad** (CDCl₃, 500MHz): δ 10.03 (m, 1H), 7.20 (s, 1H), 6.88 (s, 1H), 6.81 (s, 1H), 6.72 (m, 1H), 5.38 (m, 1H), 4.85 (m, 1H), 4.59-4.68 (m, 2H), 4.43-4.51 (m, 4H), 4.18-4.20 (m, 5H), 3.85 (m, 2H), 2.86-2.96 (m, 2H), 2.42 (m, 1H), 2.34 (m, 1H), 2.19 (m, 2H),
10 1.60-1.70 (m, 5H), 1.51-1.58 (m, 5H), 1.44 (s, 9H), 1.36-1.39 (m, 3H), 1.13-1.21 (m, 2H), 1.04-1.07 (m, 4H), 1.01 (s, 9H), 0.97-0.99 (m, 3H). ESI-MS [(M+H)⁺]: m/z calculated 915.5, founded 915.6.

Example 10215 Synthesis of compound **30ae**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30ae**. After purification, 31mg of product **30ae** was obtained.

¹H-NMR for the product **30ae** (CDCl₃, 500MHz): δ 10.03 (m, 1H), 7.19 (s, 1H), 6.88 (s, 1H), 6.80 (s, 1H), 6.64 (m, 1H), 5.38 (m, 1H), 5.07 (m, 1H), 4.89 (m, 1H), 4.60-4.69 (m, 2H),
20 4.45-4.54 (m, 4H), 4.20 (m, 5H), 3.86 (m, 2H), 2.91-2.96 (m, 1H), 2.44-2.49 (m, 1H), 2.32-2.34 (m, 1H), 2.17-2.21 (m, 2H), 1.81-1.90 (m, 4H), 1.64-1.71 (m, 8H), 1.52-1.57 (m, 7H), 1.33-1.36 (m, 2H), 1.05-1.28 (m, 7H), 1.01 (s, 9H), 0.93-0.99 (m, 3H). ESI-MS [(M+H)⁺]: m/z calculated 927.5, founded 927.6

25

Example 103Synthesis of compound **30af**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30af**. After purification, 31mg of product **30af** was obtained.

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¹H-NMR for the product **30af** (CDCl₃, 500MHz): δ 10.03 (s, 1H), 7.20 (s, 1H), 6.70 (s, 1H), 6.58 (s, 1H), 5.97 (s, 2H), 5.74 (m, 1H), 5.40 (br, 1H), 5.21-5.28 (m, 2H), 5.14-5.16 (m, 1H), 4.66 (m, 2H), 4.44-4.55 (m, 3H), 4.21-4.23 (m, 2H), 3.87 (m, 1H), 2.89 (m, 1H), 2.37 (m, 2H), 2.08 (m, 1H), 1.94 (m, 1H), 1.78 (m, 1H), 1.40-1.48 (m, 2H), 1.34 (s, 9H), 1.07 (m, 2H), 1.02 (s, 9H). ESI-MS [(M+H)⁺]: m/z calculated 746.3, founded 746.4

Example 104

Synthesis of compound **30ag**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30ag**. After purification, 31mg of product **30ag** was obtained.

Confirmed by ESI-MS [(M+H)⁺]: m/z calculated 748.3, founded 748.4..

Example 105

Synthesis of compound **30ah**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30ah**. After purification, 31mg of product **30ah** was obtained.

¹H-NMR for the product **30ah** (CDCl₃, 500MHz): δ 10.02 (s, 1H), 7.16-7.18 (m, 1H), 6.76 (m, 1H), 6.62-6.72 (m, 1H), 5.98 (s, 1H), 5.97 (m, 1H), 5.76 (m, 1H), 5.41 (s, 1H), 5.29 (m, 1H), 5.21 (m, 1H), 5.14-5.16 (m, 1H), 4.66-4.69 (m, 2H), 4.53-4.58 (m, 2H), 4.46 (m, 1H), 4.20-4.25 (m, 2H), 3.85 (m, 1H), 2.92 (m, 1H), 2.37-2.43 (m, 2H), 2.08 (m, 1H), 1.96 (m, 1H), 1.71 (m, 1H), 1.44-1.48 (m, 2H), 1.30-1.33 (m, 9H), 1.04-1.05 (m, 2H), 1.02 (s, 9H). ESI-MS [(M+H)⁺]: m/z calculated 746.3, founded 746.4

Example 106

Synthesis of compound **30aj**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30aj**. After purification, 23mg of product **30aj** was obtained.

Confirmed by ESI-MS $[(M+H)^+]$: m/z calculated 720.3, founded 720.4..

Example 107

Synthesis of compound **30ak**

5 The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30ak**. After purification, 39mg of product **30ak** was obtained.

$^1\text{H-NMR}$ for the product **30ak** (CDCl_3 , 500MHz): δ 10.01 (s, 1H), 7.21 (s, 1H), 6.71 (s, 1H), 6.68 (s, 1H), 5.96 (m, 2H), 5.76 (m, 1H), 5.40 (s, 1H), 5.26-5.30 (m, 2H), 5.15-5.17 (m, 1H), 4.73 (br, 1H), 4.60-4.69 (m, 2H), 4.47-4.52 (m, 2H), 4.23 (m, 2H), 3.83 (m, 1H), 2.93 (m, 1H),
10 2.42 (m, 1H), 2.36 (m, 1H), 2.09 (m, 1H), 1.98 (m, 1H), 1.63-1.68 (m, 7H), 1.44-1.47 (m, 4H), 1.36 (m, 3H), 1.02 (s, 9H). ESI-MS $[(M+H)^+]$: m/z calculated 758.3, founded 758.4

Example 108

Synthesis of compound **30am**

15 The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30am**. After purification, 40mg of product **30am** was obtained.

Confirmed by ESI-MS $[(M+H)^+]$: m/z calculated 760.3,

Example 109

20 Synthesis of compound **30an**

The synthetic procedure was carried out as the same as in Example 76 for preparation of compound **30an**. After purification, 31mg of product **30an** was obtained.

$^1\text{H-NMR}$ for the product **30an** (CDCl_3 , 500MHz): δ 9.98 (s, 1H), 7.25 (s, 1H), 6.77 (m, 1H), 6.62-6.75 (m, 1H), 5.95 (m, 2H), 5.75 (m, 1H), 5.40 (s, 1H), 5.25-5.32 (m, 2H), 5.14-5.16 (m, 1H),
25 4.65-4.75 (m, 3H), 4.47-4.62 (m, 3H), 4.22-4.27 (m, 2H), 3.85 (m, 1H), 2.90 (m, 1H), 2.42 (m, 1H), 2.37 (m, 1H), 2.08 (m, 1H), 1.96 (m, 1H), 1.73 (m, 1H), 1.54-1.62 (m, 6H), 1.44 (m, 3H), 1.34 (m, 2H), 1.01-1.05 (m, 11H). ESI-MS $[(M+H)^+]$: m/z calculated 758.3, founded 758.4.

Example 110

Synthesis of compound **30ap**

The synthetic procedure was carried out as the same as in Example 76 for preparation of
5 compound **30ap**. After purification, 23mg of product **30ap** was obtained.

Confirmed by ESI-MS $[(M+H)^+]$: m/z calculated 762.3, founded 762.4.

Example 111

Synthesis of compound **30aq**

10 The synthetic procedure was carried out as the same as in Example 76 for preparation of
compound **30aq**. After purification, 39mg of product **30aq** was obtained.

$^1\text{H-NMR}$ for the product **30aq** (CDCl_3 , 500MHz): δ 10.08 (s, 1H), 7.18 (brs, 1H), 6.69 (s, 1H),
6.58 (s, 1H), 5.96 (s, 2H), 5.40 (m, 1H), 4.47-4.64 (m, 4H), 4.3-4.44 (m, 2H), 4.29-4.31 (m, 1H),
3.89 (m, 1H), 2.92 (m, 1H), 2.34 (m, 2H), 1.58-1.68 (m, 3H), 1.36-1.43 (m, 2H), 1.28-1.33 (m, 1H),
15 1.26 (s, 9H), 1.05-1.07 (m, 3H), 1.01 (s, 9H), 0.95-0.98 (t, $J = 7.5$ Hz, 1H). ESI-MS $[(M+H)^+]$: m/z
calculated 747.4, founded 747.5

Example 112

Synthesis of compound **30ar**

20 The synthetic procedure was carried out as the same as in Example 76 for preparation of
compound **30ar**. After purification, 33mg of product **30ar** was obtained.

$^1\text{H-NMR}$ for the product **30ar** (CDCl_3 , 500MHz): δ 10.18 (s, 1H), 7.11 (brs, 1H), 6.71 (s,
1H), 6.60 (s, 1H), 5.97 (s, 2H), 5.80-5.88 (m, 1H), 5.25-5.27 (d, $J = 9.5$ Hz, 1H), 5.14-5.16 (d, $J =$
10.5 Hz, 1H), 4.57-4.67 (m, 3H), 4.45-4.50 (m, 1H), 4.36-4.37 (m, 2H), 4.25-4.29 (m, 1H), 3.89
25 (m, 1H), 2.92 (m, 1H), 2.34-2.41 (m, 2H), 2.08-2.13 (m, 1H), 1.96-1.98 (m, 1H), 1.51-1.54 (m,
1H), 1.30-1.39 (m, 3H), 1.26 (s, 9H), 1.14-1.23 (m, 2H), 1.05 (m, 1H), 1.02 (s, 9H). ESI-MS
 $[(M+H)^+]$: m/z calculated 745.4, founded 745.5.

Example 113

Synthesis of compound **30-Ref**

The synthetic procedure was carried out as the same as in Example 76 for preparation of
5 compound **30-Ref**. After purification, 37mg of product **30-Ref** was obtained.

¹H-NMR for the product **30-Ref** (CDCl₃, 500MHz): δ 9.99 (s, 1H), 7.28 (s, 1H), 7.07 (m, 1H), 6.96 (m, 2H), 5.75 (m, 1H), 5.41 (s, 1H), 5.26-5.31 (m, 2H), 5.15-5.17 (m, 1H), 4.63-4.85 (m, 5H), 4.50-4.53 (m, 1H), 4.29-4.32 (m, 1H), 4.22-4.24 (m, 1H), 3.83 (m, 1H), 2.91 (m, 1H), 2.42 (m, 1H), 2.38 (m, 1H), 2.09 (m, 1H), 1.94 (m, 1H), 1.60 (m, 4H), 1.51 (m, 3H), 1.44 (m, 3H), 1.35 (m, 10 2H), 1.01-1.05 (m, 11H). ESI-MS [(M+H)⁺]: m/z calculated 732.3, founded 732.4.

Example 114

Synthesis of compound **33a**

Chemical **SM-15a** (5.4g, 10mmol), **SM-16** (1.1eq) and DMF (80mL) were added into
15 250mL flask reactor, followed by adding coupling reagent EDCI (1.3eq) to keep the amidation at 55°C until completed. The reaction mixture was worked out to obtain crude product **31a**, followed by removing Boc group with HCl-THF solution to obtain **32a** (3.9g, yield: 86%), which was purified by precipitation in hexane-EtOAc and dried directly for next step. ESI-MS (M+H⁺): m/z calculated 487.2, founded 487.2.

20 In the presence of coupling reagent HATU (1.3eq) in DMF (1.0mL), compound **32a** (60mg, 0.1mmol) was reacted with another acid derivative **SM-14a** to obtain product **33a**. After purification by flash column, 41mg of **33a** was obtained.

¹H-NMR for the product **33a** (CDCl₃, 500MHz): δ 9.40 (s, 1H), 8.77 (s, 1H), 8.55 (s, 1H), 8.16-8.17 (m, 1H), 7.32-7.33 (m, 1H), 7.04 (m, 1H), 6.72 (s, 1H), 6.68 (s, 1H), 5.94-5.95 (m, 2H),
25 5.36 (m, 1H), 4.77-4.80 (m, 1H), 4.69-4.72 (m, 1H), 4.59-4.64 (m, 2H), 4.51-4.53 (m, 2H), 4.44-4.47 (m, 2H), 4.18-4.20 (m, 1H), 3.80-3.83 (m, 1H), 2.78 (m, 1H), 2.64 (m, 1H), 2.26 (m, 1H), 1.88-1.92 (m, 1H), 1.77-1.79 (m, 1H), 1.66-1.69 (m, 3H), 1.59-1.61 (m, 4H), 1.38-1.42 (m, 2H), 1.10-1.19 (m, 3H), 1.00-1.07 (m, 3H), 0.97-0.99 (m, 9H), 0.89-0.93 (m, 3H), 0.85-0.86 (m, 2H),

0.61 (m, 2H), ESI-MS $[(M+H)^+]$: m/z calculated 845.4, founded 845.4

Example 115

Synthesis of compound **33b**

5 The synthetic procedure was carried out as the same as in Example 114 for preparation of compound **33b**. After purification, 41mg of product **33b** was obtained.

^1H -NMR for the product **33b** (CDCl_3 , 500MHz): δ 9.39 (m, 1H), 8.77 (m, 1H), 8.57 (m, 1H), 8.33 (m, 1H), 7.75 (m, 1H), 6.76 (s, 2H), 6.69 (s, 1H), 6.62 (m, 1H), 6.06 (br, 1H), 5.70 (br, 1H), 4.86 (m, 1H), 4.54-4.66 (m, 3H), 4.44-4.51 (m, 2H), 4.25-4.41 (m, 1H), 4.25 (m, 4H), 4.09 (m, 10 1H), 2.82 (m, 1H), 2.58 (m, 1H), 2.22 (m, 1H), 1.97 (m, 2H), 2.19 (m, 2H), 1.78 (m, 4H), 1.68 (m, 2H), 1.25-1.29 (m, 6H), 1.05-1.16 (m, 4H), 1.05 (s, 9H), 0.84-0.85 (m, 2H), 0.76-0.79 (m, 3H). ESI-MS $[(M+H)^+]$: m/z calculated 859.4, founded 859.5

Example 116

15 Synthesis of compound **33c**

The synthetic procedure was carried out as the same as in Example 114 for preparation of compound **33c**. After purification, 21mg of product **33c** was obtained.

^1H -NMR for the product **33c** (CDCl_3 , 500MHz): δ 9.28 (s, 1H), 8.75 (s, 1H), 8.56 (m, 2H), 7.72 (m, 1H), 6.76-6.78 (m, 1H), 6.65-6.67 (m, 1H), 6.68 (s, 1H), 5.99 (m, 2H), 5.32 (s, 1H), 4.86 20 (m, 1H), 4.44-4.67 (m, 6H), 4.09 (m, 2H), 2.82 (m, 1H), 2.61 (m, 1H), 2.24 (m, 1H), 2.03 (m, 2H), 1.84-1.87 (m, 2H), 1.65-1.78 (m, 5H), 1.21-1.34 (m, 5H), 1.09-1.25 (m, 4H), 1.05-1.09 (m, 9H), 0.84-0.85 (m, 2H), 0.76 (m, 4H). ESI-MS $[(M+H)^+]$: m/z calculated 845.4, founded 845.4.

Example 117

25 Synthesis of compound **33d**

The synthetic procedure was carried out as the same as in Example 114 for preparation of compound **33d**. After purification, 22mg of product **33d** was obtained.

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- ¹H-NMR for the product **33d** (CDCl₃, 500MHz): δ 9.28 (m, 1H), 8.76 (m, 1H), 8.56 (m, 2H), 7.77 (m, 1H), 6.80 (m, 1H), 6.76 (m, 1H), 6.65 (m, 1H), 6.60 (br, 1H), 4.47-4.69 (m, 6H), 4.26 (m, 4H), 4.09 (m, 1H), 2.83 (m, 1H), 2.59 (m, 1H), 2.22 (m, 1H), 1.85-1.87 (m, 2H), 1.62-1.72 (m, 8H), 1.26 (m, 6H), 1.05-1.19 (m, 4H), 1.01-1.05 (m, 9H), 0.85-0.86 (m, 2H), 0.76-0.79 (m, 3H).
- 5 ESI-MS [(M+H)⁺]: m/z calculated 859.4, founded 859.5.

Example 118

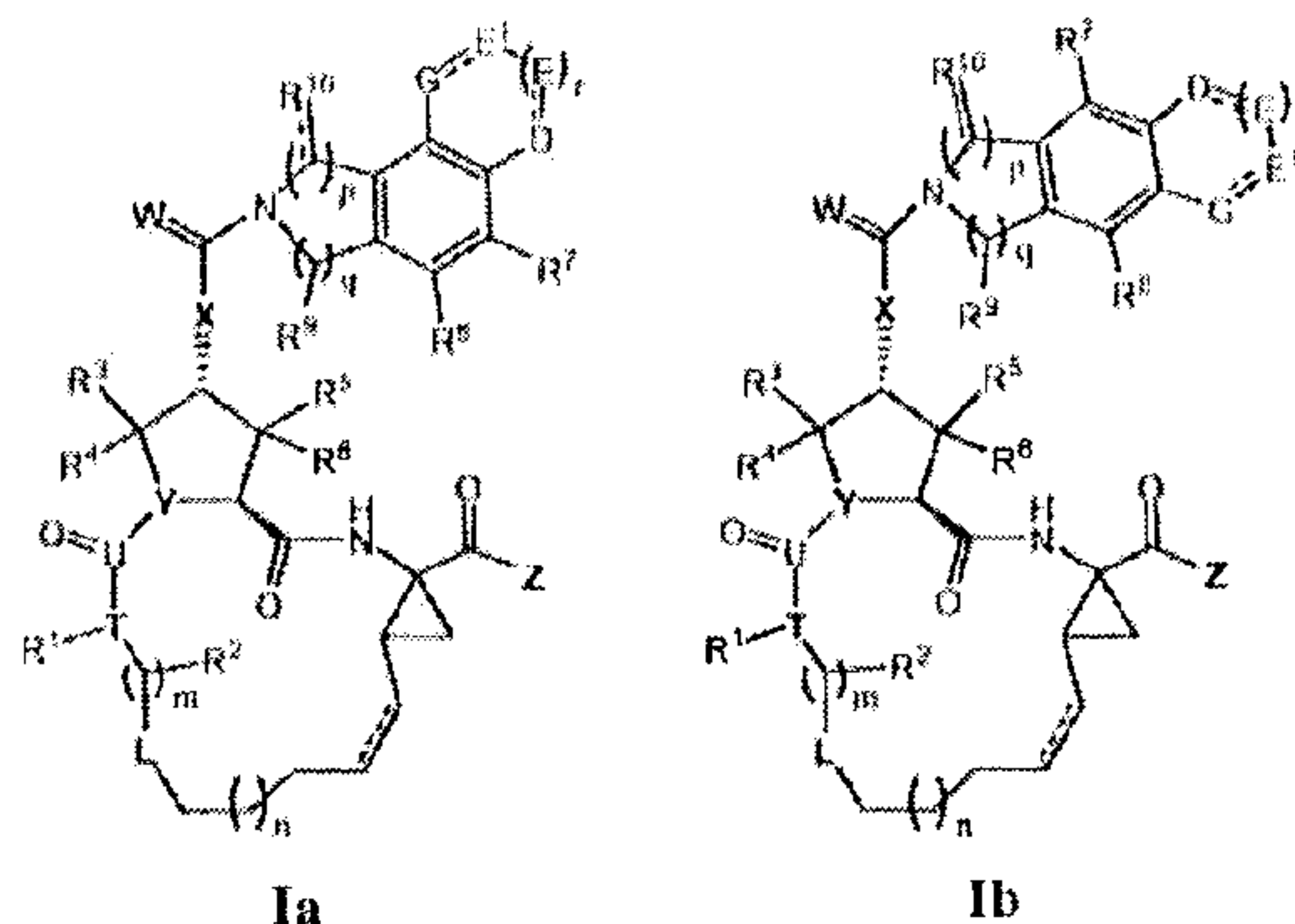
Synthesis of compound **33-Ref**

- The synthetic procedure was carried out as the same as in Example 114 for preparation of compound **33-Ref**. After purification, 28mg of product **33-Ref** was obtained.
- 10

- ¹H-NMR for the product **33-Ref** (CDCl₃, 500MHz): δ 9.28 (m, 1H), 8.75 (s, 1H), 8.57 (m, 2H), 7.71 (m, 1H), 7.07 (m, 1H), 6.97-7.00 (m, 2H), 6.63 (m, 1H), 5.92 (m, 1H), 5.41 (s, 1H), 5.30-5.33 (m, 1H), 5.13-5.15 (m, 2H), 4.75 (m, 3H), 4.65-4.68 (m, 1H), 4.59 (m, 1H), 4.47-4.51 (m, 1H), 4.38-4.42 (m, 1H), 2.87 (m, 1H), 2.49 (m, 1H), 2.37 (m, 1H), 2.23-2.26 (m, 1H), 2.03 (m, 2H), 1.84-1.87 (m, 2H), 1.65-1.78 (m, 5H), 1.21-1.34 (m, 5H), 1.09-1.25 (m, 4H), 1.05-1.09 (m, 9H), 0.84-0.85 (m, 2H), 0.76 (m, 4H), ESI-MS [(M+H)⁺]: m/z calculated 819.4, founded 819.4.
- 15

What is claimed is:

1. A compound represented by the formula **Ia** or **Ib**,



stereoisomers, solvates, hydrates, tautomers, pharmaceutically acceptable salt, or mixtures thereof,

wherein:

$m = 0, 1$ or 2 ;

$n = 0, 1$ or 2 ;

$p = 0, 1$ or 2 ;

$q = 0, 1$ or 2 ;

$r = 0, 1, 2$ or 3 ;

the dashed line "-----" is single bond or double bond;

wherein "-----" linked to the cyclopropyl formyl inside of the macrocyclic ring is a double bond; and "-----" is a single bond in the ring consisting of D, E, E¹ and G, where D **and** G are each oxygen, E **and** E¹ are each C(Ra)(Rb);

R¹⁰ is hydrogen;

Ra, Rb and Rc are each hydrogen;

wherein when $r = 0$, E is nothing, and D is directly linked to E¹;

L is -C(Rb)(Rc)-;

T is nitrogen or CH;

U is carbon;

W is oxygen;

X is oxygen;

Y is nitrogen or CH group;

Z is hydroxyl, C₁-C₂₀ alkyl, C₃-C₂₀ cycloalkyl, C₁-C₂₀ alkoxy, C₃-C₂₀ cycloalkoxy, C₁-C₂₀ alkylamino, C₃-C₂₀ cycloalkylamino, C₂-C₂₀ heterocyclic amino, C₆-C₂₀ aryl, C₆-C₂₀ arylamino, C₄-C₂₀ heteroaryl amino, C₁-C₂₀ alkyl sulfonamido, C₃-C₂₀ cycloalkylsulfonamido, C₆-C₂₀ arylsulfonamido, C₁-C₂₀ alkoxy sulfonamido, C₃-C₂₀ cycloalkoxy sulfonamido, C₁-C₂₀ alkylamino sulfonamido, C₃-C₂₀ cycloalkylamino sulfonamido, C₆-C₂₀ arylamino sulfonamido, C₁-C₂₀ uramido, C₁-C₂₀ thioureido, C₁-C₂₀ phosphate, or C₁-C₂₀ borate;

R¹ and R² are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C₁-C₂₀ alkyl, C₃-C₂₀ cycloalkyl, C₁-C₂₀ alkoxy, C₃-C₂₀ cycloalkoxy, C₁-C₂₀ alkoxycarbonyl, C₁-C₂₀ alkylamino, C₃-C₂₀ cycloalkylamino, C₂-C₂₀ heterocyclic amino, C₆-C₂₀ arylamino, C₁-C₂₀ alkoxycarbonylamino, C₆-C₂₀ aryloxycarbonylamino, C₁-C₂₀ alkylsulfonamido, C₃-C₂₀ cycloalkylsulfonamido, C₂-C₂₀ heterocyclic sulfonamido, C₆-C₂₀ arylsulfonamido, and C₁-C₂₀ aminosulfonamido group;

R³, R⁴, R⁵ and R⁶ are each hydrogen; and

R⁷, R⁸ and R⁹ are each hydrogen.

2. The compound according to claim 1,

wherein:

Z is hydroxyl, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₁-C₁₅ alkoxy, C₃-C₁₅ cycloalkoxy, C₁-C₁₅ alkylamino, C₃-C₁₅ cycloalkylamino, C₂-C₁₅ heterocyclic amino, C₆-C₁₅ aryl, C₆-C₁₅ arylamino, C₄-C₁₅ heteroaryl amino, C₁-C₁₅ alkyl sulfonamido, C₃-C₁₅ cycloalkylsulfonamido, C₆-C₁₅ arylsulfonamido, C₁-C₁₅ alkoxy sulfonamido, C₃-C₁₅ cycloalkoxy sulfonamido, C₁-C₁₅ alkylamino sulfonamido, C₃-C₁₅ cycloalkylamino sulfonamido, C₆-C₁₅ arylamino sulfonamido, C₁-C₁₅ uramido, C₁-C₁₅ thioureido, C₁-C₁₅ phosphate, or C₁-C₁₅ borate;

R¹ and R² are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C₁-C₁₅ alkyl, C₃-C₁₅ cycloalkyl, C₁-C₁₅ alkoxy, C₃-C₁₅ cycloalkoxy, C₁-C₁₅ alkoxycarbonyl, C₁-C₁₅ alkylamino, C₃-C₁₅ cycloalkylamino, C₂-C₁₅ heterocyclic amino, C₆-C₁₅ arylamino, C₁-C₁₅ alkoxycarbonylamino, C₆-C₁₅ aryloxycarbonylamino, C₁-C₁₅ alkylsulfonamido, C₃-C₁₅ cycloalkylsulfonamido, C₂-C₁₅ heterocyclic sulfonamido, C₆-C₁₅

arylsulfonamido, and C₁-C₁₅ aminosulfonamido group.

3. The compound according to claim 2,

wherein:

Z is hydroxyl, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₁-C₈ alkoxy, C₃-C₈ cycloalkoxy, C₁-C₈ alkylamino, C₃-C₈ cycloalkylamino, C₂-C₈ heterocyclic amino, C₆-C₁₂ aryl, C₆-C₁₂ arylamino, C₄-C₁₂ heteroaryl, C₁-C₈ alkyl sulfonamido, C₃-C₈ cycloalkylsulfonamido, C₆-C₁₂ arylsulfonamido, C₁-C₈ alkoxy sulfonamido, C₃-C₈ cycloalkoxy sulfonamido, C₁-C₈ alkylamino sulfonamido, C₃-C₈ cycloalkylamino sulfonamido, C₆-C₁₂ arylamino sulfonamido, C₁-C₈ ureamido, C₁-C₈ thioureido, C₁-C₈ phosphate, or C₁-C₈ borate;

R¹ and R² are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₁-C₈ alkoxy, C₃-C₈ cycloalkoxy, C₁-C₈ alkoxycarbonyl, C₁-C₈ alkylamino, C₃-C₈ cycloalkylamino, C₂-C₈ heterocyclic amino, C₆-C₁₂ arylamino, C₁-C₈ alkoxycarbonylamino, C₆-C₁₂ aryloxy carbonylamino, C₁-C₈ alkylsulfonamido, C₃-C₈ cycloalkylsulfonamido, C₂-C₈ heterocyclic sulfonamido, C₆-C₁₂ arylsulfonamido, and C₁-C₈ aminosulfonamido group.

4. The compound according to claim 3,

wherein:

m = 1 or 2;

n = 1 or 2;

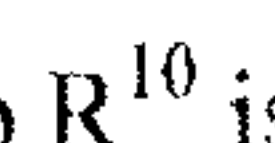
p = 1;

q = 1;

r = 0, 1 or 2;

the dashed line “” is a single bond or double bond;

the dashed line “” linked to the cyclopropylaminocarbonyl group inside of the macrocyclic ring is a double bond;

the dashed line “” linked to R¹⁰ is a single bond, and R¹⁰ is H;

the dashed line “” is a single bond in the tricyclic ring consisting of D, E, E¹, G and

other cyclic groups; D and G are each oxygen; E and E¹ are each -CH₂-, respectively;

wherein when r = 0, E is nothing, and D is directly linked to E¹;

L is -CH₂-;

T is N or CH;

U is carbon;

W and X are each oxygen;

Y is N or CH;

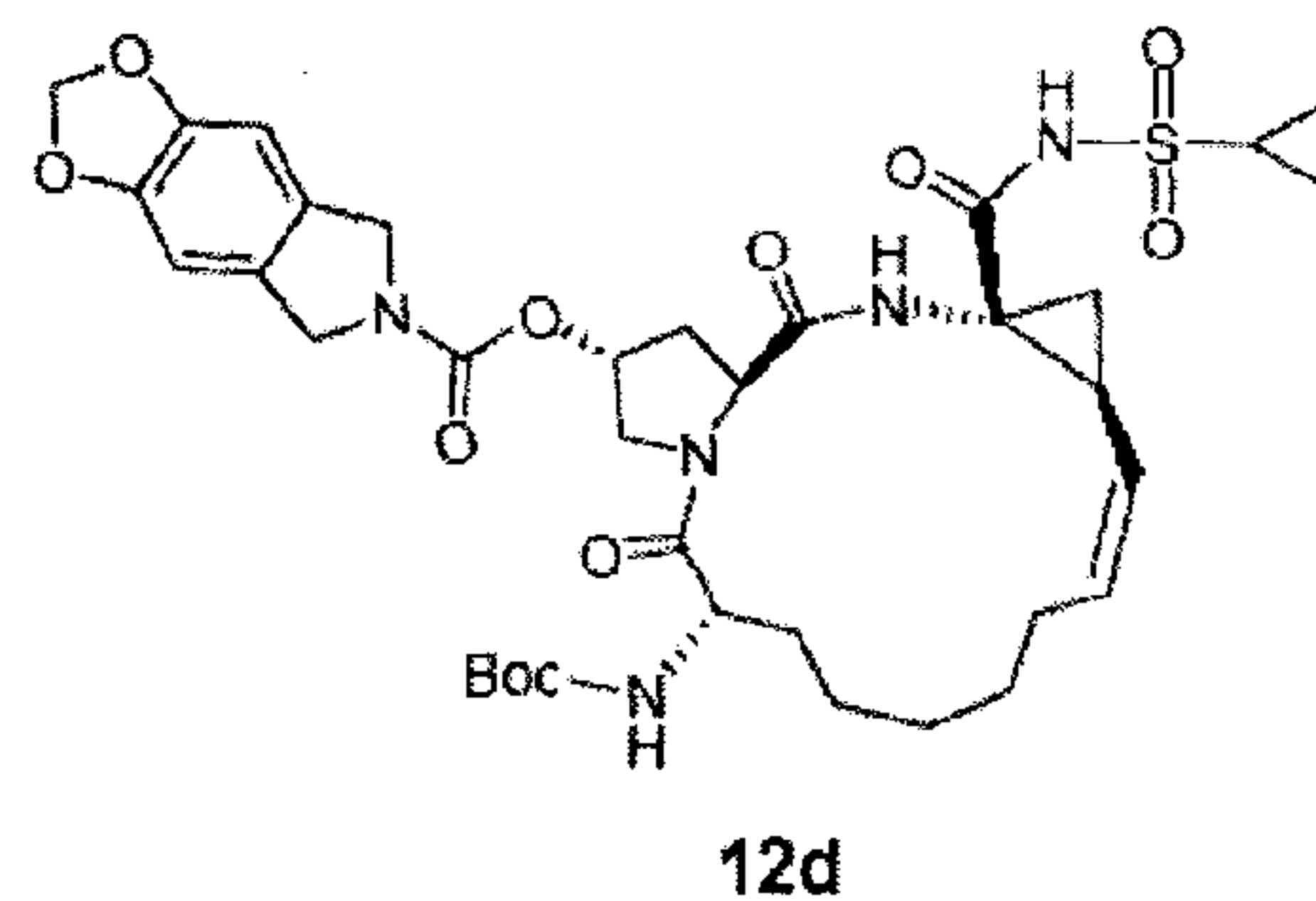
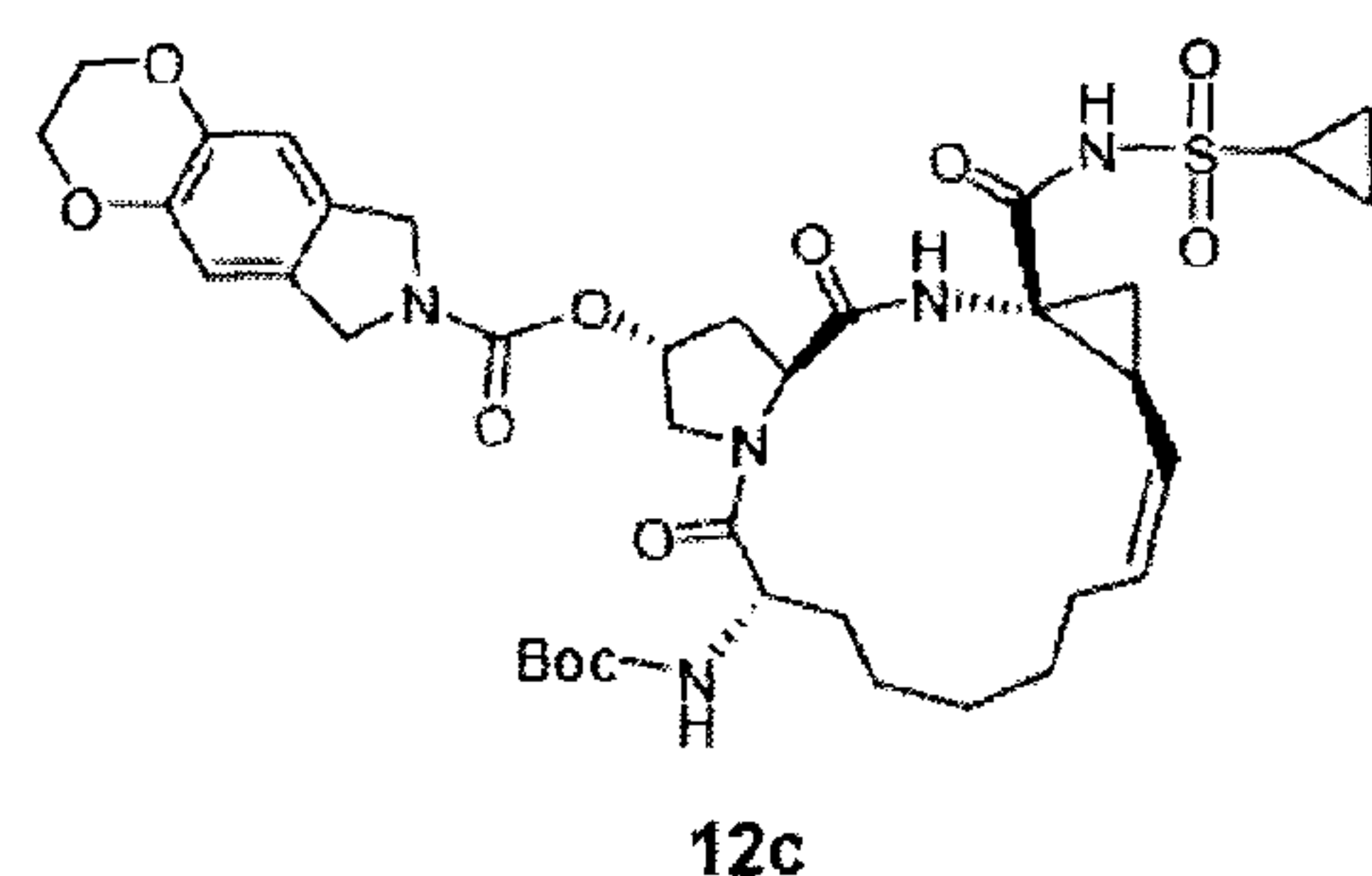
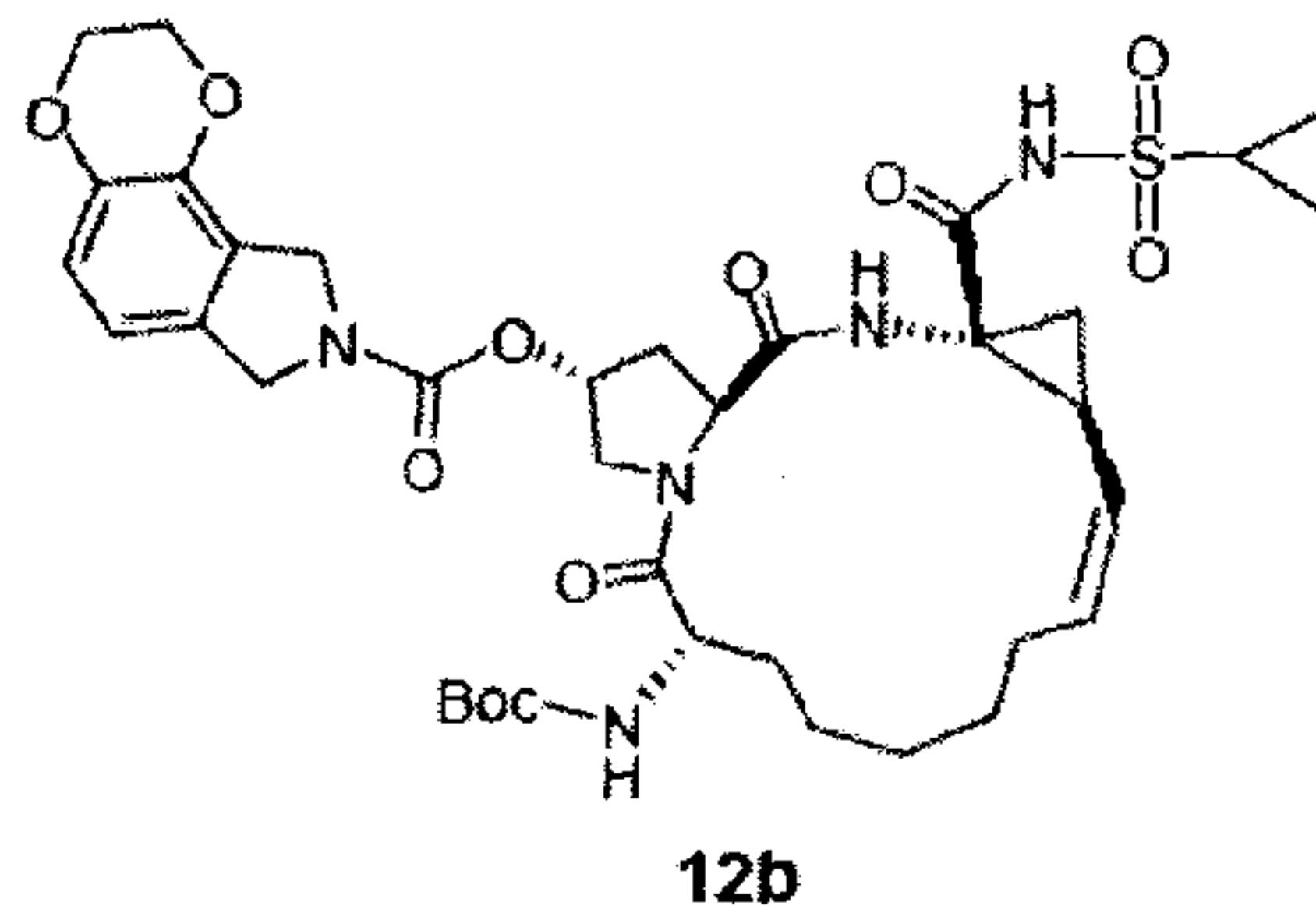
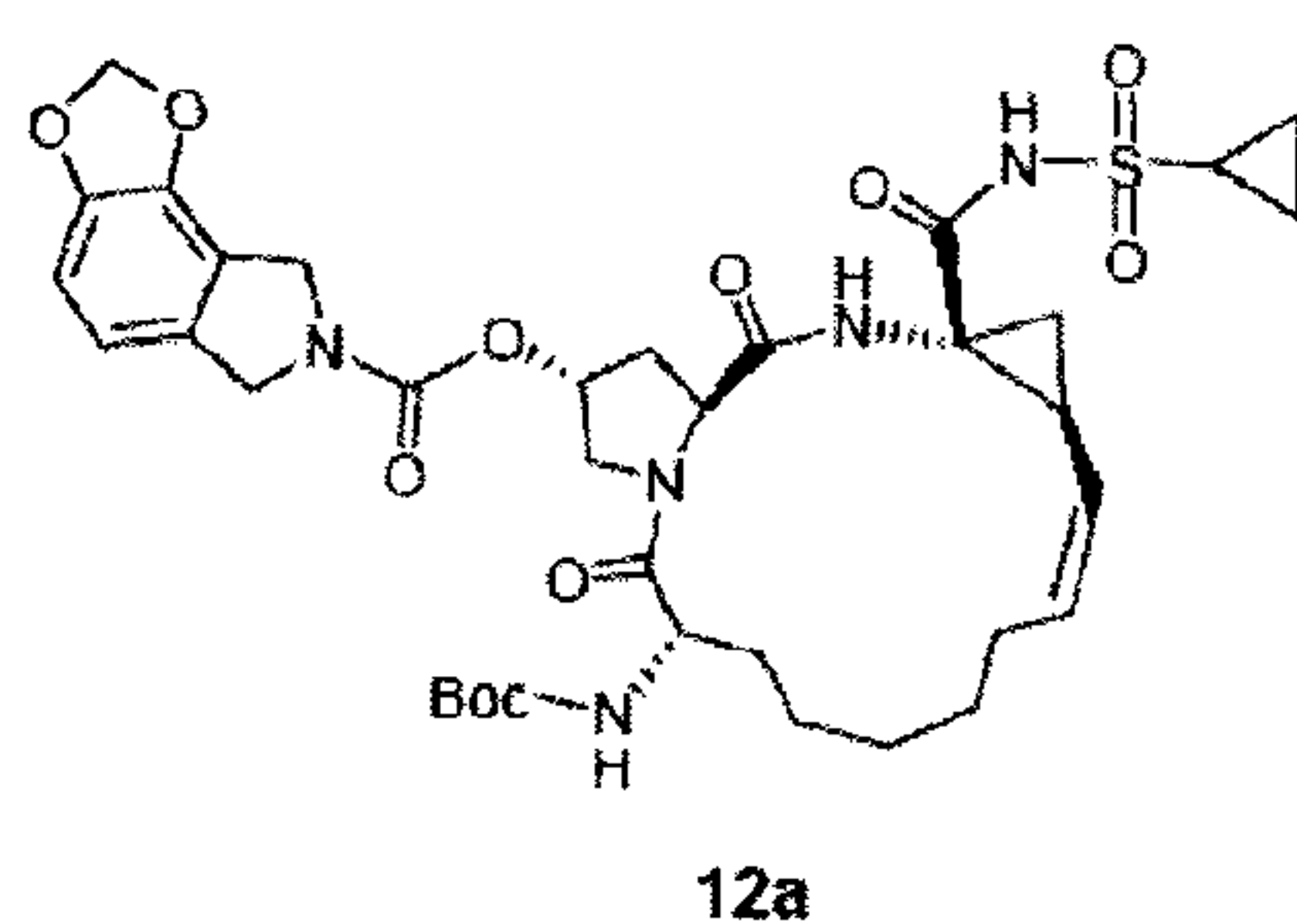
Z is hydroxyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfonamido, C₃-C₆ cycloalkylsulfonamido or C₆-C₁₀ arylsulfonamido group;

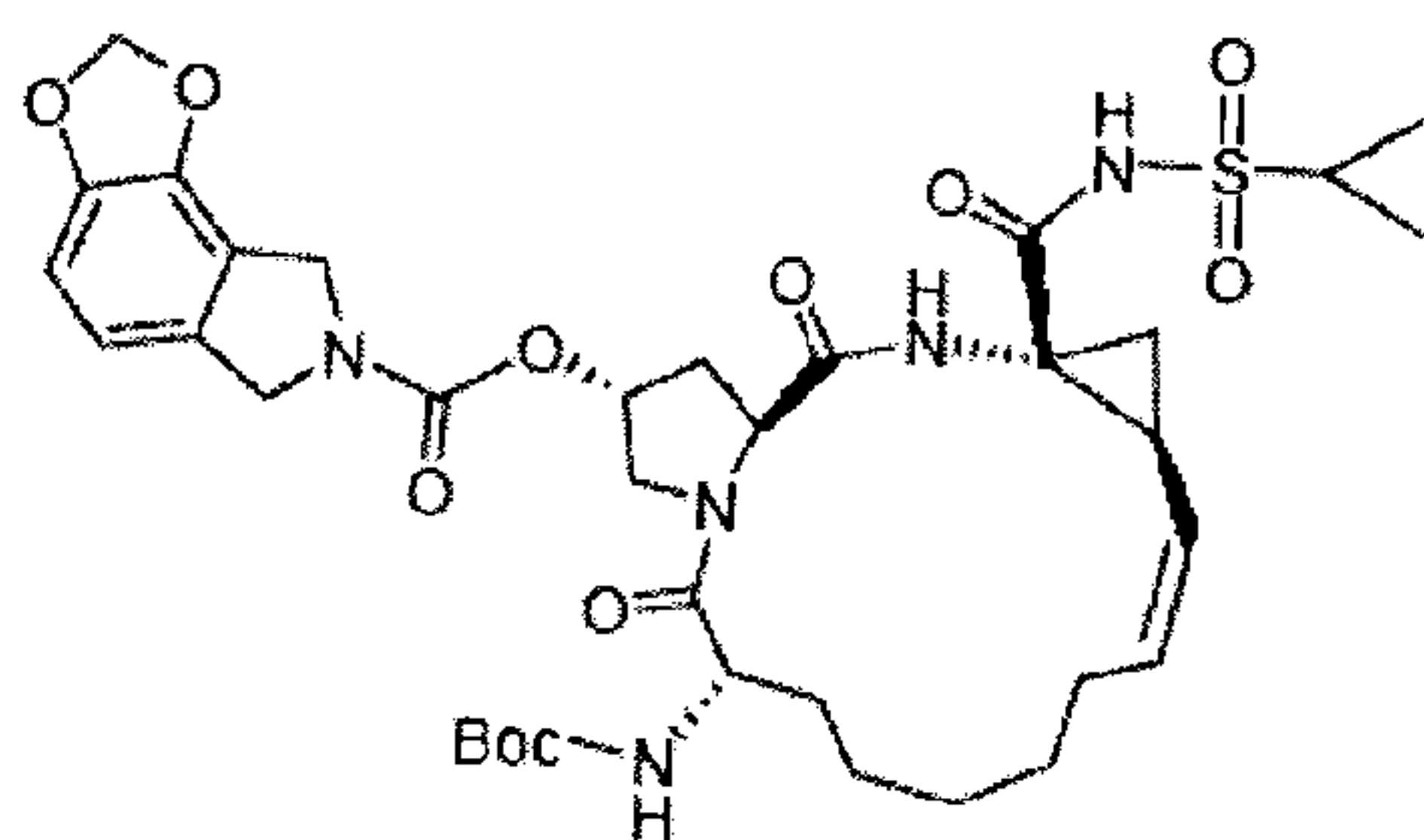
R¹ is hydrogen, C₆-C₁₀ arylamino, C₁-C₆ alkoxycarbonylamino, C₂-C₆ heterocyclic amino, C₁-C₆ alkylsulfonamido, or C₆-C₁₀ arylsulfonamido; and

R², R³, R⁴, R⁵ and R⁶ are each H;

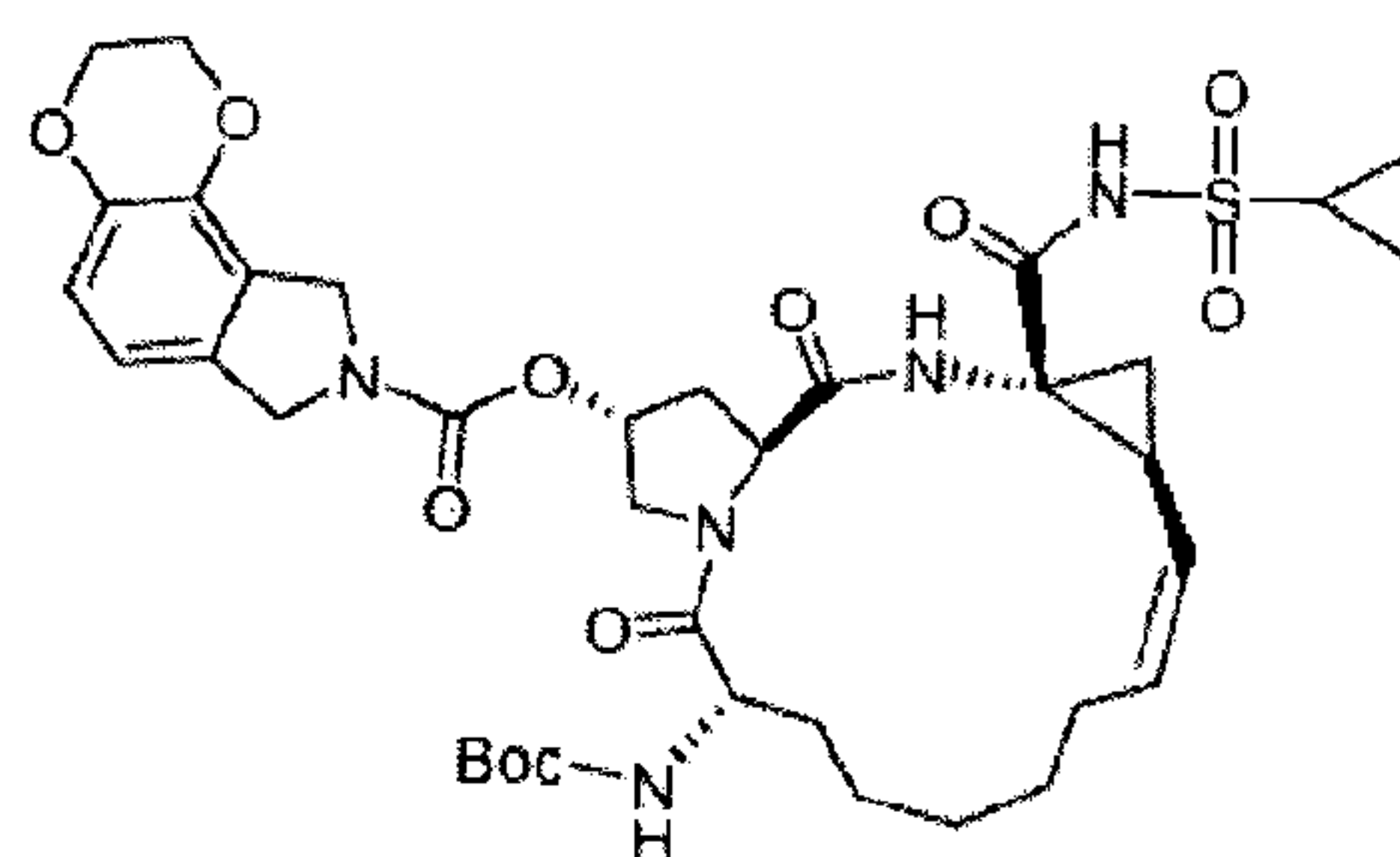
R⁷, R⁸ and R⁹ are each H.

5. A compound of claim 1, wherein the compound is selected from the group consisting of

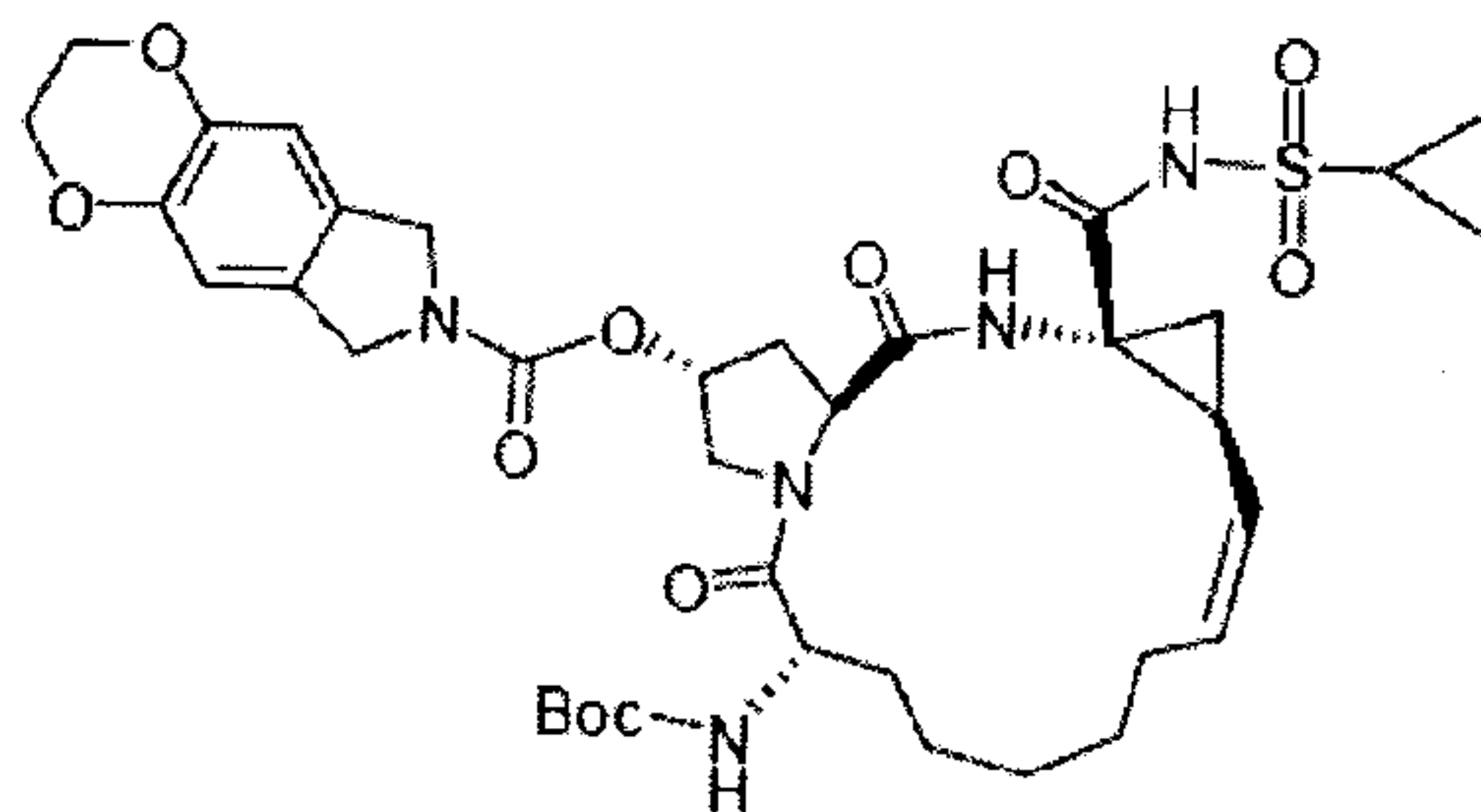




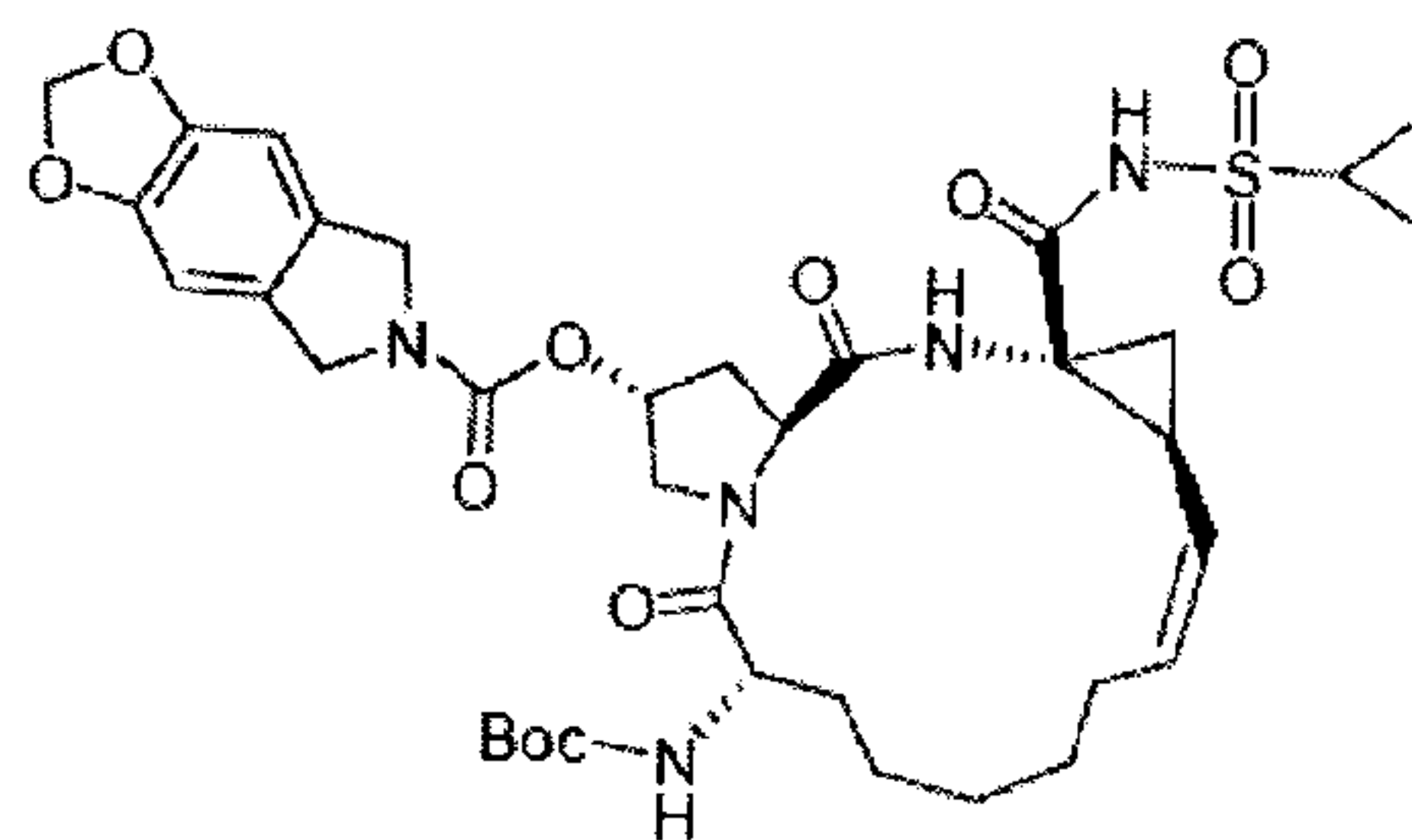
12e



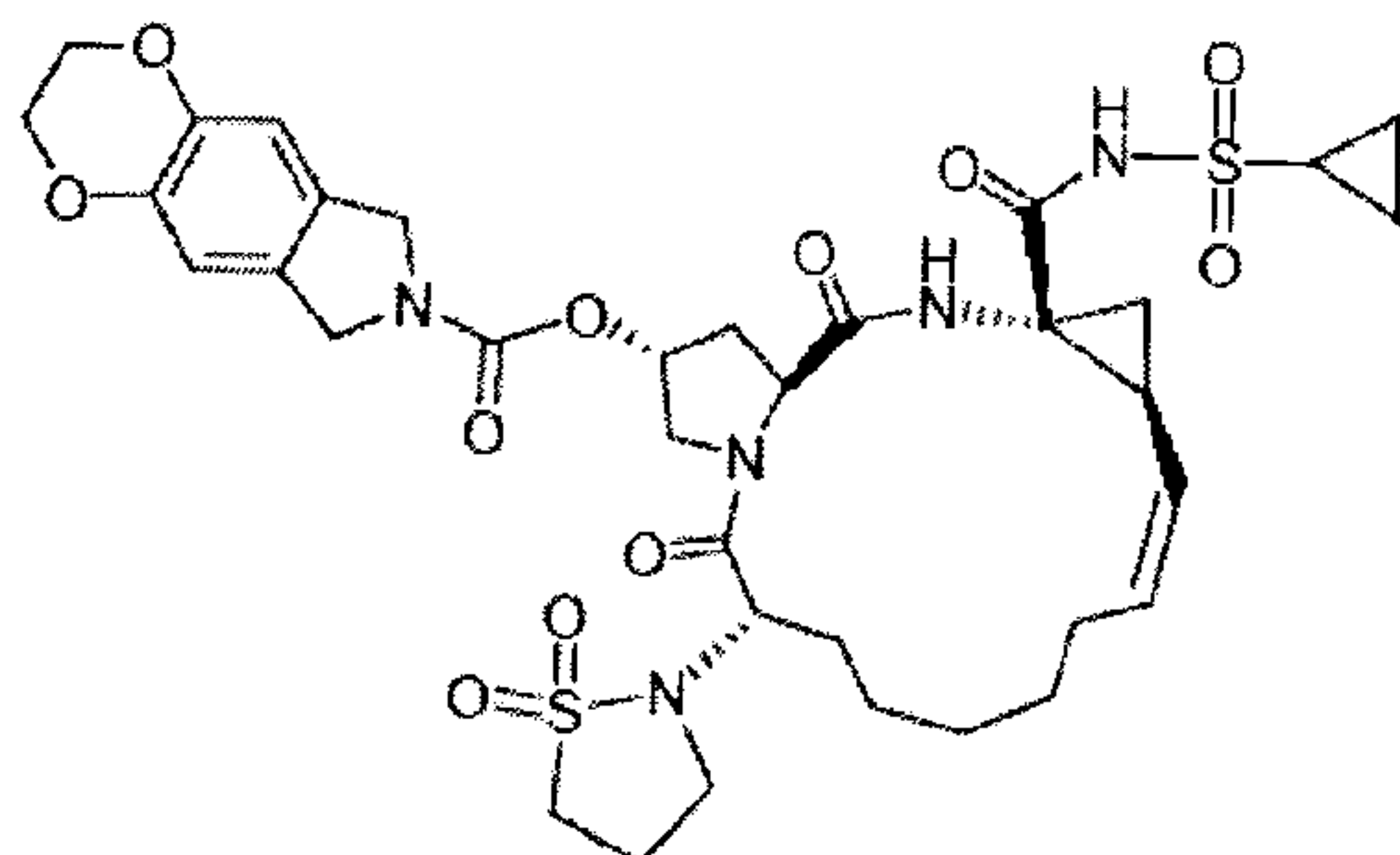
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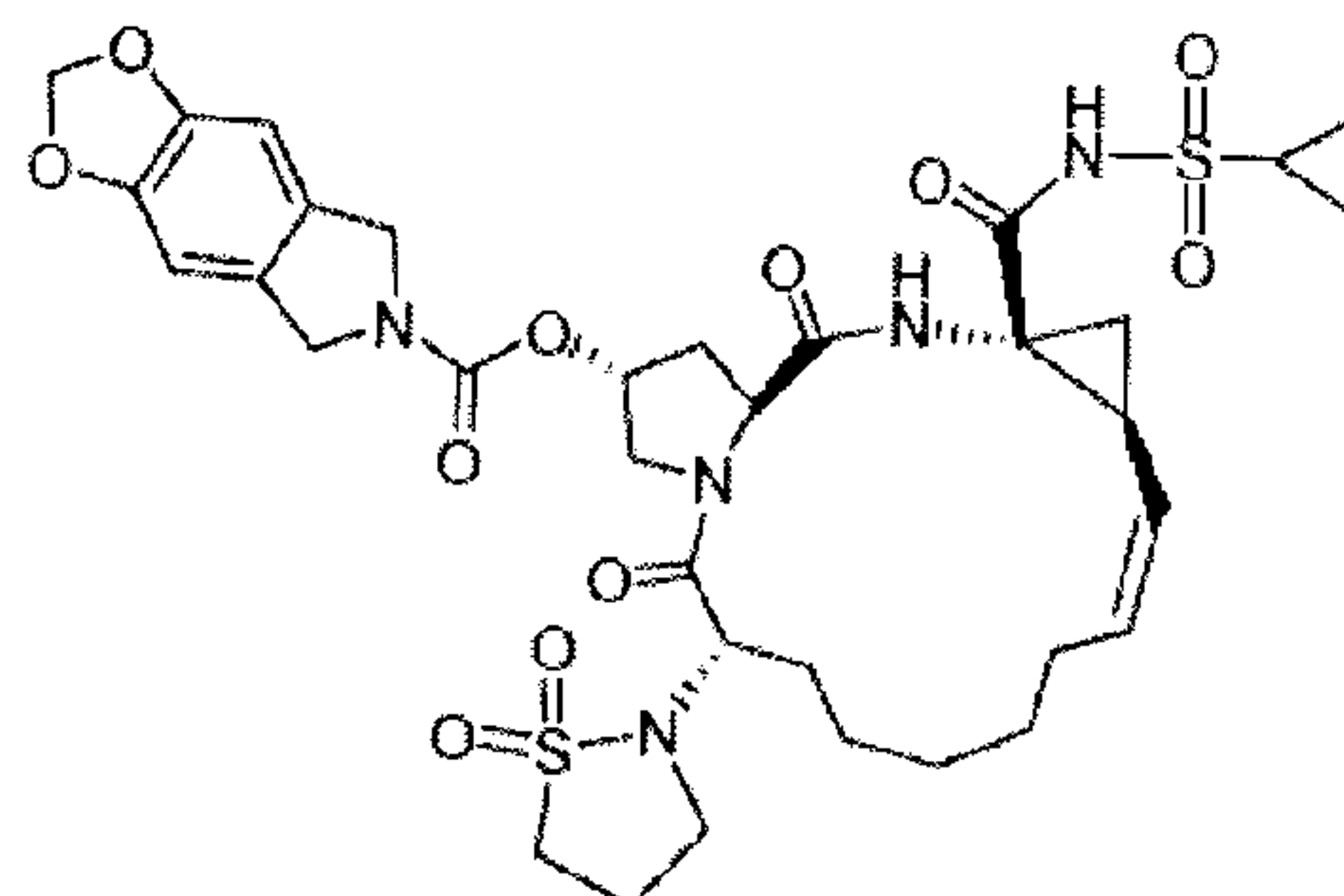
12g



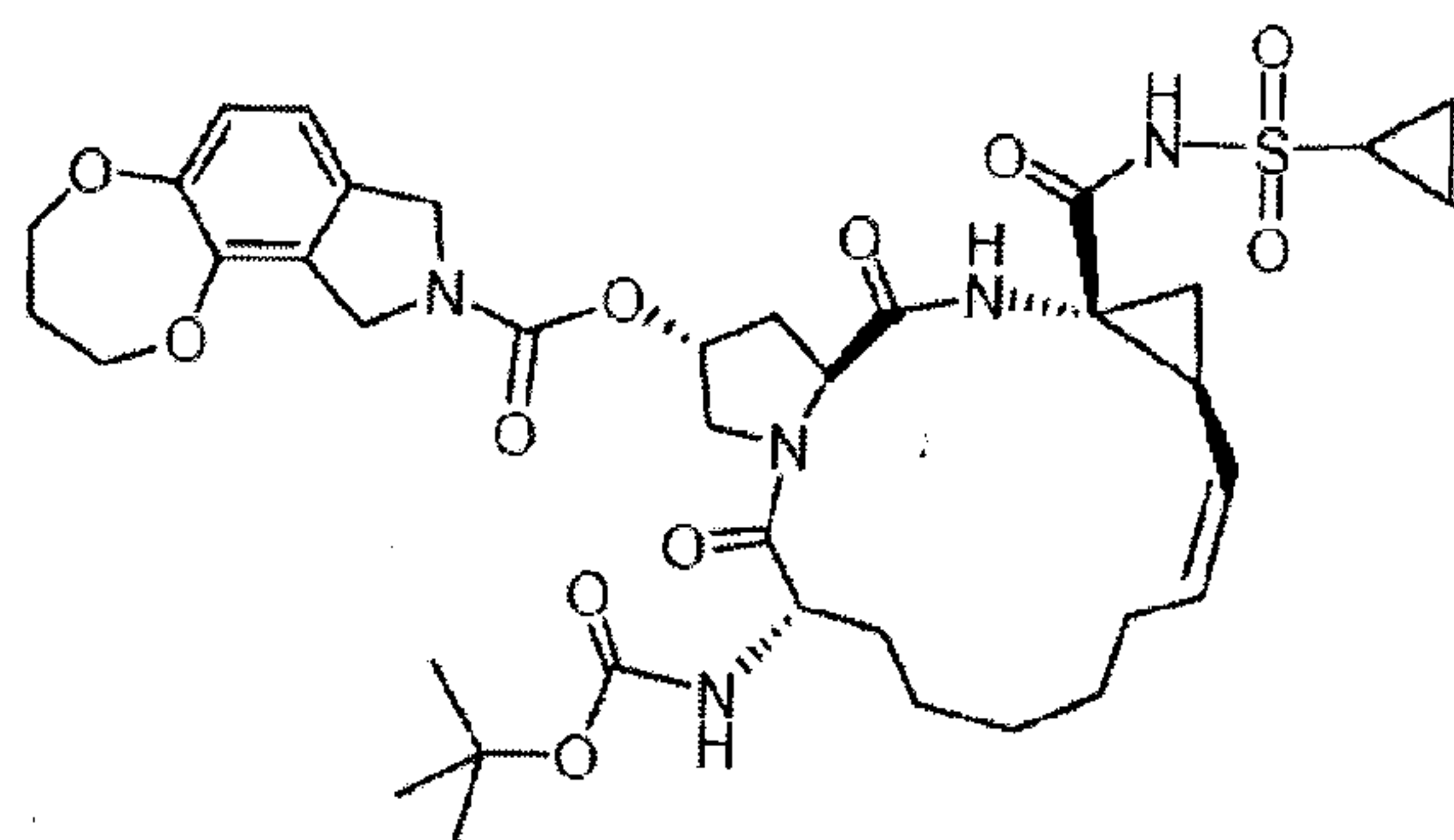
12h



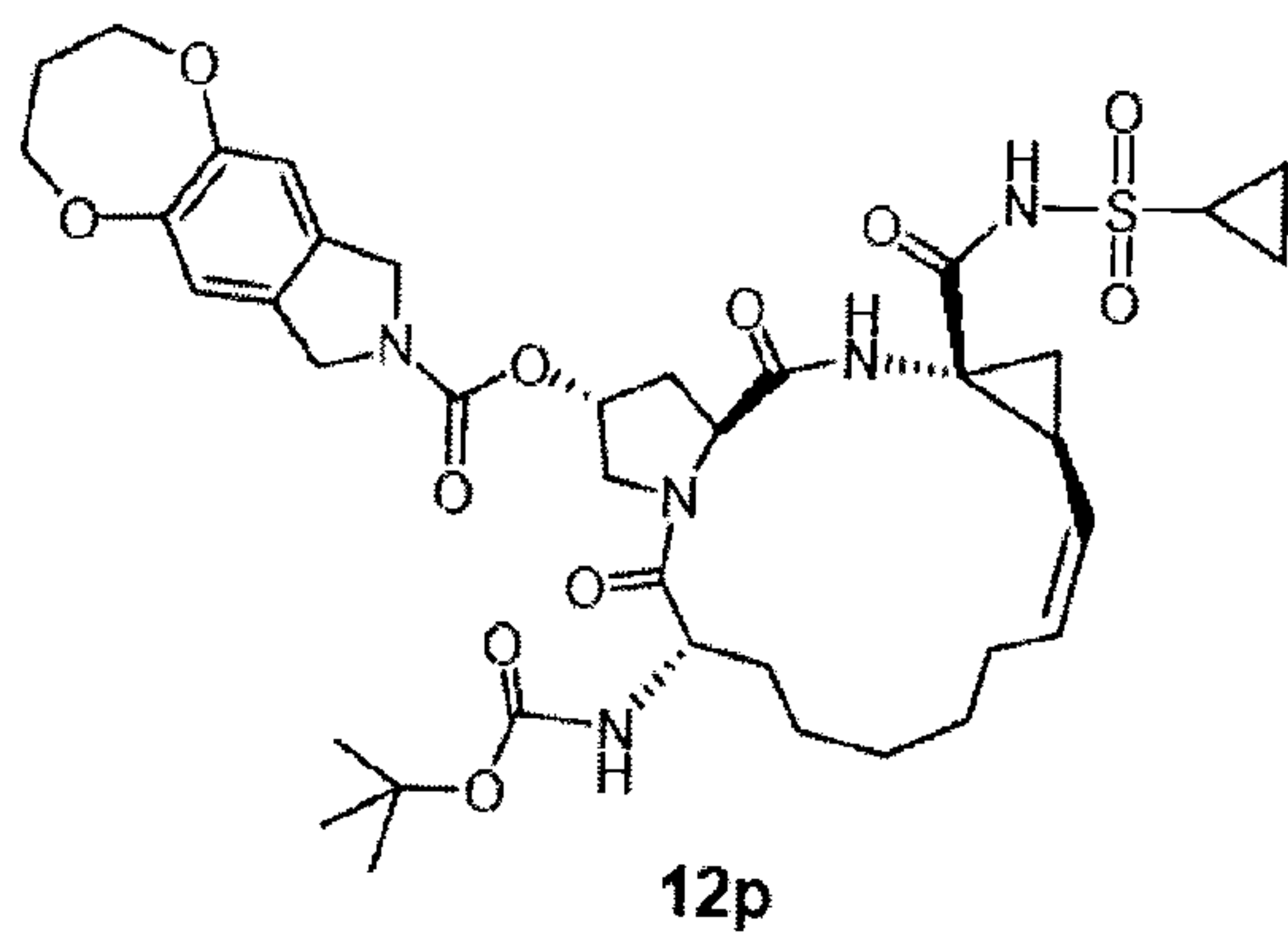
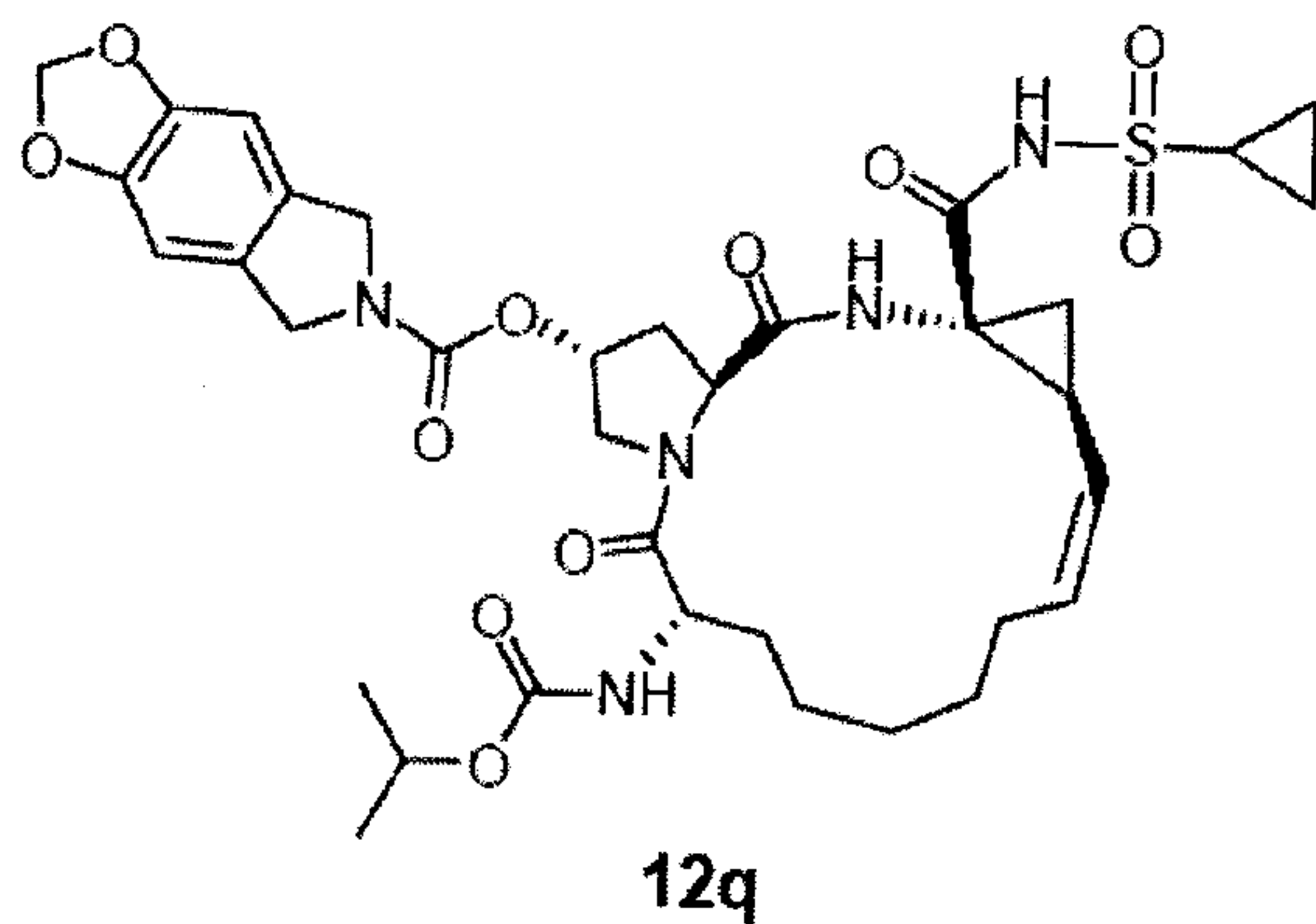
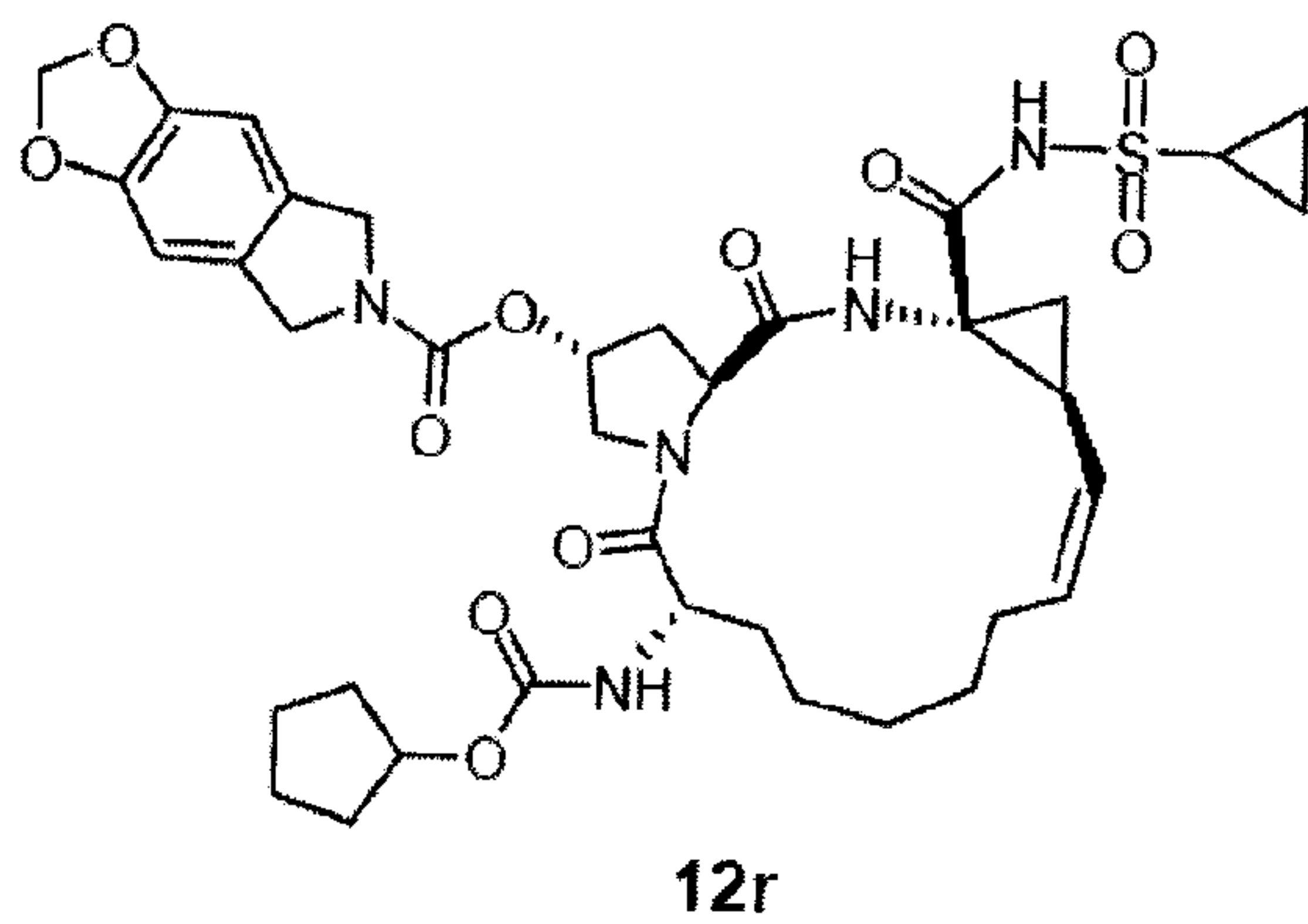
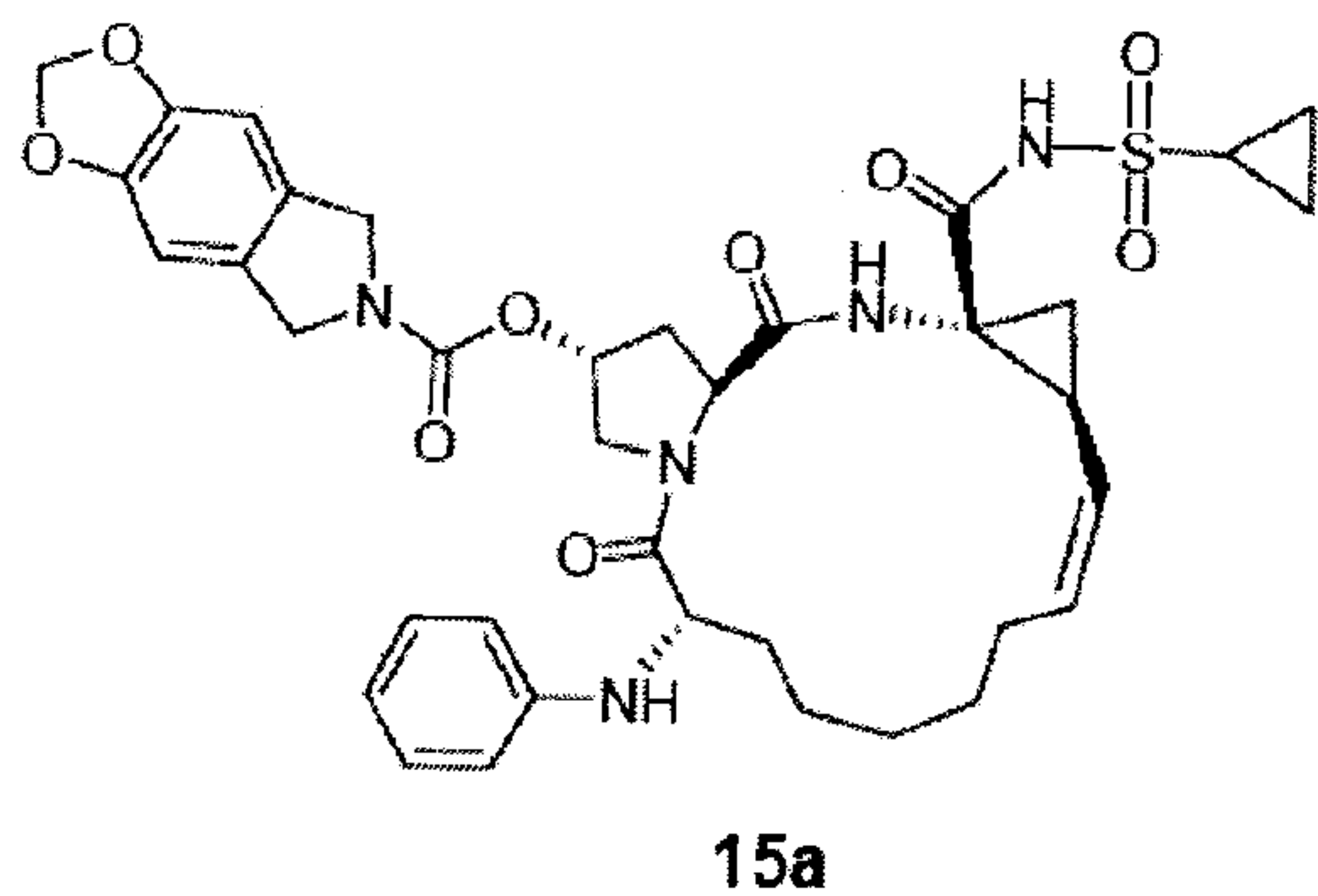
12j

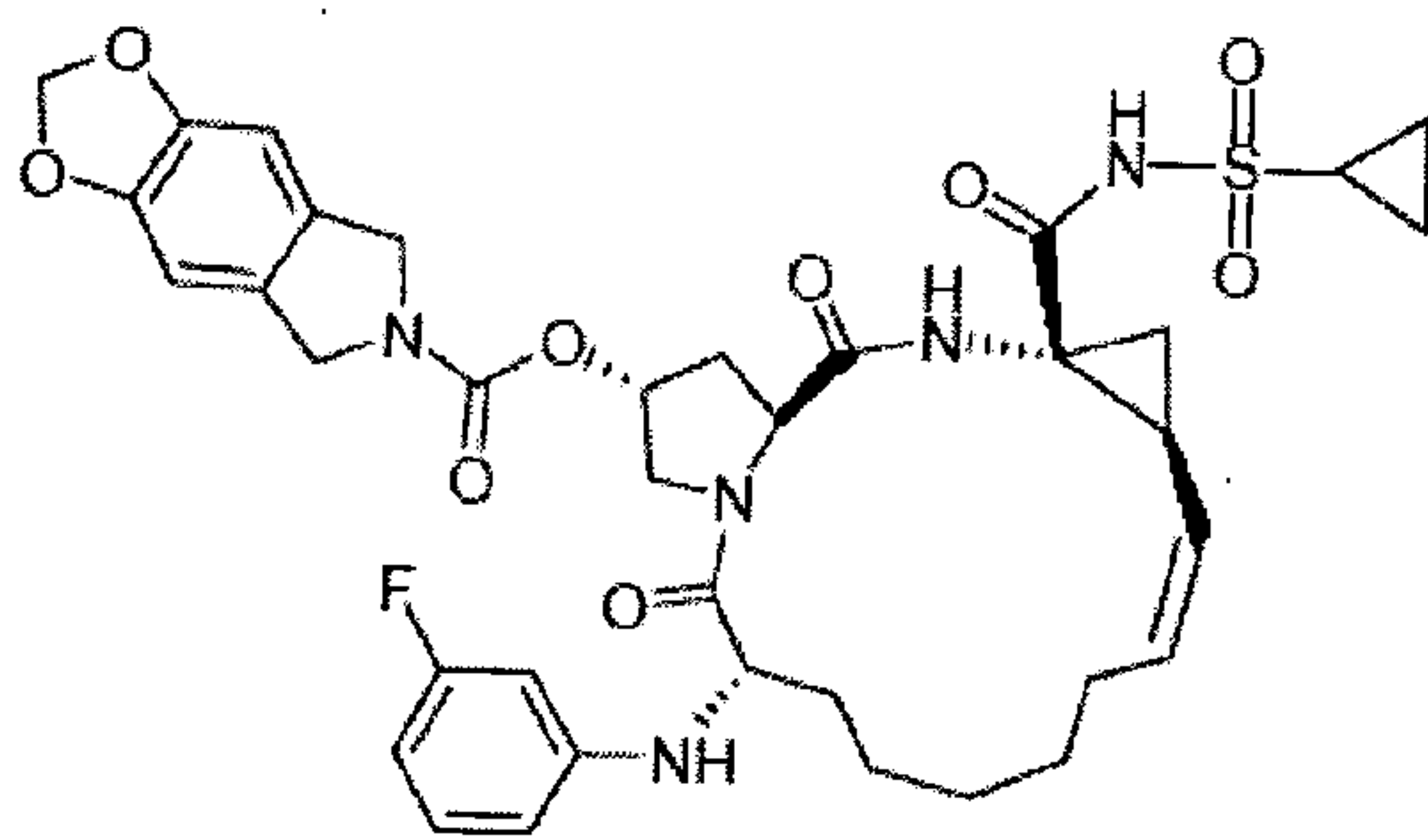
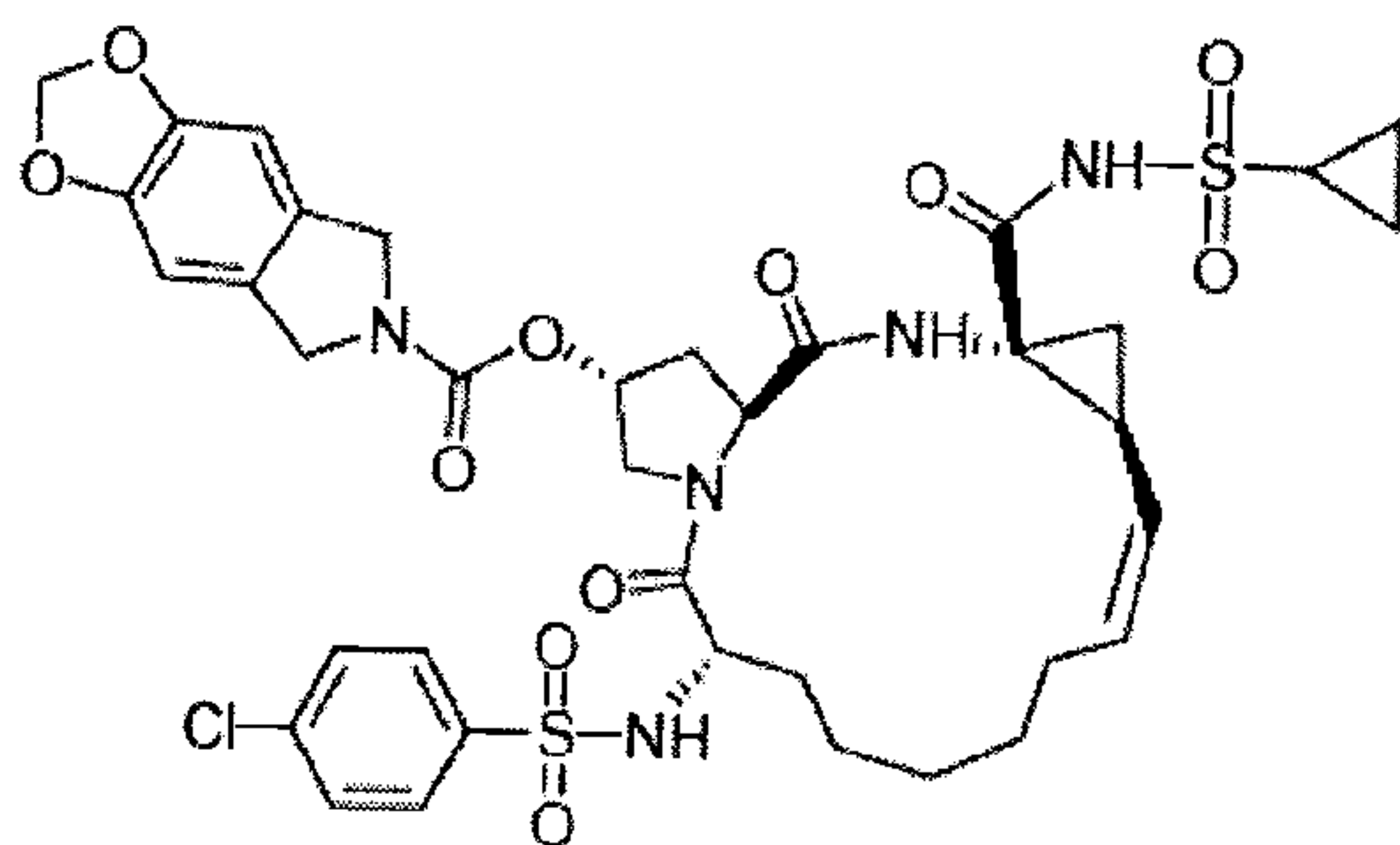
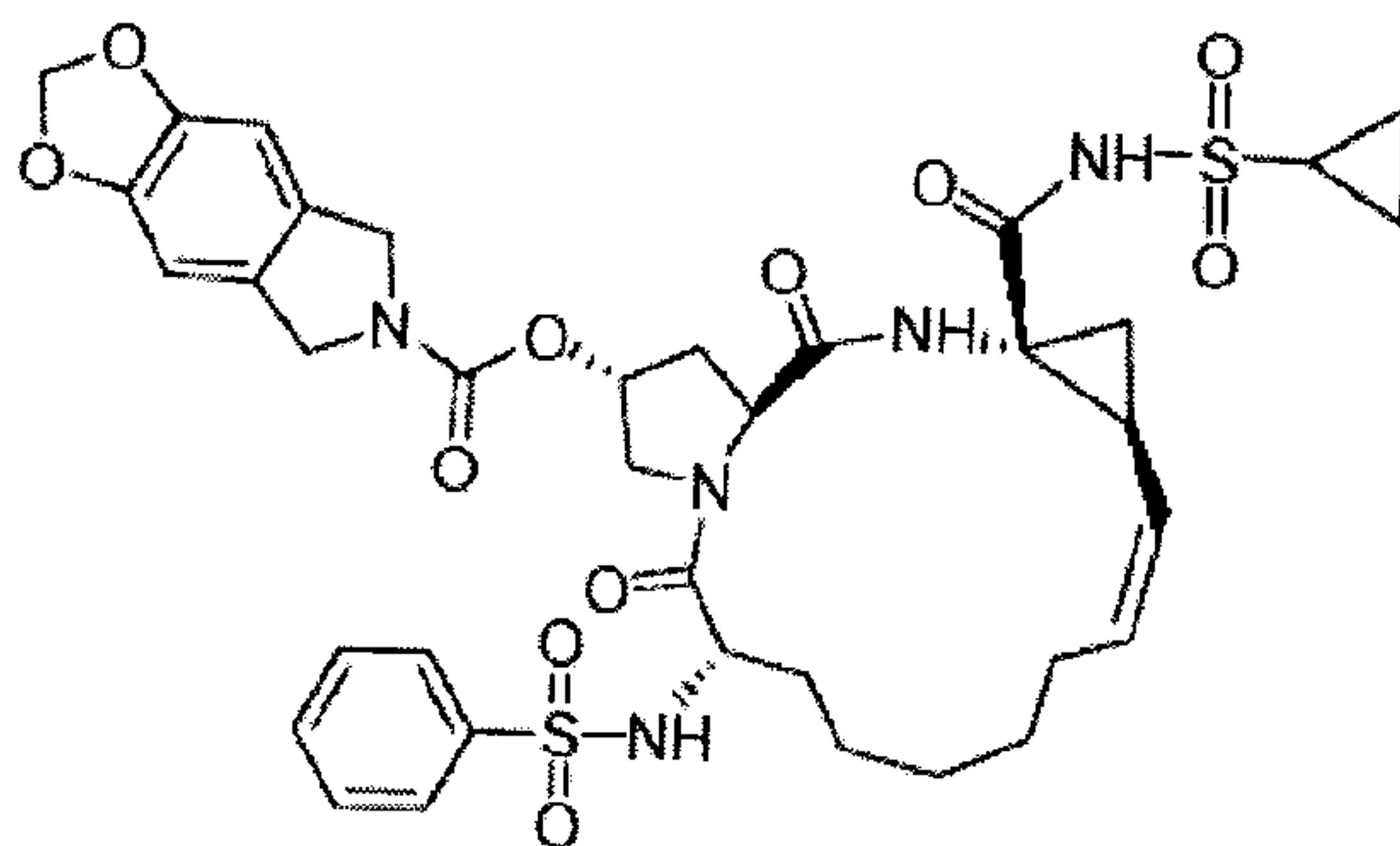
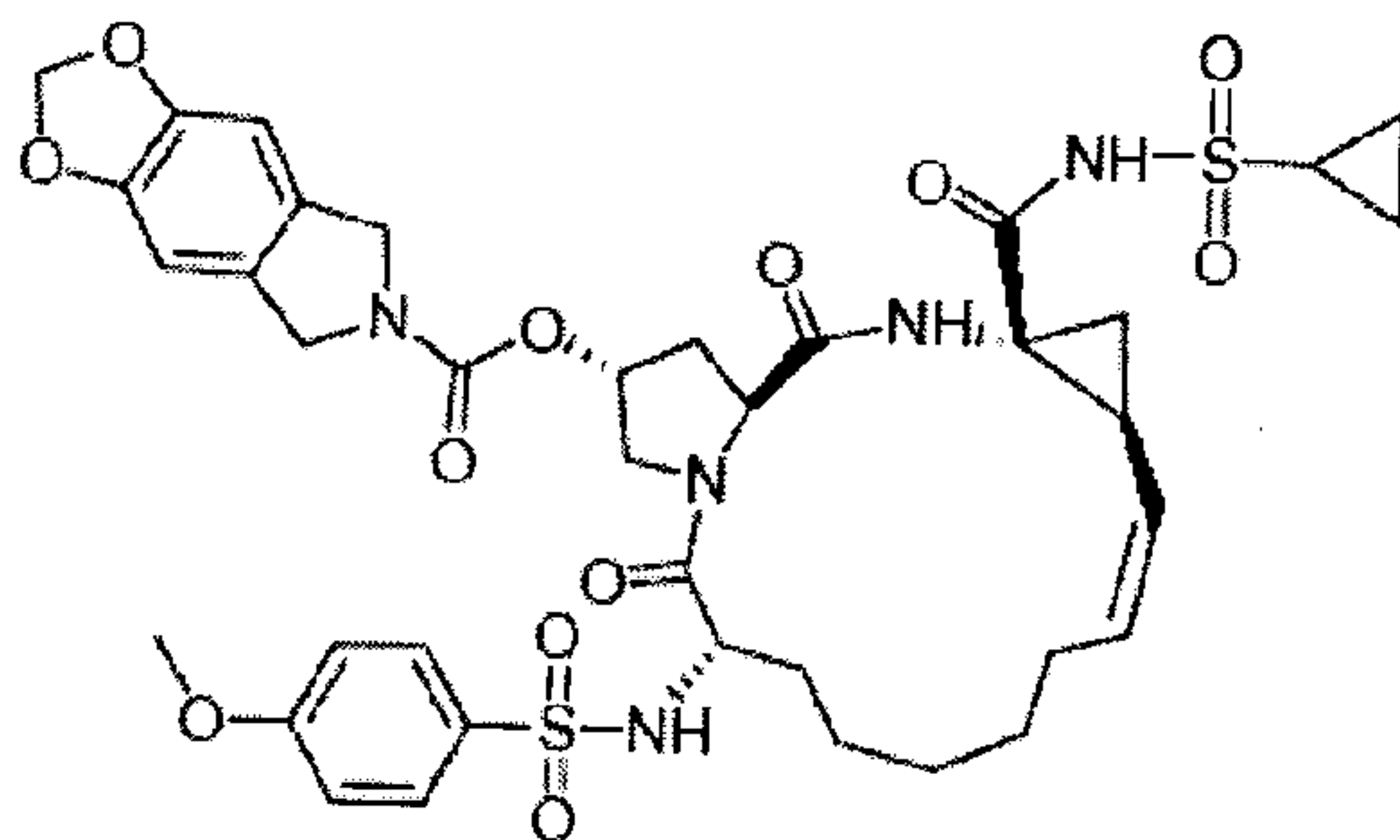


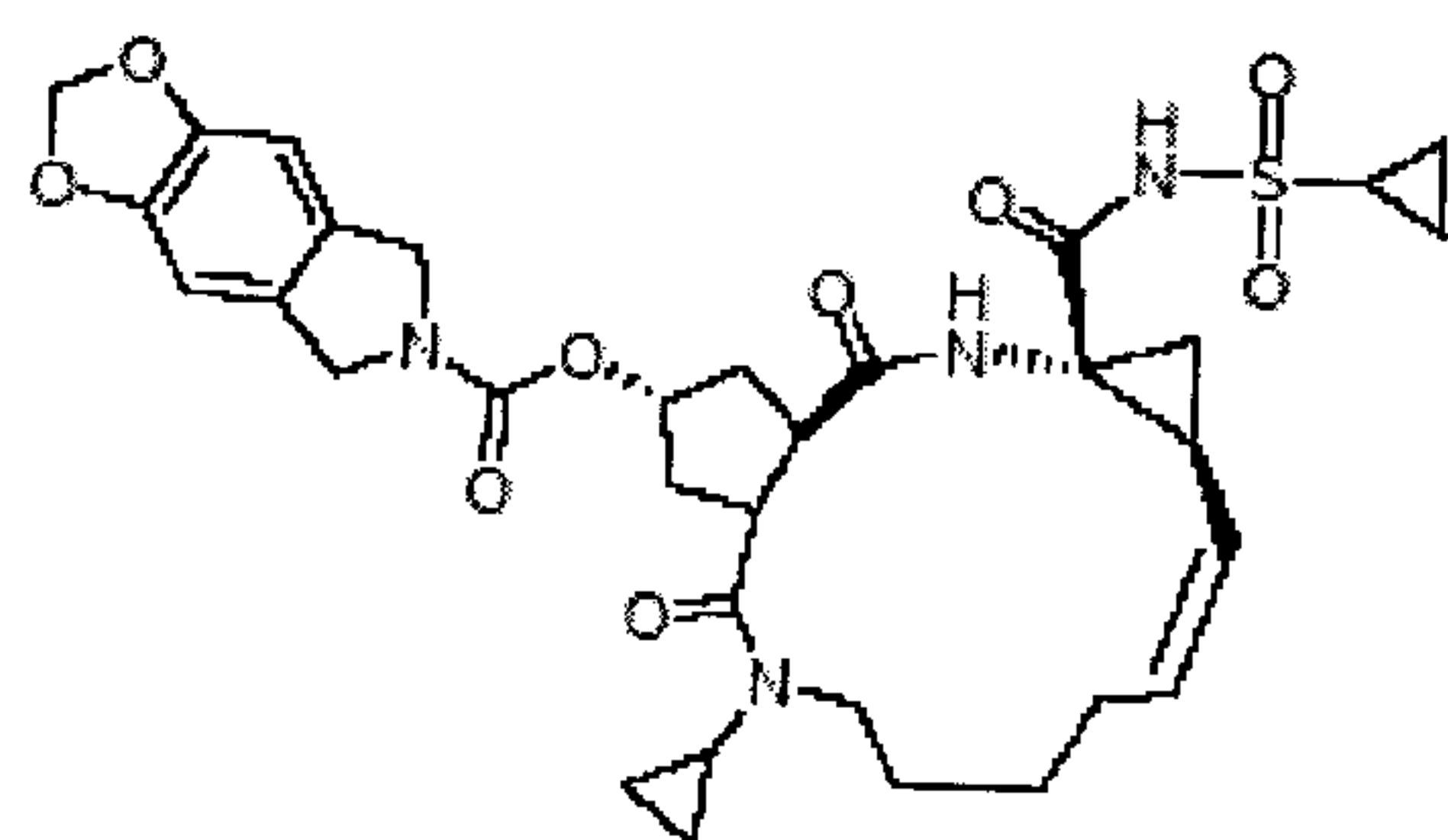
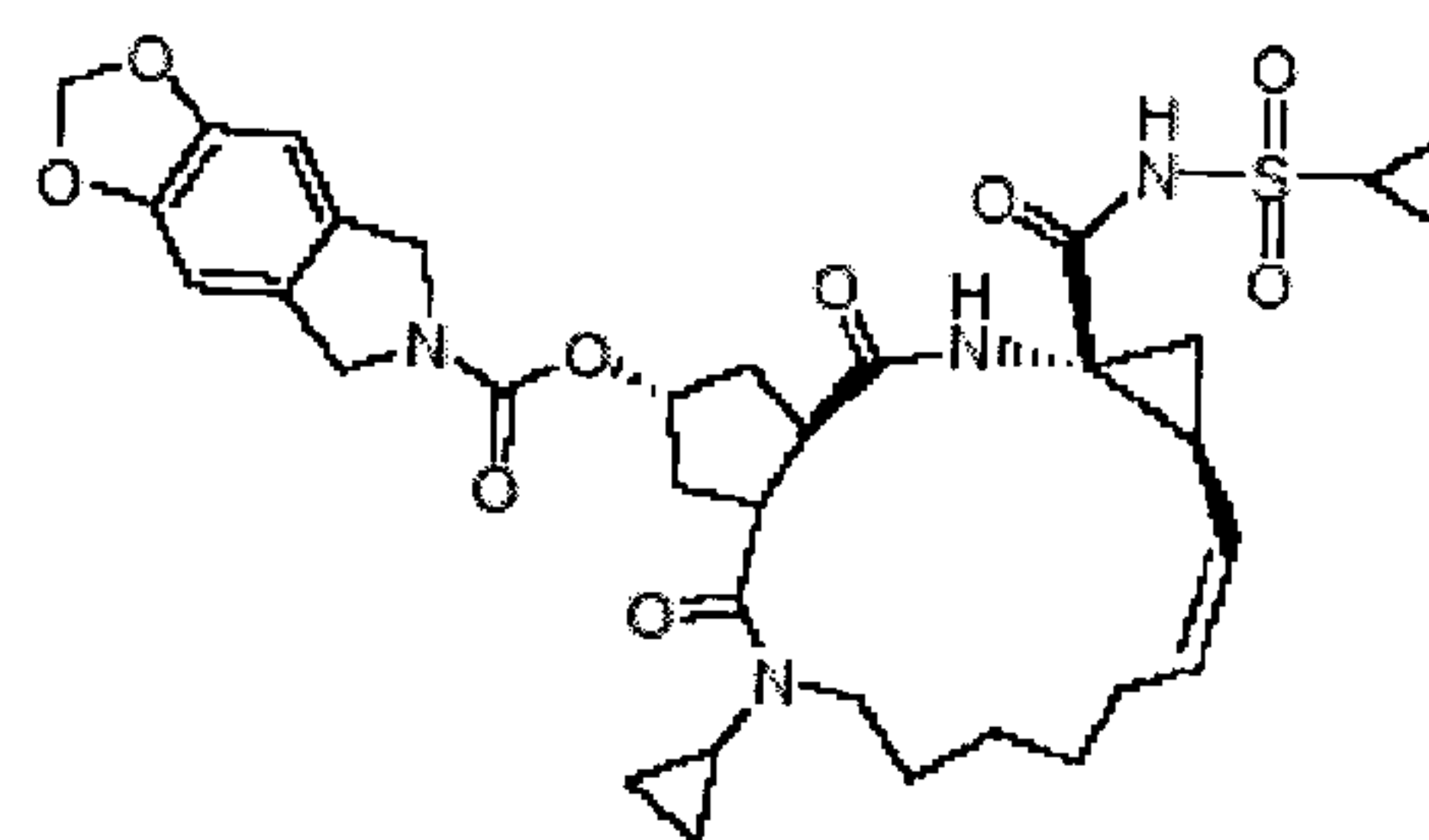
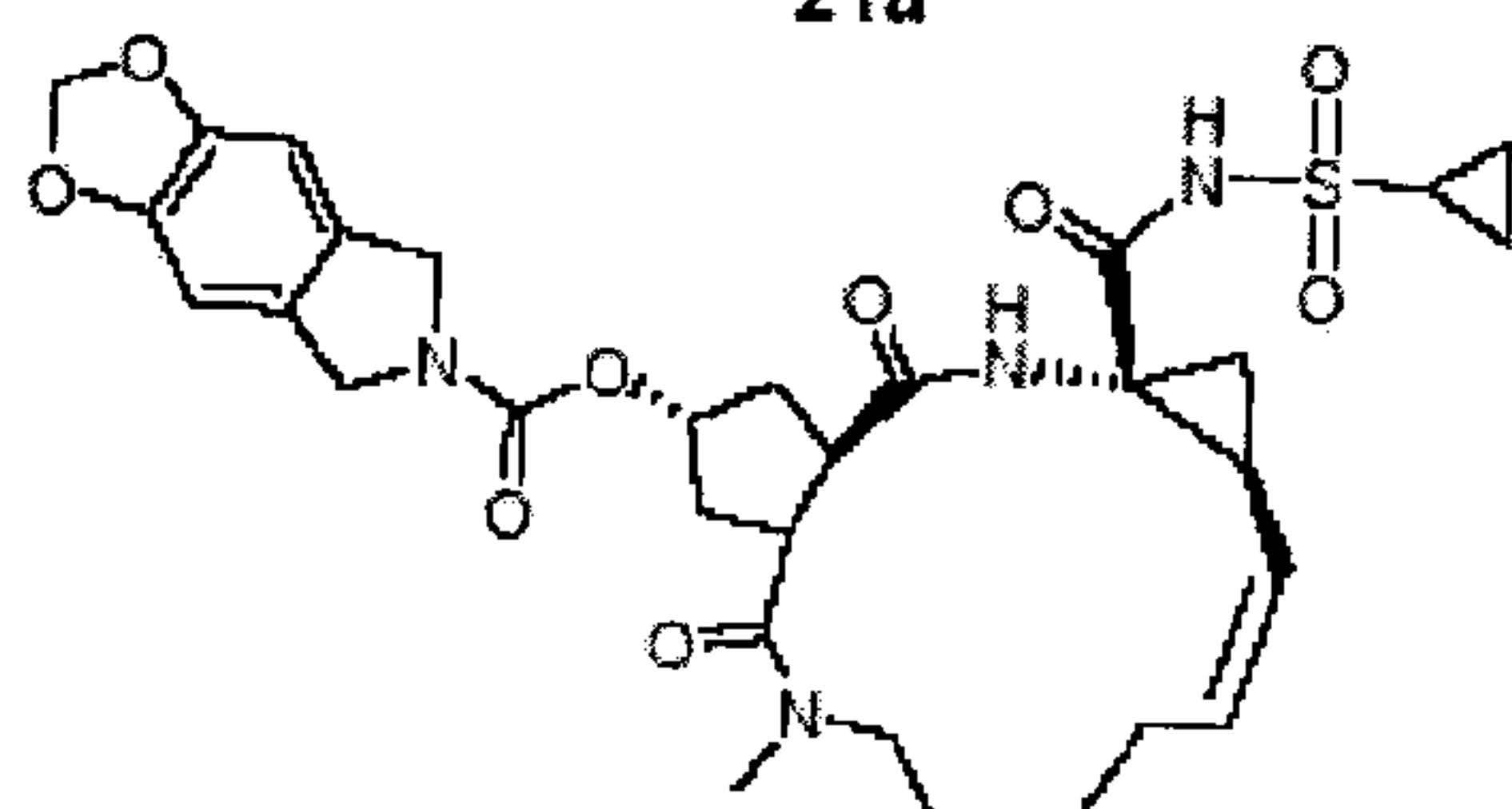
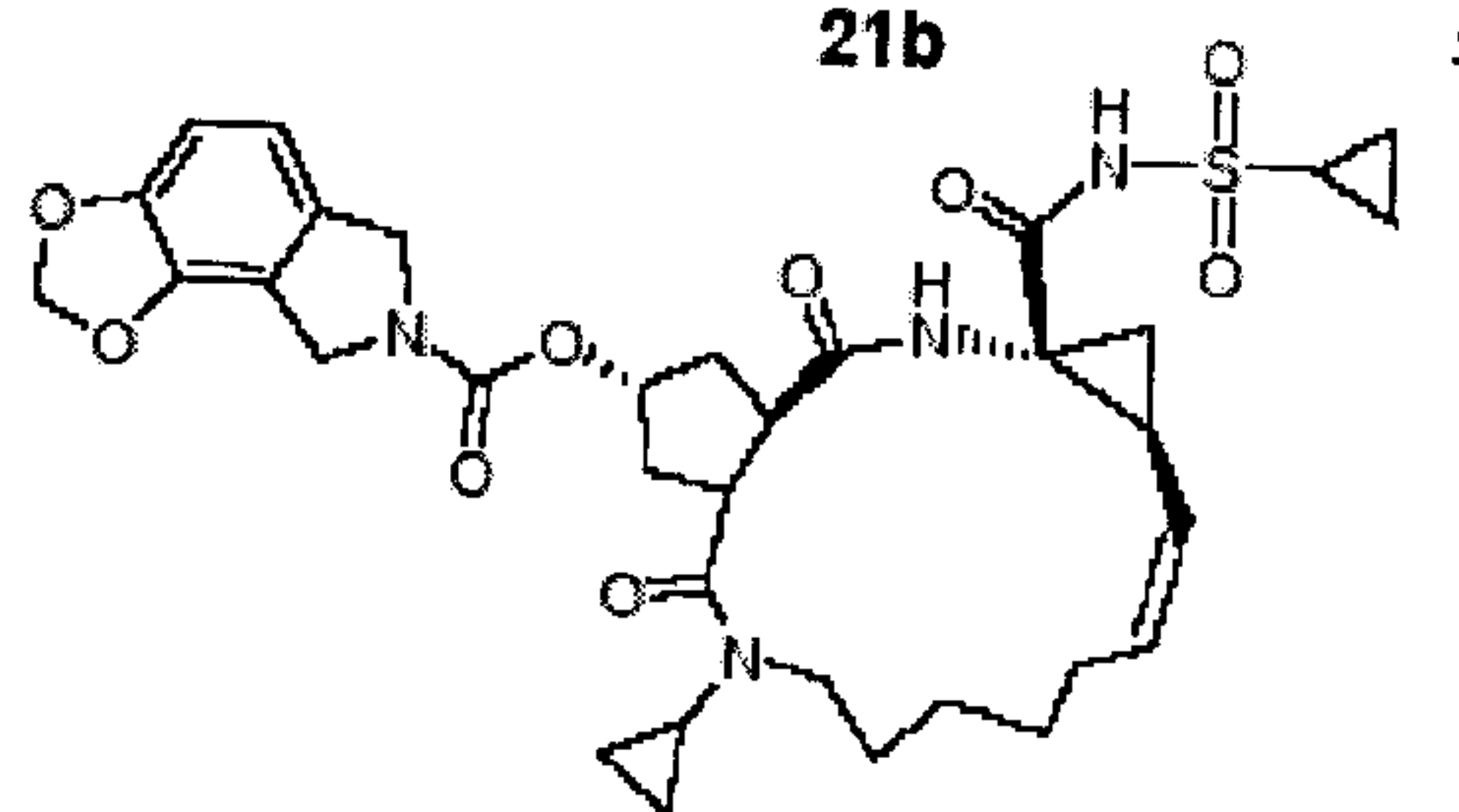
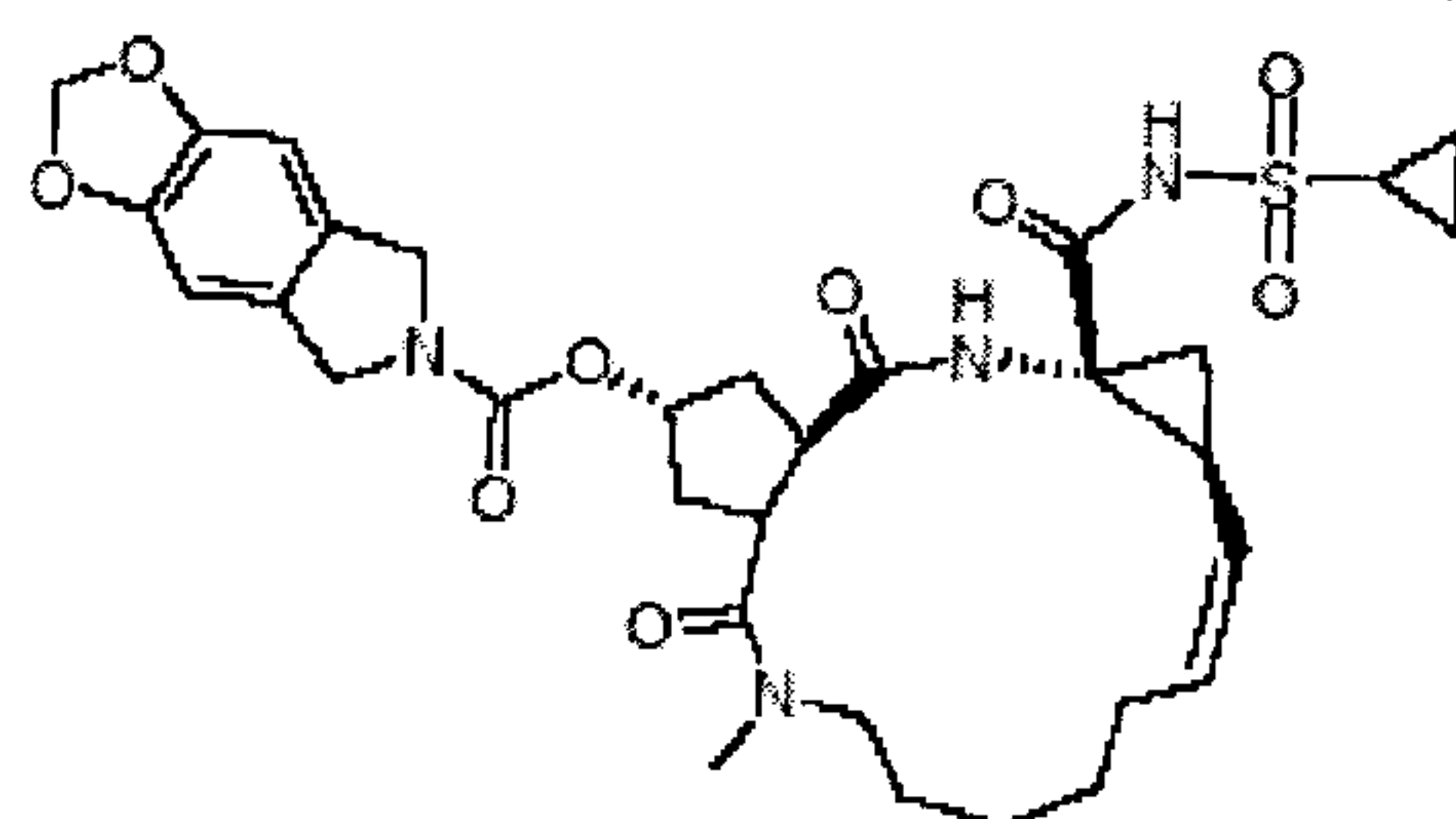
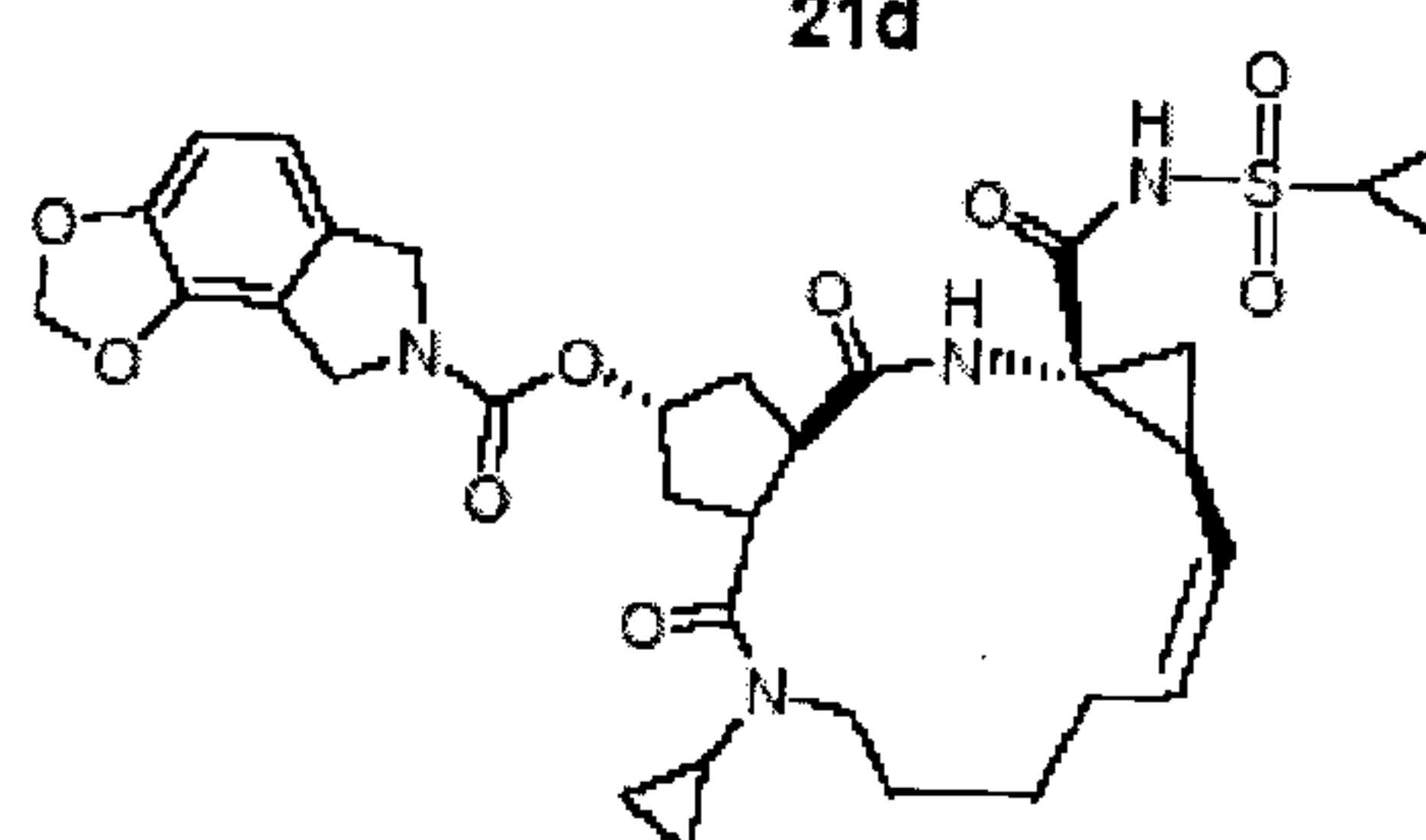
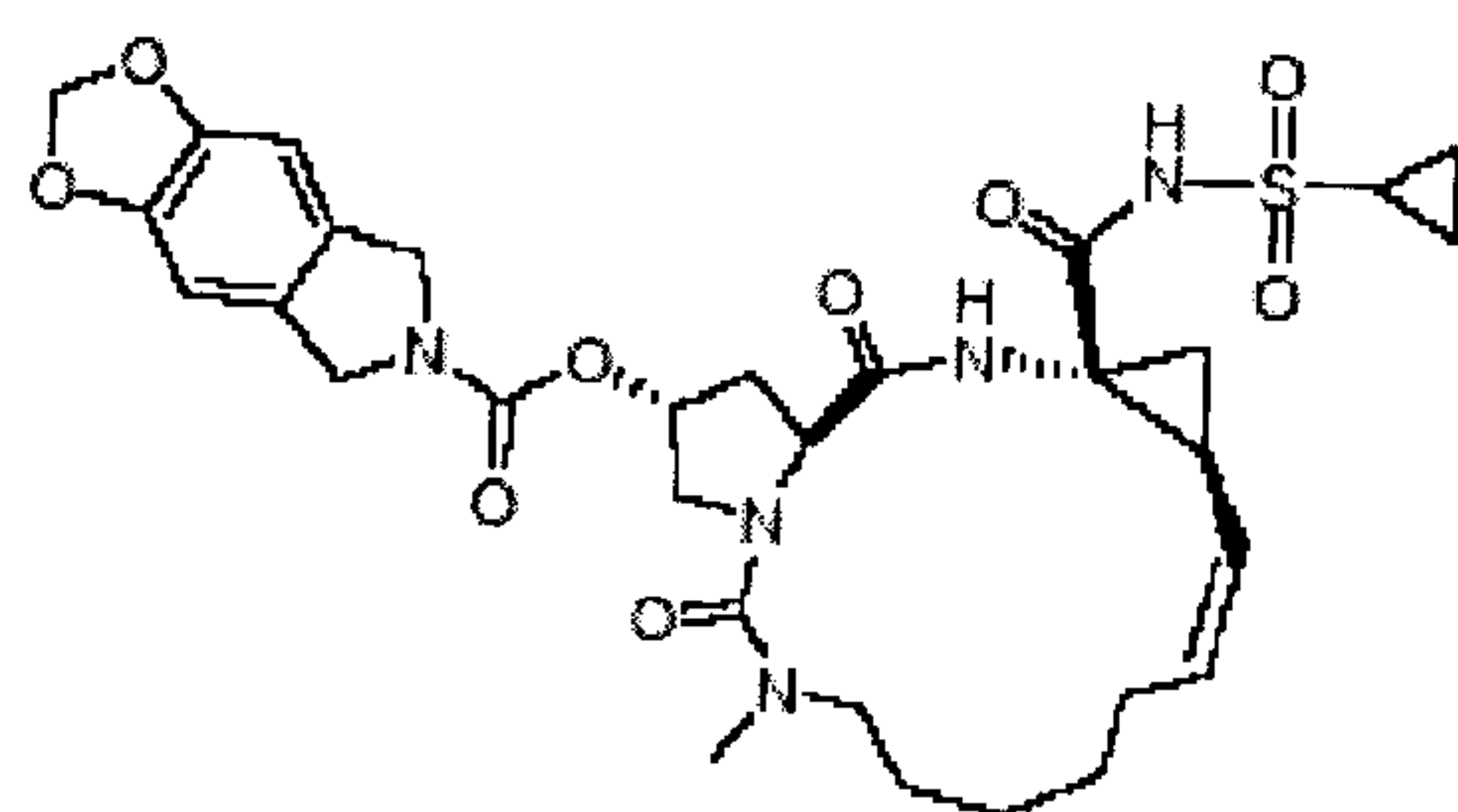
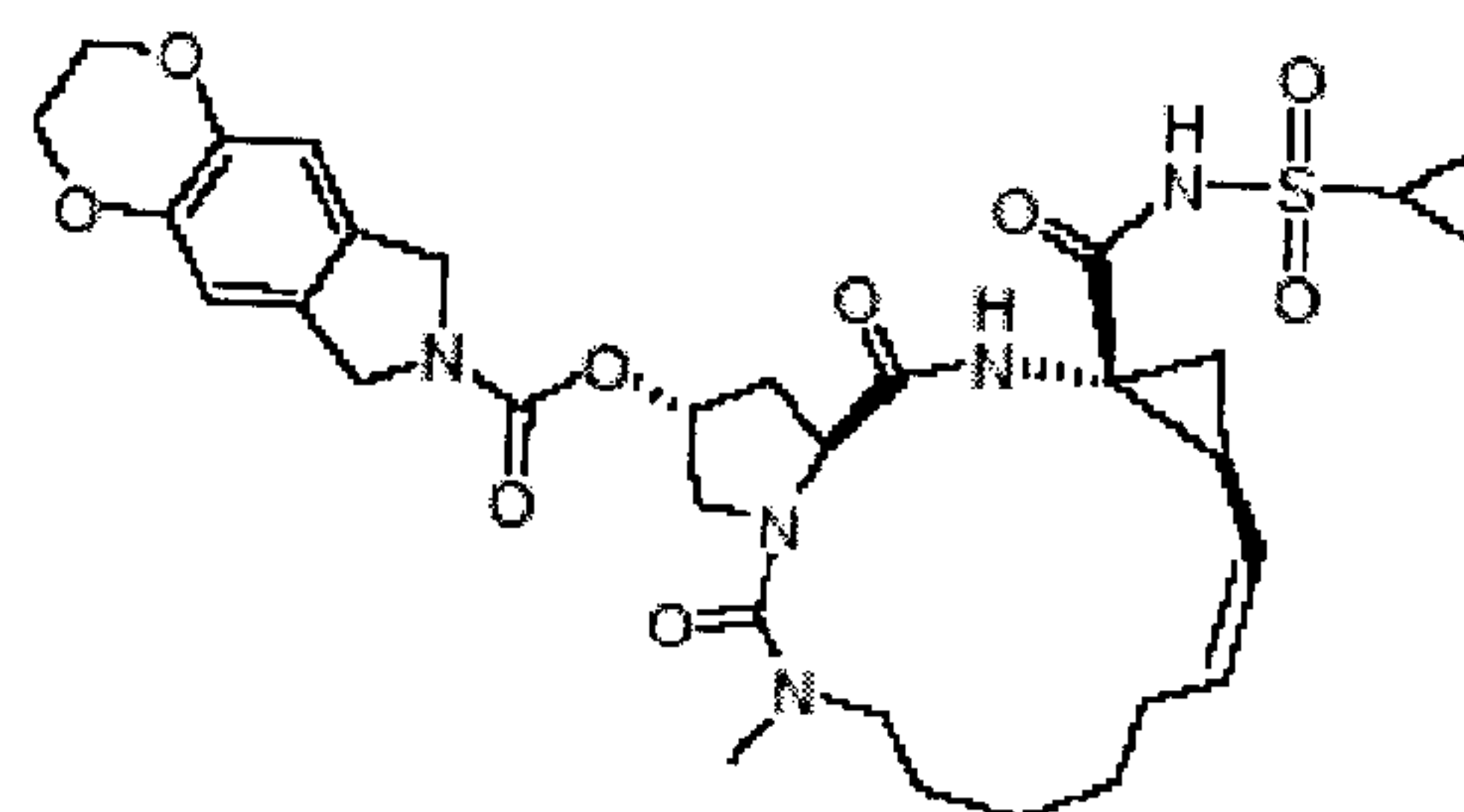
12k



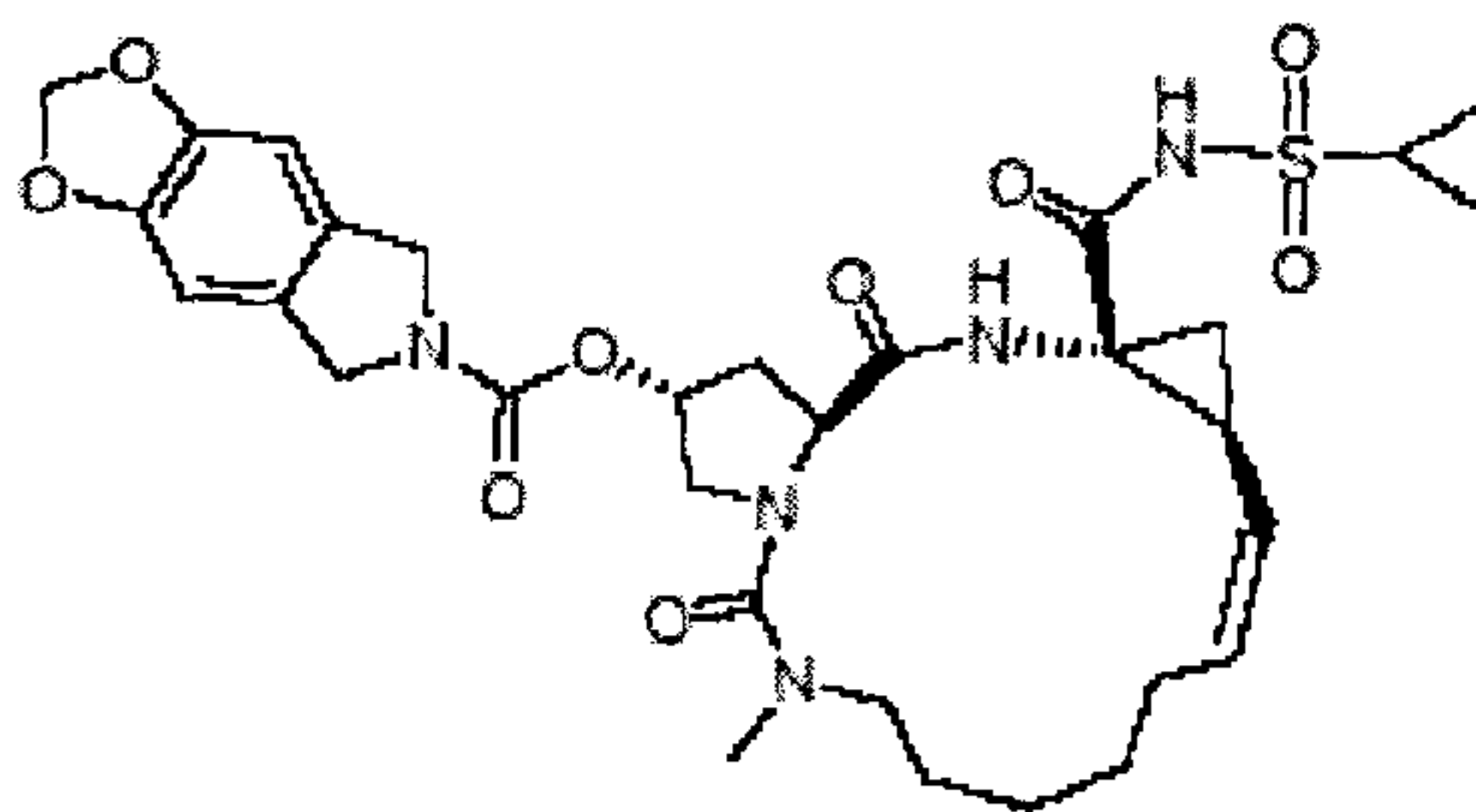
12n

**12p****12q****12r****15a**

**15b****16a****16b****16c**

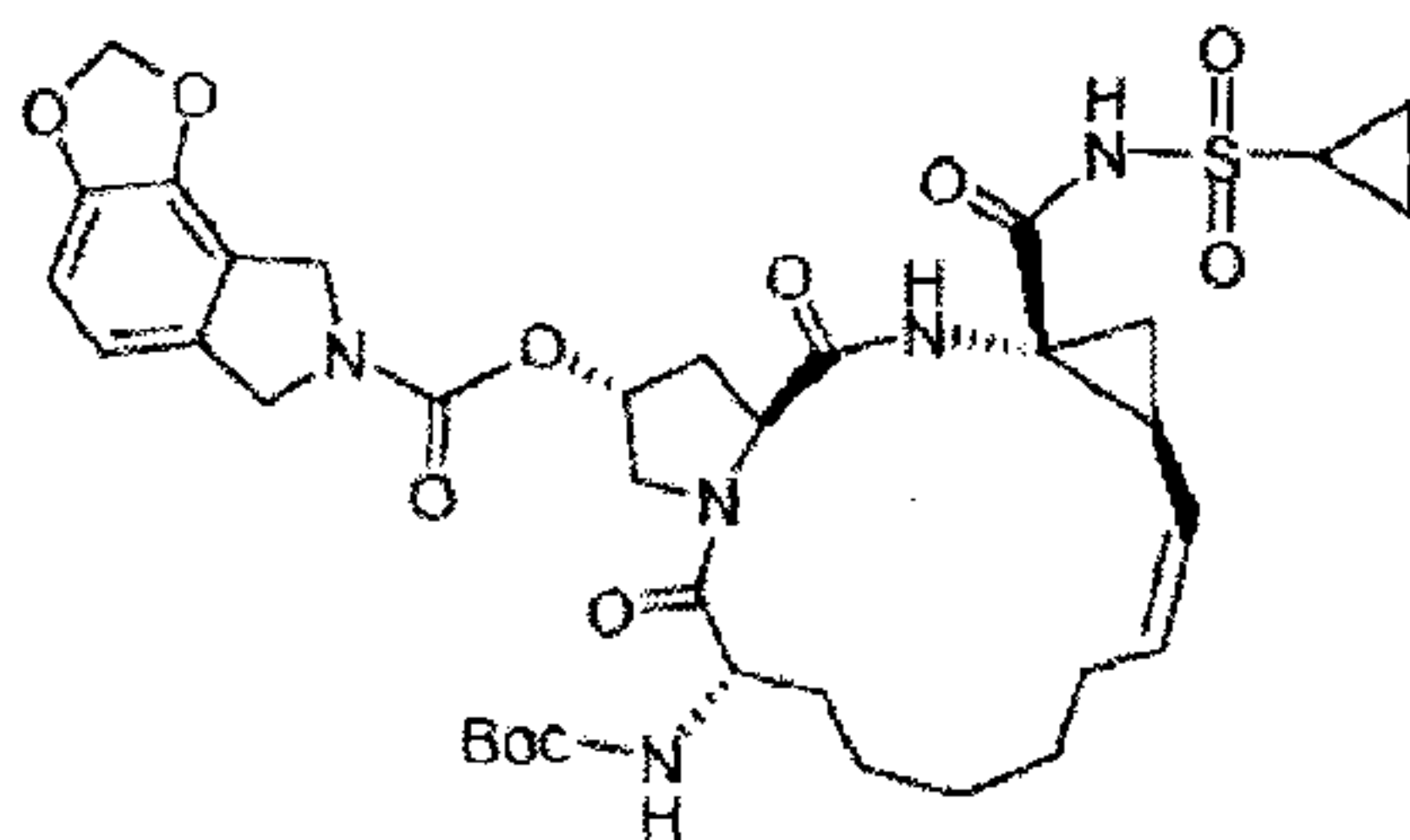
**21a****21b****21c****21d****21e****21f****27a****27b**

and



27c

6. The compound of claim 5, wherein the compound is



12a

7. A pharmaceutical composition comprising one or more compounds of any one of claims 1-6 and a pharmaceutically acceptable excipient.

8. A pharmaceutical combination of a compound of any one of claims 1-6 and an HIV inhibitor.

9. The pharmaceutical combination of claim 8, wherein the HIV inhibitor is Ritonavir.

10. A pharmaceutical combination of a compound of any one of claims 1-6 and a hepatitis B virus (HBV) inhibitor.

11. The pharmaceutical combination of claim 10, wherein the HBV inhibitor is Heptodin, Sebivo, Hepsera, Emtriva, Baraclude, or Viread.

12. A use of one or more compounds of any one of claims 1-6 in a therapeutically effective dose, in the preparation of a medicament for inhibiting hepatitis C virus (HCV).

13. A use of one or more compounds of any one of claims 1-6 in a therapeutically effective dose, for inhibiting hepatitis C virus (HCV).

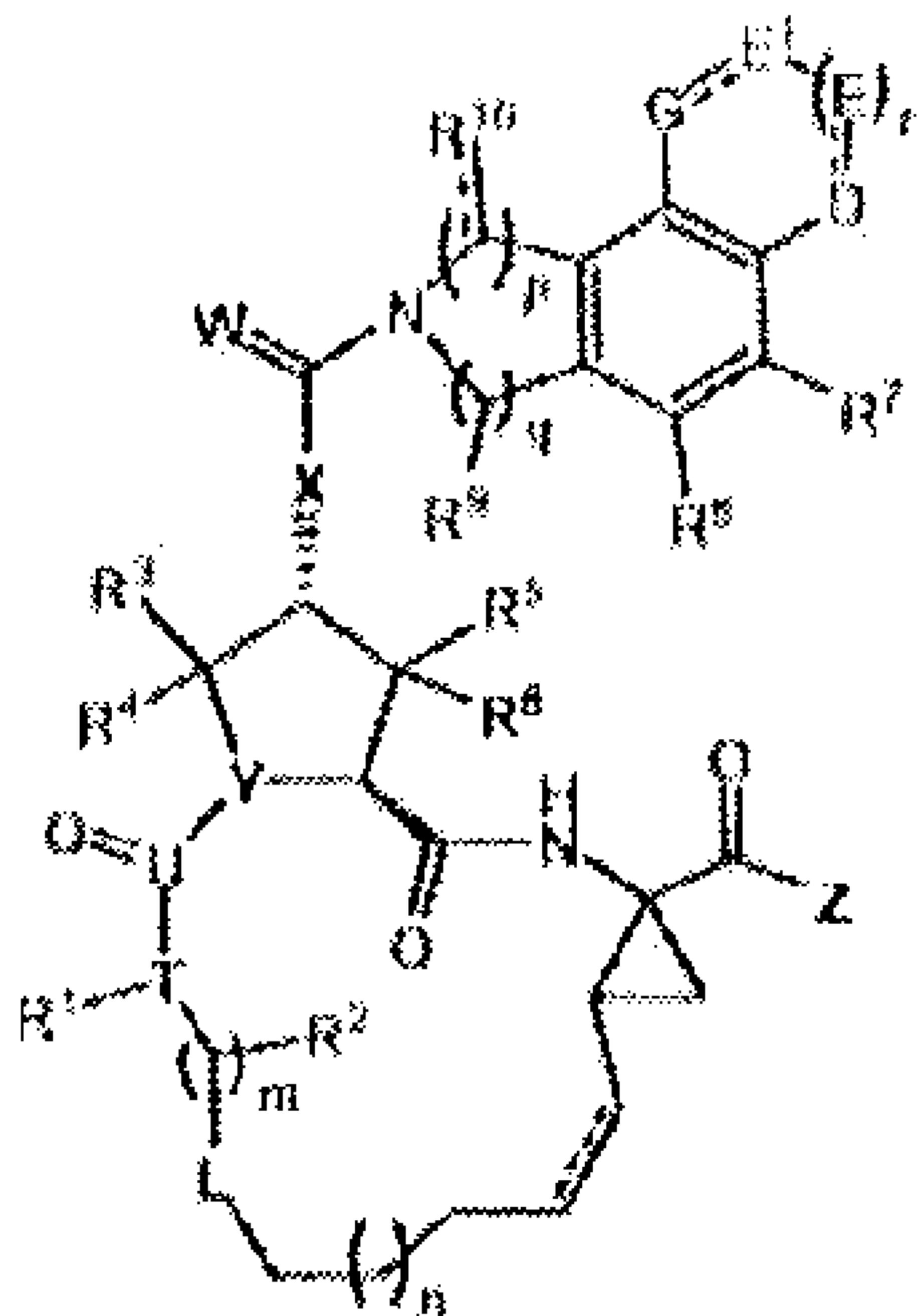
14. One or more compounds of any one of claims 1-6 in a therapeutically effective dose, for use in inhibiting hepatitis C virus (HCV).

15. A use of a combination of one or more compounds of any one of claims 1-6 with one or more of the following agent: (1) immune modulator, (2) HCV protease inhibitor, (3) HCV polymerase inhibitors, (4) nucleosides and derivative thereof, (5) cyclophilin inhibitor, (6) glucosidase I inhibitor, (7) IMPDH inhibitor, (8) caspase inhibitor, (9) TLR agonist, (10) HIV inhibitor, (11) anti-inflammatory drug, (12) cancer drug, or (13) hepatitis B virus (HBV) inhibitor, in the preparation of a medicament for inhibiting hepatitis C virus (HCV).

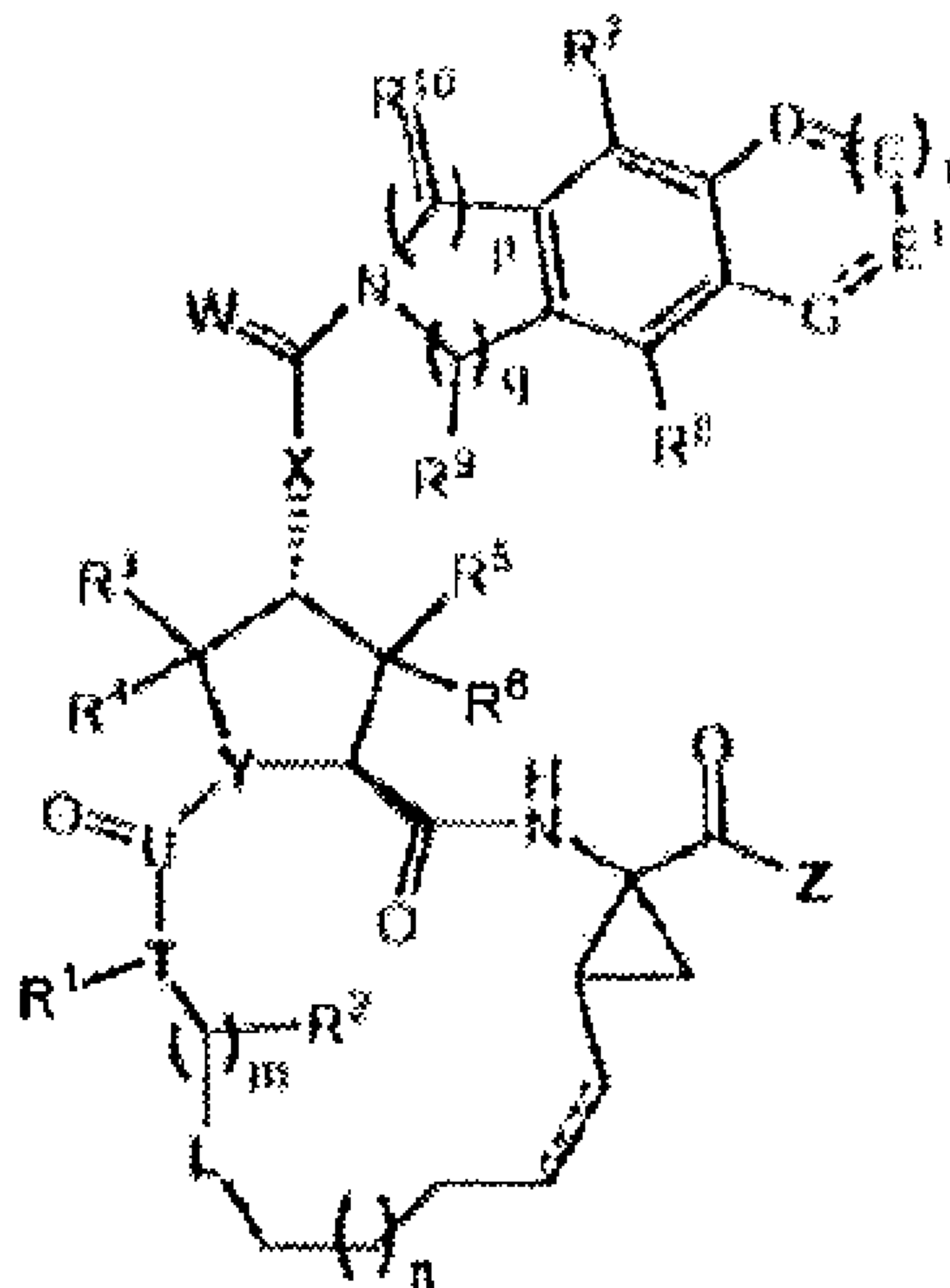
16. A use of a combination of one or more compounds of any one of claims 1-6 with one or more of the following agent: (1) immune modulator, (2) HCV protease inhibitor, (3) HCV polymerase inhibitors, (4) nucleosides and derivative thereof, (5) cyclophilin inhibitor, (6) glucosidase I inhibitor, (7) IMPDH inhibitor, (8) caspase inhibitor, (9) TLR agonist, (10) HIV inhibitor, (11) anti-inflammatory drug, (12) cancer drug, or (13) hepatitis B virus (HBV) inhibitor, for inhibiting hepatitis C virus (HCV).

17. A combination of one or more compounds of any one of claims 1-6 with one or more of the following agent: (1) immune modulator, (2) HCV protease inhibitor, (3) HCV polymerase inhibitors, (4) nucleosides and derivative thereof, (5) cyclophilin inhibitor, (6) glucosidase I inhibitor, (7) IMPDH inhibitor, (8) caspase inhibitor, (9) TLR agonist, (10) HIV inhibitor, (11) anti-inflammatory drug, (12) cancer drug, or (13) hepatitis B virus (HBV) inhibitor, for use in inhibiting hepatitis C virus (HCV).

18. The use of claim 15 or 16, or the combination for use of claim 17, wherein the immune modulator is selected from the group consisting of Interferons, pegulated-interferons, and interferon derivatives.



Ia



Ib