POLYHETEROCYCLIC COMPOUNDS HIGHLY POTENT AS HCV INHIBITORS

FIELD OF THE INVENTION

The present invention relates to novel polyheterocyclic based compounds with both 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, and it is a single-stranded positive RNA virus in the Flaviviridae family. It includes a nucleocapsid protein (C), envelope proteins (El 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 [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 89/04669; Lavanchy, *J. Viral Hepatitis*, 6, 35-47 (1999); Alter, *J. Hepatology, 3l* (Suppl. 1), 88-91 (1999); and Alberti et al, *J. Hepatology, 3l* (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 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, US20100003214, US20100022578, US20100029715, US20100041889, WO2009134624,

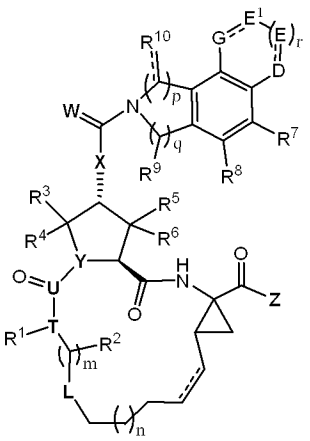
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Currently, due to lack of immunity or remission associated with HCV infection, hepatitis caused by HCV infection is more difficult to treat comparing to other forms of hepatitis. Now, the only available anti-HCV therapies are interferon-a, interferon-a/ribavirin combination, and 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 better-tolerated therapeutic drugs for inhibiting HCV NS3 protease replication.

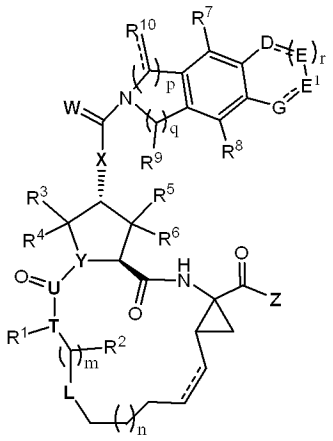
SUMMARY OF THE INVENTION

The present invention relates to two classes of novel polyheterocyclic based compounds of the following formulas **Ia-Ib** with macrocyclic structure and **IIa-IIb** with linear structure, 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 invention 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) developed as therapeutic drugs for HCV treatment.

In the first aspect, the present invention provides a kind of novel polyheterocyclic based compounds represented by the formula **Ia** or **Ib**:



Ia



Ib

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, respectively;

wherein when "⋯⋯" 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 hydrogen, oxygen, halogen atom, cyano, 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, or C_2-C_{20} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_{20} alkyl, C_3-C_{20} cycloalkyl, C_6-C_{20} aryl, C_1-C_{20} alkoxy, C_1-C_{20} alkylthio, C_1-C_{20} alkoxycarbonyl, C_6-C_{20} aryloxy, C_6-C_{20} aryloxycarbonyl, C_2-C_{20} heterocyclic alkoxycarbonyl, C_2-C_{20} heterocyclic aryl, C_1-C_{20} alkylamino, C_2-C_{20} heterocyclic amino, C_6-C_{20} aryl amino, C_1-C_{20} aminocarbonyl, C_1-C_{20} amido, C_1-C_{20} amidocarbonyl, C_1-C_{20} carbonylamino, C_1-C_{20} alkylsulfonamido, C_2 -C_{20} heterocyclic sulfonamido, C_6-C_{20} arylsulfonamido, or C_1-C_{20} 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)-, C_1-C_{20} alkenyl, C_1-C_{20} alkoxy, C_2-C_{20} heterocyclyl, C_2-C_{20} heterocyclic alkoxy, C_1-C_{20} amino, C_1-C_{20} aminocarbonyl, C_1-C_{20} alkoxycarbonyl, C_6-C_{20} aryl, C_6-C_{20} aryloxy, or C_6-C_{20} 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, E^1, and G above;

Y is nitrogen or CH group;

Z 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} heteroarylamino, 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;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C_1-C_2 alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} alkoxy, C_3-C_{20} cycloalkoxy, C_1-C_{20} alkoxycarbonyl, C_1-C_{20} alkylamino, C_3-C_{20} cycloalkylamino, C_2-C_{20} heterocyclic amino, C_6-C_{20} arylamino, C_1-C_{20} alkoxycarbonylamino, C_6-C_{20} aryloxycarbonylamino, C_1-C_{20} alkylsulfonamido, C_3-C_{20} cycloalkylsulfonamido, C_2-C_{20} heterocyclic sulfonamido, C_6-C_{20} arylsulfonamido, and C_1-C_{20} aminosulfonamido group;

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} heterocyclicamino, 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

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.

In one preferred embodiment of the compounds of formula **Ia-Ib** in the present invention, 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, respectively;

wherein when "⋯⋯" 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 hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C_1-C_{15} alkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} aminocarbonyl, C_1-C_{15} carbonylamino, C_6-C_{15} aryl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, or C_2-C_{15} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_6-C_{15} aryl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, C_2-C_{15} heterocyclic alkoxycarbonyl, C_2-C_{15} heterocyclic aryl, C_1-C_{15} alkylamino, C_2-C_{15} heterocyclic amino, C_6-C_{15} aryl amino, C_1-C_{15} aminocarbonyl, C_1-C_{15} amido, C_1-C_{15} amidocarbonyl, C_1-C_{15} carbonylamino, C_1-C_{15} alkylsulfonamido, C_2-C_{15} heterocyclic sulfonamido, C_6-C_{15} arylsulfonamido, or C_1-C_{15} 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)-, C_1-C_{15} alkenyl, C_1-C_{15} alkoxy, C_2-C_{15} heterocyclyl, C_2-C_{15} heterocyclic alkoxy, C_1-C_{15} amino, C_1-C_{15} aminocarbonyl, C_1-C_{15} alkoxycarbonyl, C_6-C_{15} aryl, C_6-C_{15} aryloxy, or C_6-C_{15} 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, E^1, and G above;

Y is nitrogen or CH group;

Z is hydroxyl, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_1-C_{15} alkoxy, C_3-C_{15} cycloalkoxy, C_1-C_{15} alkylamino, C_3-C_{15} cycloalkylamino , C_2-C_{15} heterocyclic amino, C_6-C_{15} aryl, C_6-C_{15} arylamino, C_4-C_{15} heteroarylamino, C_1-C_{15} alkyl sulfonamido, C_3-C_{15} cycloalkylsulfonamido, C_6-C_{15}

arylsulfonamido, C_1-C_{15} alkoxy sulfonamido, C_3-C_{15} cycloalkoxy sulfonamido, C_1-C_{15} alkylamino sulfonamido, C_3-C_{15} cycloalkylamino sulfonamido, C_6-C_{15} arylamino sulfonamido, C_1-C_{15} uramido, C_1-C_{15} thioureido, C_1-C_{15} phosphate, or C_1-C_{15} borate;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_1-C_{15} alkoxy, C_3-C_{15} cycloalkoxy, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} alkylamino, C_3-C_{15} cycloalkylamino, C_2-C_{15} heterocyclic amino, C_6-C_{15} arylamino, C_1-C_{15} alkoxycarbonylamino, C_6-C_{15} aryloxycarbonylamino, C_1-C_{15} alkylsulfonamido, C_3-C_{15} cycloalkylsulfonamido, C_2-C_{15} heterocyclic sulfonamido, C_6-C_{15} arylsulfonamido, and C_1-C_{15} aminosulfonamido group;

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_{15} alkyl, C_3-C_{15} cycloalkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylamino, C_2-C_{15} heterocyclicamino, C_6-C_{15} aryl, C_6-C_{15} arylamino, C_1-C_{15} alkylsulfonamido, C_2-C_{15} heterocyclic sulfonamido, and C_6-C_{15} arylsulfonamido group; and

R^7, R^8 and R^9 are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C_1-C_{15} alkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} aminocarbonyl, C_1-C_{15} carbonylamino, C_6-C_{15} aryl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, and C_2-C_{15} heterocyclic group.

In a more preferred embodiment of the compounds of formula **Ia-Ib** in the present invention,

werein:

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, respectively;

wherein when "⋯⋯" 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 hydrogen, oxygen, halogen atom, cyano, 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, or C_2-C_{12} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the

group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{12} aryl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, C_1-C_8 alkoxycarbonyl, C_6-C_{12} aryloxy, C_6-C_{12} aryloxycarbonyl, C_2-C_8 heterocyclic alkoxycarbonyl, C_2-C_{12} heterocyclic aryl, C_1-C_8 alkylamino, C_2-C_8 heterocyclic amino, C_6-C_{12} aryl amino, C_1-C_8 aminocarbonyl, C_1-C_8 amido, C_1-C_8 amidocarbonyl, C_1-C_8 carbonylamino, C_1-C_8 alkylsulfonamido, C_2–C_8 heterocyclic sulfonamido, C_6-C_{12} arylsulfonamido, or C_1-C_8 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)-, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_2-C_8 heterocyclyl, C_2-C_8 heterocyclic alkoxy, C_1-C_8 amino, C_1-C_8 aminocarbonyl, C_1-C_8 alkoxycarbonyl, C_6-C_{12} aryl, C_6-C_{12} aryloxy, or C_6-C_{12} 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, E^1, and G above;

Y is nitrogen or CH group;

Z is hydroxyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, C_1-C_8 alkylamino, C_3-C_8 cycloalkylamino , C_2-C_8 heterocyclic amino, C_6-C_{12} aryl, C_6-C_{12} arylamino, C_4-C_{12} heteroarylamino, C_1-C_8 alkyl sulfonamido, C_3-C_8 cycloalkylsulfonamido, C_6-C_{12} arylsulfonamido, C_1-C_8 alkoxy sulfonamido, C_3-C_8 cycloalkoxy sulfonamido, C_1-C_8 alkylamino sulfonamido, C_3-C_8 cycloalkylamino sulfonamido, C_6-C_{12} arylamino sulfonamido, C_1-C_8 uramido, C_1-C_8 thioureido, C_1-C_8 phosphate, or C_1-C_8 borate;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, C_1-C_8 alkoxycarbonyl, C_1-C_8 alkylamino, C_3-C_8 cycloalkylamino, C_2-C_8 heterocyclic amino, C_6-C_{12} arylamino, C_1-C_8 alkoxycarbonylamino, C_6-C_{12} aryloxycarbonylamino, C_1-C_8 alkylsulfonamido, C_3-C_8 cycloalkylsulfonamido, C_2-C_8 heterocyclic sulfonamido, C_6-C_{12} arylsulfonamido, and C_1-C_8 aminosulfonamido group;

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_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkylamino,

C_2-C_8 heterocyclicamino, C_6-C_{12} aryl, C_6-C_{12} arylamino, C_1-C_8 alkylsulfonamido, C_2-C_8 heterocyclic sulfonamido, and C_6-C_{12} arylsulfonamido group; and

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.

In one most preferred embodiment in the present invention, the formula **Ia-Ib**;

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 R^{10} is a single bond, and R^{10} is H;

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;

L is -CH_2-;

T is N or CH;

U is carbon;

W and X are each oxygen;

Y is N or CH;

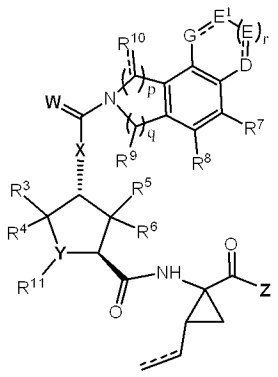
Z is hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfonamido, C_3-C_6 cycloalkylsulfonamido or C_6-C_{10} arylsulfonamido group;

R^1 is hydrogen, C_6-C_{10} arylamino, C_1-C_6 alkoxycarbonylamino, C_2-C_6 heterocyclic amino, C_1-C_6 alkylsulfonamido, or C_6-C_{10} arylsulfonamido; and

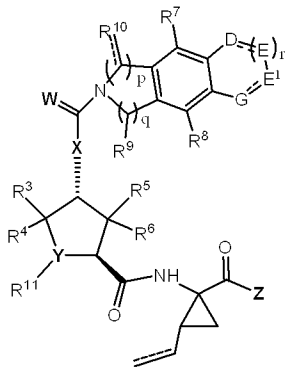
R^2, R^3, R^4, R^5 and R^6 are each H;

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

In the second aspect, the present invention provides a kind of novel polyheterocyclic based compounds represented by the formula **IIa** and **IIb**:



IIa



IIb

and/or stereoisomers, solvates, hydrates, tautomers, esterification or amidation prodrugs, pharmaceutically acceptable salt, or mixtures thereof.

Wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, 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, or C_2-C_{20} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_{20} alkyl, C_3-C_{20} cycloalkyl, C_6-C_{20} aryl, C_1-C_{20} alkoxy, C_1-C_{20} alkylthio, C_1-C_{20} alkoxycarbonyl, C_6-C_{20} aryloxy, C_6-C_{20} aryloxycarbonyl, C_2-C_{20} heterocyclic alkoxycarbonyl, C_2-C_{20} heterocyclic aryl, C_1-C_{20} alkylamino, C_2-C_{20} heterocyclic amino, C_6-C_{20} aryl amino, C_1-C_{20} aminocarbonyl, C_1-C_{20} amido, C_1-C_{20} amidocarbonyl, C_1-C_{20} carbonylamino, C_1-C_{20} alkylsulfonamido, C_2-C_{20} heterocyclic sulfonamido, C_6-C_{20} arylsulfonamido, or C_1-C_{20} 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;

Z 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} heteroarylamino, 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;

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} heterocyclicamino, 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

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.

R^{11} 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 a preferred embodiment of the compounds of formula **IIa** or **IIb**,

Wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C_1-C_{15} alkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} aminocarbonyl, C_1-C_{15} carbonylamino, C_6-C_{15} aryl, C_6-C_{15} aryloxy,

C_6-C_{15} aryloxycarbonyl, or C_2-C_{15} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_6-C_{15} aryl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, C_2-C_{15} heterocyclic alkoxycarbonyl, C_2-C_{15} heterocyclic aryl, C_1-C_{15} alkylamino, C_2-C_{15} heterocyclic amino, C_6-C_{15} aryl amino, C_1-C_{15} aminocarbonyl, C_1-C_{15} amido, C_1-C_{15} amidocarbonyl, C_1-C_{15} carbonylamino, C_1-C_{15} alkylsulfonamido, C_2 -C_{15} heterocyclic sulfonamido, C_6-C_{15} arylsulfonamido, or C_1-C_{15} 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;

Z is hydroxyl, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_1-C_{15} alkoxy, C_3-C_{15} cycloalkoxy, C_1-C_{15} alkylamino, C_3-C_{15} cycloalkylamino , C_2-C_{15} heterocyclic amino, C_6-C_{15} aryl, C_6-C_{15} arylamino, C_4-C_{15} heteroarylamino, C_1-C_{15} alkyl sulfonamido, C_3-C_{15} cycloalkylsulfonamido, C_6-C_{15} arylsulfonamido, C_1-C_{15} alkoxy sulfonamido, C_3-C_{15} cycloalkoxy sulfonamido, C_1-C_{15} alkylamino sulfonamido, C_3-C_{15} cycloalkylamino sulfonamido, C_6-C_{15} arylamino sulfonamido, C_1-C_{15} uramido, C_1-C_{15} thioureido, C_1-C_{15} phosphate, or C_1-C_{15} borate;

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_{15} alkyl, C_3-C_{15} cycloalkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylamino, C_2-C_{15} heterocyclicamino, C_6-C_{15} aryl, C_6-C_{15} arylamino, C_1-C_{15} alkylsulfonamido, C_2-C_{15} heterocyclic sulfonamido, and C_6-C_{15} arylsulfonamido group; and

R^7, R^8 and R^9 are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C_1-C_{15} alkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} aminocarbonyl, C_1-C_{15} carbonylamino, C_6-C_{15} aryl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, and C_2-C_{15} heterocyclic group.

R^{11} is H, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_6-C_{15} aryl, C_4-C_{15} heteroaryl, C_1-C_{15} alkylcarbonyl, C_1-C_{15} alkoxycarbonyl, C_6-C_{15} aryloxycarbonyl, C_1-C_{15} alkylaminocarbonyl, C_6-C_{15} arylsulfonyl, C_1-C_{15} alkylaminosulfonyl, C_3-C_{15} cycloalkylaminosulfonyl, C_6-C_{15} arylaminosulfonyl, C_3-C_{15}

heterocyclicaminosulfonyl group.

In one more preferred embodiment of the formula **IIa** or **IIb** in the present invention, ,

wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, 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, or C_2-C_{12} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{12} aryl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, C_1-C_8 alkoxycarbonyl, C_6-C_{12} aryloxy, C_6-C_{12} aryloxycarbonyl, C_2-C_8 heterocyclic alkoxycarbonyl, C_2-C_{12} heterocyclic aryl, C_1-C_8 alkylamino, C_2-C_8 heterocyclic amino, C_6-C_{12} aryl amino, C_1-C_8 aminocarbonyl, C_1-C_8 amido, C_1-C_8 amidocarbonyl, C_1-C_8 carbonylamino, C_1-C_8 alkylsulfonamido, C_2–C_8 heterocyclic sulfonamido, C_6-C_{12} arylsulfonamido, or C_1-C_8 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;

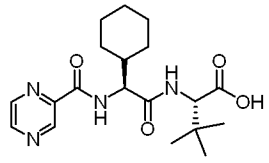
Z is hydroxyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, C_1-C_8 alkylamino, C_3-C_8 cycloalkylamino , C_2-C_8 heterocyclic amino, C_6-C_{12} aryl, C_6-C_{12} arylamino, C_4-C_{12} heteroarylamino, C_1-C_8 alkyl sulfonamido, C_3-C_8 cycloalkylsulfonamido, C_6-C_{12} arylsulfonamido, C_1-C_8 alkoxy sulfonamido, C_3-C_8 cycloalkoxy sulfonamido, C_1-C_8 alkylamino sulfonamido, C_3-C_8 cycloalkylamino sulfonamido, C_6-C_{12} arylamino sulfonamido, C_1-C_8 uramido, C_1-C_8 thioureido, C_1-C_8 phosphate, or C_1-C_8 borate;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, C_1-C_8 alkoxycarbonyl, C_1-C_8 alkylamino, C_3-C_8 cycloalkylamino, C_2-C_8 heterocyclic amino, C_6-C_{12} arylamino, C_1-C_8 alkoxycarbonylamino, C_6-C_{12} aryloxycarbonylamino, C_1-C_8 alkylsulfonamido, C_3-C_8 cycloalkylsulfonamido, C_2-C_8 heterocyclic sulfonamido, C_6-C_{12} arylsulfonamido, and C_1-C_8 aminosulfonamido group;

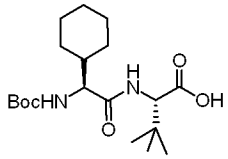
R^3, R^4, R^5 and R^6 are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, nitro, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkylamino, C_2-C_8 heterocyclicamino, C_6-C_{12} aryl, C_6-C_{12} arylamino, C_1-C_8 alkylsulfonamido, C_2-C_8 heterocyclic sulfonamido, and C_6-C_{12} arylsulfonamido group; and

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.

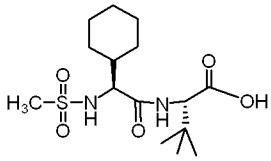
R^{11} is H, C_1-C_8 alkyl, C_1-C_8 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, C_6-C_{12} aryloxycarbonyl, or preferably a group having the formula selected from the following structure **SM-14a** to **SM-14v**:



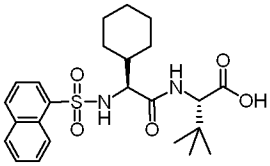
SM-14a



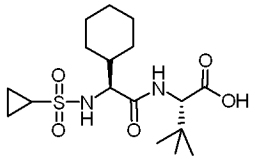
SM-14b



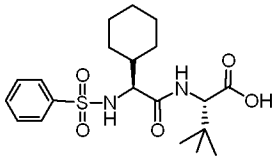
SM-14c



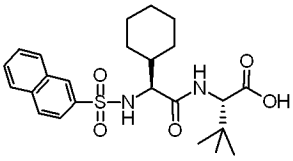
SM-14d



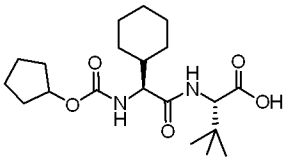
SM-14e



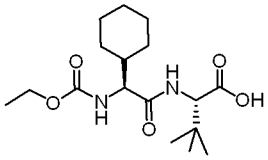
SM-14f



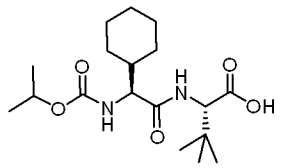
SM-14g



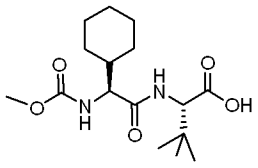
SM-14h



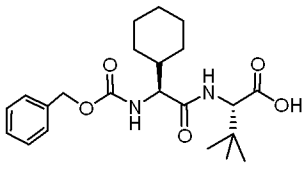
SM-14j



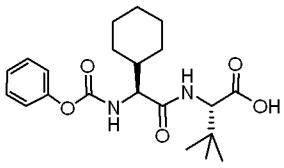
SM-14k



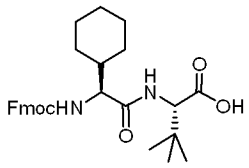
SM-14m



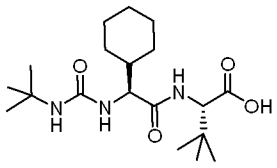
SM-14n



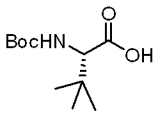
SM-14p



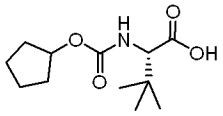
SM-14q



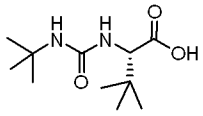
SM-14r



SM-14s



SM-14t



SM-14v

In one most preferred embodiment of the formula **IIa** or **IIb** in the present invention,

Wherein:

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 is a double bond;

the dashed line "⋯⋯" linked to R^{10} is a single bond, and R^{10} is H;

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;

W and X are each oxygen;

Y is N or CH;

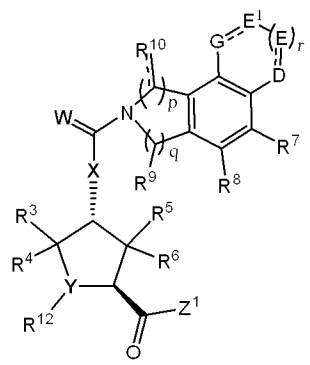
Z is hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfonamido, C_3-C_6 cycloalkylsulfonamido or C_6-C_{10} arylsulfonamido group;

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

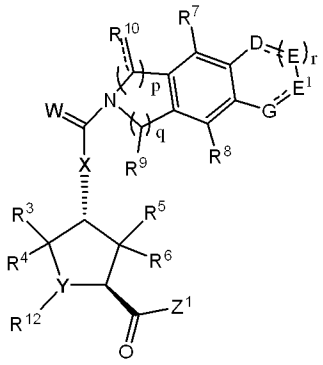
R^7, R^8 and R^9 are each H.

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

The third aspect of the present invention provides a new type of polyheterocyclic based compounds represented by the formula **IIIa** or **IIIb**:



IIIa



IIIb

Wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, 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, or C_2-C_{20} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_{20} alkyl, C_3-C_{20} cycloalkyl, C_6-C_{20} aryl, C_1-C_{20} alkoxy, C_1-C_{20} alkylthio, C_1-C_{20} alkoxycarbonyl, C_6-C_{20} aryloxy, C_6-C_{20} aryloxycarbonyl, C_2-C_{20} heterocyclic alkoxycarbonyl, C_2-C_{20} heterocyclic aryl, C_1-C_{20} alkylamino, C_2-C_{20} heterocyclic amino, C_6-C_{20} aryl amino, C_1-C_{20} aminocarbonyl, C_1-C_{20} amido, C_1-C_{20} amidocarbonyl, C_1-C_{20} carbonylamino, C_1-C_{20} alkylsulfonamido, C_2 -C_{20} heterocyclic sulfonamido, C_6-C_{20} arylsulfonamido, or C_1-C_{20} 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;

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} heteroarylamino, 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;

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} heterocyclicamino, 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

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.

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** in the present invention, wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C_1-C_{15} alkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} aminocarbonyl, C_1-C_{15} carbonylamino, C_6-C_{15} aryl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, or C_2-C_{15} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the

group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_6-C_{15} aryl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, C_2-C_{15} heterocyclic alkoxycarbonyl, C_2-C_{15} heterocyclic aryl, C_1-C_{15} alkylamino, C_2-C_{15} heterocyclic amino, C_6-C_{15} aryl amino, C_1-C_{15} aminocarbonyl, C_1-C_{15} amido, C_1-C_{15} amidocarbonyl, C_1-C_{15} carbonylamino, C_1-C_{15} alkylsulfonamido, C_2 -C_{15} heterocyclic sulfonamido, C_6-C_{15} arylsulfonamido, or C_1-C_{15} 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;

Z^1 is hydroxyl, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_1-C_{15} alkoxy, C_3-C_{15} cycloalkoxy, C_1-C_{15} alkylamino, C_3-C_{15} cycloalkylamino , C_2-C_{15} heterocyclic amino, C_6-C_{15} aryl, C_6-C_{15} arylamino, C_4-C_{15} heteroarylamino, C_1-C_{15} alkyl sulfonamido, C_3-C_{15} cycloalkylsulfonamido, C_6-C_{15} arylsulfonamido, C_1-C_{15} alkoxy sulfonamido, C_3-C_{15} cycloalkoxy sulfonamido, C_1-C_{15} alkylamino sulfonamido, C_3-C_{15} cycloalkylamino sulfonamido, C_6-C_{15} arylamino sulfonamido, C_1-C_{15} uramido, C_1-C_{15} thioureido, C_1-C_{15} phosphate, or C_1-C_{15} borate;

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_{15} alkyl, C_3-C_{15} cycloalkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylamino, C_2-C_{15} heterocyclicamino, C_6-C_{15} aryl, C_6-C_{15} arylamino, C_1-C_{15} alkylsulfonamido, C_2-C_{15} heterocyclic sulfonamido, and C_6-C_{15} arylsulfonamido group; and

R^7, R^8 and R^9 are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C_1-C_{15} alkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} aminocarbonyl, C_1-C_{15} carbonylamino, C_6-C_{15} aryl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, and C_2-C_{15} heterocyclic group.

R^{12} is H, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_6-C_{15} aryl, C_4-C_{15} heteroaryl, C_1-C_{15} alkylcarbonyl, C_1-C_{15} alkoxycarbonyl, C_6-C_{15} aryloxycarbonyl, C_1-C_{15} alkylaminocarbonyl, C_6-C_{15} arylsulfonyl, C_1-C_{15} alkylaminosulfonyl, C_3-C_{15} cycloalkylaminosulfonyl, C_6-C_{15} arylaminosulfonyl, C_3-C_{15} heterocyclicaminosulfonyl group.

In one more preferred embodiment of the formula **IIIa-IIIb** in the present invention,

wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, 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, or C_2-C_{12} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{12} aryl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, C_1-C_8 alkoxycarbonyl, C_6-C_{12} aryloxy, C_6-C_{12} aryloxycarbonyl, C_2-C_8 heterocyclic alkoxycarbonyl, C_2-C_{12} heterocyclic aryl, C_1-C_8 alkylamino, C_2-C_8 heterocyclic amino, C_6-C_{12} aryl amino, C_1-C_8 aminocarbonyl, C_1-C_8 amido, C_1-C_8 amidocarbonyl, C_1-C_8 carbonylamino, C_1-C_8 alkylsulfonamido, C_2–C_8 heterocyclic sulfonamido, C_6-C_{12} arylsulfonamido, or C_1-C_8 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;

Z^1 is hydroxyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, C_1-C_8 alkylamino, C_3-C_8 cycloalkylamino , C_2-C_8 heterocyclic amino, C_6-C_{12} aryl, C_6-C_{12} arylamino, C_4-C_{12} heteroarylamino, C_1-C_8 alkyl sulfonamido, C_3-C_8 cycloalkylsulfonamido, C_6-C_{12} arylsulfonamido, C_1-C_8 alkoxy sulfonamido, C_3-C_8 cycloalkoxy sulfonamido, C_1-C_8 alkylamino sulfonamido, C_3-C_8 cycloalkylamino sulfonamido, C_6-C_{12} arylamino sulfonamido, C_1-C_8 uramido, C_1-C_8 thioureido, C_1-C_8 phosphate, or C_1-C_8 borate;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, C_1-C_8 alkoxycarbonyl,

C_1-C_8 alkylamino, C_3-C_8 cycloalkylamino, C_2-C_8 heterocyclic amino, C_6-C_{12} arylamino, C_1-C_8 alkoxycarbonylamino, C_6-C_{12} aryloxycarbonylamino, C_1-C_8 alkylsulfonamido, C_3-C_8 cycloalkylsulfonamido, C_2-C_8 heterocyclic sulfonamido, C_6-C_{12} arylsulfonamido, and C_1-C_8 aminosulfonamido group;

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_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkylamino, C_2-C_8 heterocyclicamino, C_6-C_{12} aryl, C_6-C_{12} arylamino, C_1-C_8 alkylsulfonamido, C_2-C_8 heterocyclic sulfonamido, and C_6-C_{12} arylsulfonamido group; and

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.

R^{12} 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_6-C_{12} arylsulfonyl, C_1-C_8 alkylaminosulfonyl, C_3-C_8 cycloalkylaminosulfonyl, C_6-C_{12} arylaminosulfonyl, C_3-C_8 heterocyclicaminosulfonyl group.

In one most preferred embodiment of the formula **III-IIIb** in the present invention **,**

Wherein:

p = 1;

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;

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;

W and X are each oxygen;

Y is N or CH;

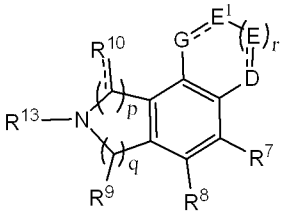
Z^1 is hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfonamido, C_3-C_6 cycloalkylsulfonamido or C_6-C_{10} arylsulfonamido group;

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

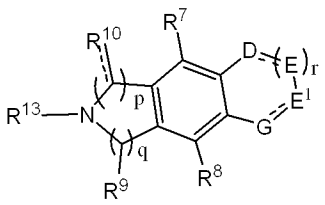
R^7, R^8 and R^9 are each H.

R^{12} is H, C_1-C_8 alkyl, C_1-C_6 alkoxycarbonyl, C_6-C_{10} aryloxycarbonyl, or C_6-C_{10} arylsulfonyl group.

The fourth aspect of the present invention provides a new type of polyheterocyclic based compounds represented by the formula **Va** and **Vb**:



Va



Vb

wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, 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, or C_2-C_{20} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_{20} alkyl, C_3-C_{20} cycloalkyl, C_6-C_{20} aryl, C_1-C_{20} alkoxy, C_1-C_{20} alkylthio, C_1-C_{20} alkoxycarbonyl, C_6-C_{20} aryloxy, C_6-C_{20} aryloxycarbonyl, C_2-C_{20} heterocyclic alkoxycarbonyl, C_2-C_{20} heterocyclic aryl, C_1-C_{20} alkylamino, C_2-C_{20} heterocyclic amino, C_6-C_{20} aryl amino, C_1-C_{20} aminocarbonyl, C_1-C_{20} amido, C_1-C_{20} amidocarbonyl, C_1-C_{20} carbonylamino, C_1-C_{20} alkylsulfonamido, C_2-C_{20} heterocyclic sulfonamido, C_6-C_{20} arylsulfonamido, or C_1-C_{20} aminosulfonamido group, 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 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.

R^{13} 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_1-C_{20} alkoxysulfonyl, C_6-C_{20} aryloxysulfonyl, C_6-C_{20} arylsulfonyl and C_2-C_{20} heterocyclic group,

In one preferred embodiment of the formula **Va-Vb** in the present invention,

Wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C_1-C_{15} alkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} aminocarbonyl, C_1-C_{15} carbonylamino, C_6-C_{15} aryl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, or C_2-C_{15} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_6-C_{15} aryl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, C_2-C_{15} heterocyclic alkoxycarbonyl, C_2-C_{15} heterocyclic aryl, C_1-C_{15} alkylamino, C_2-C_{15} heterocyclic amino, C_6-C_{15} aryl amino, C_1-C_{15} aminocarbonyl, C_1-C_{15} amido, C_1-C_{15} amidocarbonyl, C_1-C_{15} carbonylamino, C_1-C_{15} alkylsulfonamido, C_2-C_{15} heterocyclic sulfonamido, C_6-C_{15} arylsulfonamido, or C_1-C_{15} aminosulfonamido group, 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 independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C_1-C_{15} alkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} aminocarbonyl, C_1-C_{15} carbonylamino, C_6-C_{15} aryl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, and C_2-C_{15} heterocyclic group.

R^{13} is H, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_6-C_{15} aryl, C_4-C_{15} heteroaryl, C_1-C_{15} alkylcarbonyl, C_1-C_{15} alkoxycarbonyl, C_6-C_{15} aryloxycarbonyl, C_1-C_{15} alkylaminocarbonyl, C_1-C_{15} alkoxysulfonyl, C_6-C_{15} aryloxysulfonyl, C_6-C_{15} arylsulfonyl and C_2-C_{15} heterocyclic group.

In one more preferred embodiment of the formula **Va-Vb** in the present invention,

Wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, 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, or C_2-C_{12} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{12} aryl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, C_1-C_8 alkoxycarbonyl, C_6-C_{12} aryloxy, C_6-C_{12} aryloxycarbonyl, C_2-C_8 heterocyclic alkoxycarbonyl, C_2-C_{12} heterocyclic aryl, C_1-C_8 alkylamino, C_2-C_8 heterocyclic amino, C_6-C_{12} aryl amino, C_1-C_8 aminocarbonyl, C_1-C_8 amido, C_1-C_8 amidocarbonyl, C_1-C_8 carbonylamino, C_1-C_8 alkylsulfonamido, C_2–C_8 heterocyclic sulfonamido, C_6-C_{12} arylsulfonamido, or C_1-C_8 aminosulfonamido group, 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 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.

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** in the present invention,

Wherein:

p = 1;

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;

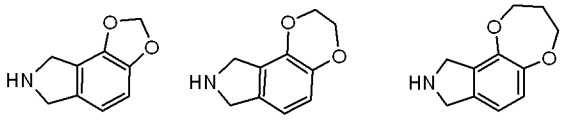
the dashed line "⋯⋯" is a single bond in the tricyclic ring consisting of D, E, E^1, G and other cyclic groups; D and G are each oxygen; E and E^1 are each $-CH_2-$, respectively;

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

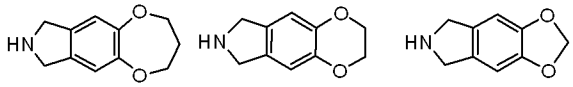
R^7, R^8 and R^9 are each H. and

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,

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



VIa **VIb** **VIc**



VId **VIe** **VIf**

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

The seventh aspect of the present invention provides a method for inhibiting HCV by using one or more compounds of claims 1-28, or one or more of these compounds in 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 covered from above (1)-(12).

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:

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.

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

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 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.

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 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 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 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.

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 **Ia-Ib** and **IIa-IIb**, and pharmaceutically acceptable salts, and/or hydrates as HCV NS3 protease

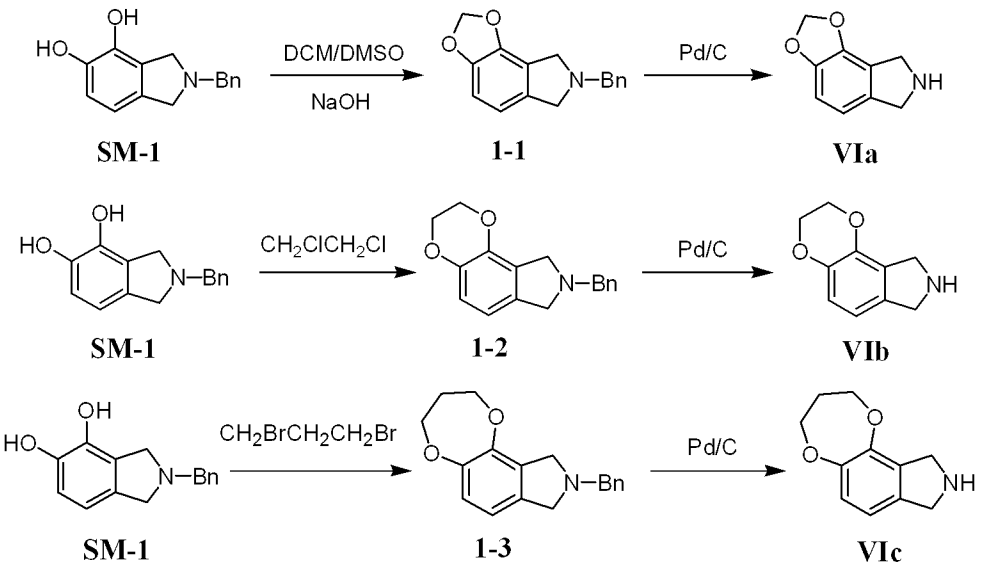
inhibitors with high potency. Moreover, toxicity study is determined to be non-toxic (LD_{50} >10,000) for most of highly potent HCV inhibitors.

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.

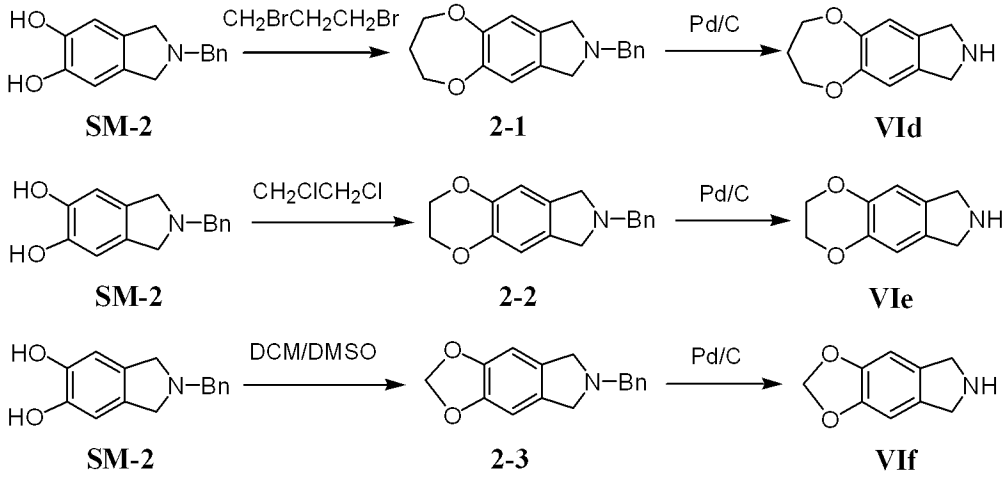
In the present invention, compounds **VIa-VIf** are prepared first as in the following Scheme 1:

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□, then reacted with $ClCH_2Cl$, $ClCH_2CH_2Cl$, or $BrCH_2CH_2CH_2Br$, 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.

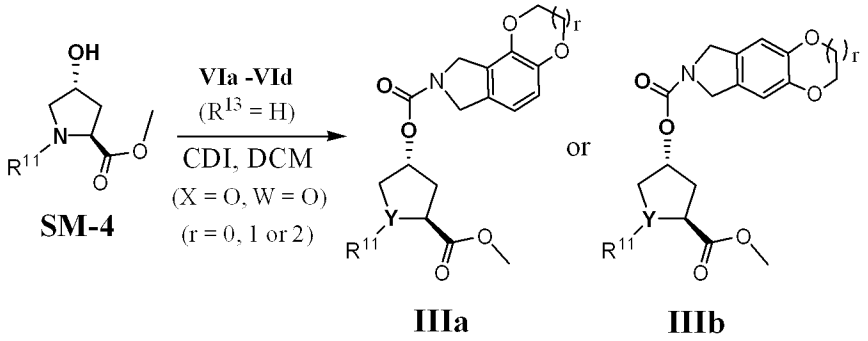
Scheme 2:



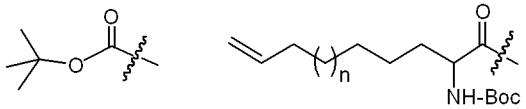
In Scheme 2, **SM-2** was dissolved in organic solvents (methanol, THF, DMF, or DMSO) and heated to 30-120℃, then reacted with $BrCH_2CH_2CH_2Br$, $ClCH_2CH_2Cl$ or $ClCH_2Cl$, respectively, to form seven, six or five membered polyheterocyclic compound **2-1**, **2-2**, or **2-3**, followed by deprotection 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.

Scheme 3:



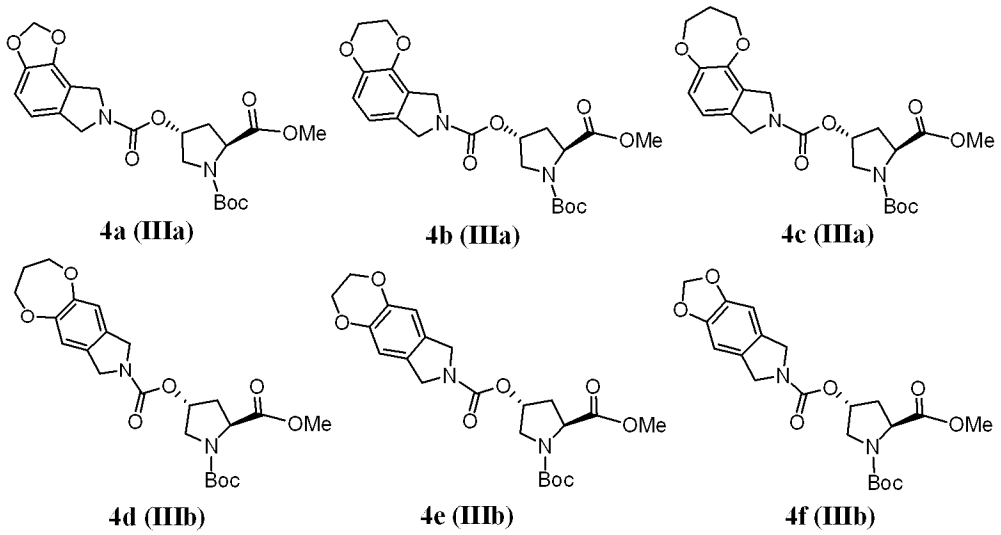
R^{11} is preferred to be selected from the following group: **SM-4a** (Boc) or **SM-4b**:



SM-4a (R^{11} = Boc) **SM-4b** (n = 0, 1, or 2)

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

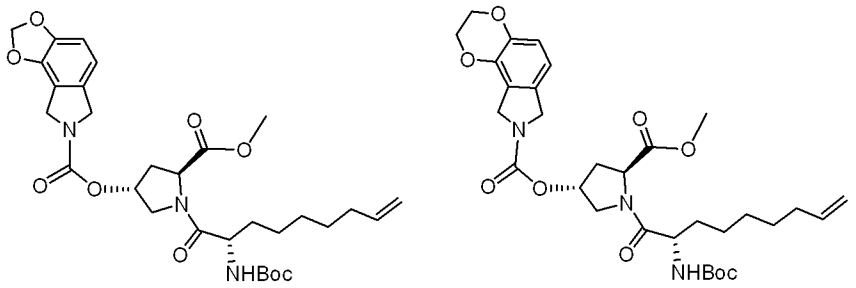
was reacted with compounds **VIa-VIf**, respectively to obtain polyheterocyclic compounds **4a-4h** and **6a-6d (IIIa-IIIb)** as shown in Figure 1-1 and Figure 1-2 by amidation reaction.



4a (IIIa) **4b (IIIa)** **4c (IIIa)**

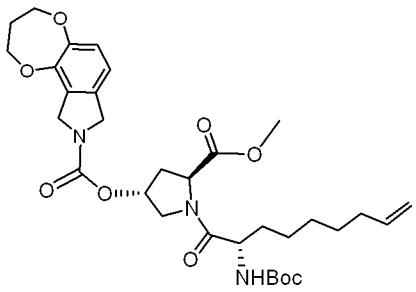
4d (IIIb) **4e (IIIb)** **4f (IIIb)**

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

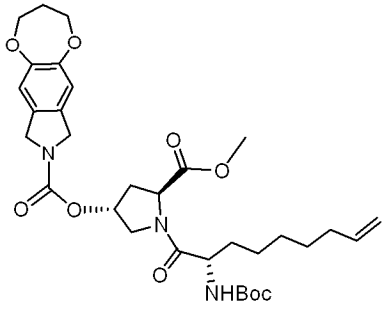


6a

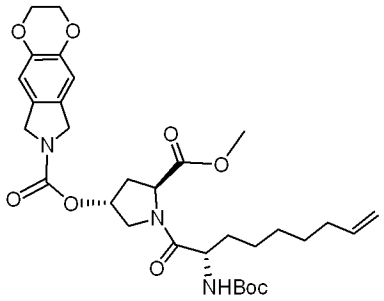
6b



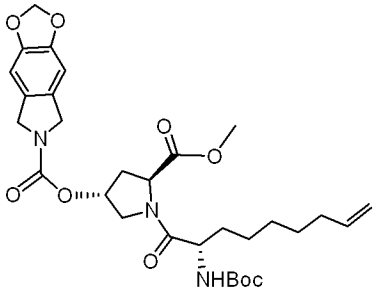
6c



6d



6e

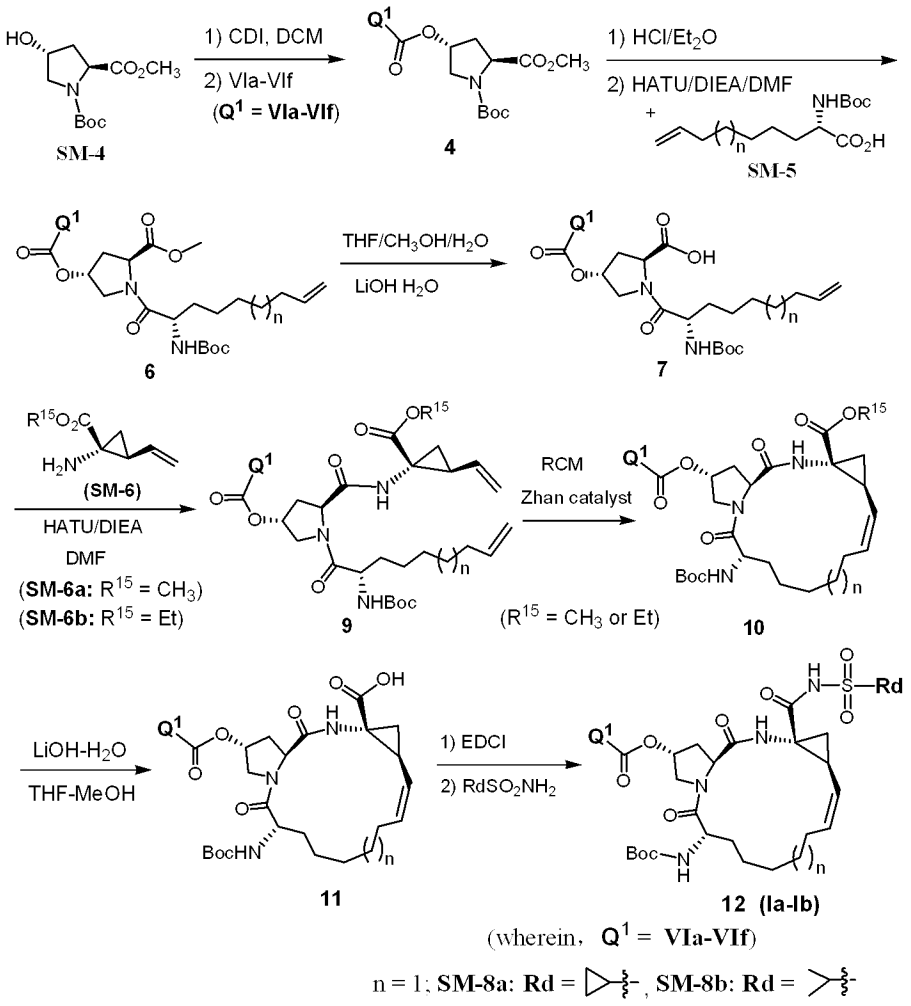


6f

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

After the key intermediates **4a-4f** and **6a-6f** were prepared, there were several synthetic 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 □ 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

[RdS(O)$_2$NH$_2$], respectively, to form a series of novel polyheterocyclic based macrocyclic compounds **Ia-Ib**, such as **12a-12xx** shown in Figure 4).

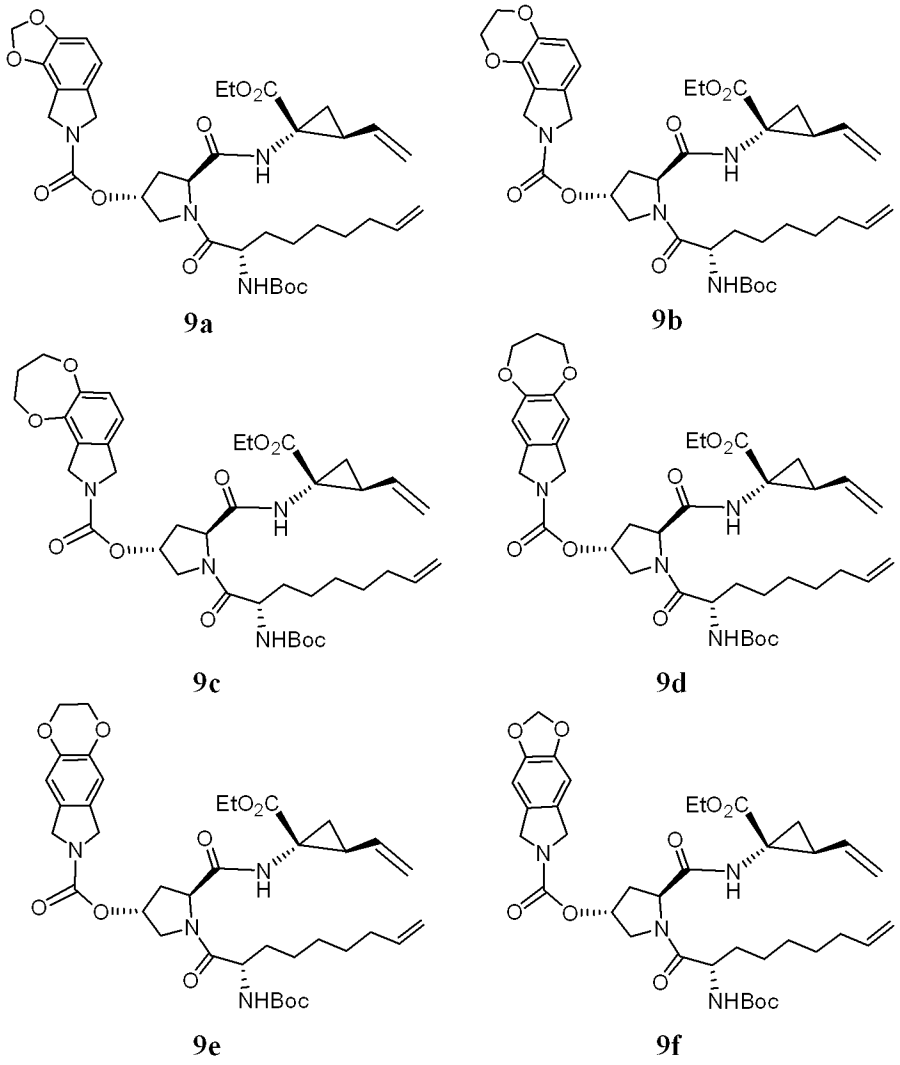
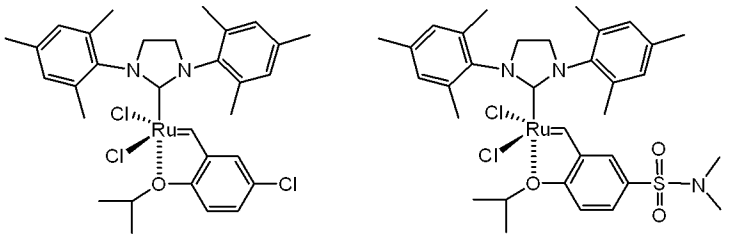


Figure 2-1: Structure of Compounds **9a-9f**

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

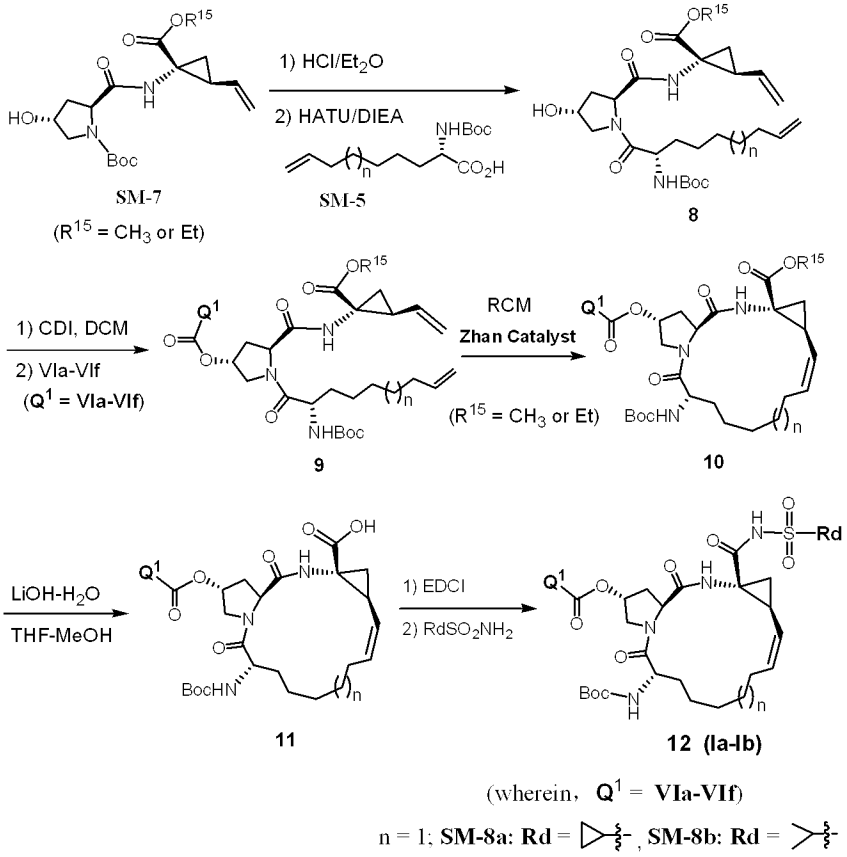


Zhan Catalyst-1 Zhan Catalyst-1B

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

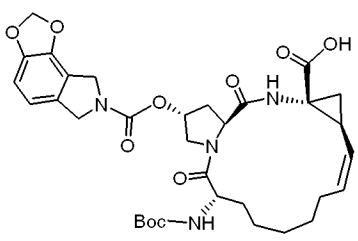
In order to obtain more compounds efficiently for potency screening, there is another alternative synthetic route developed effectively for preparation of different new macrocyclic compounds **Ia-Ib** in Scheme 5.

Scheme 5:

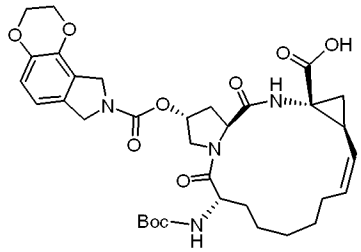


In Scheme 5, first of all, the protecting group (Boc) in the starting material **SM-7** was removed by HCl acid, followed by amidation with an N-Boc protected amino acid **SM-5** to form compound **8** in the presence of coupling reagent HATU. In the presence of coupling reagent CDI,

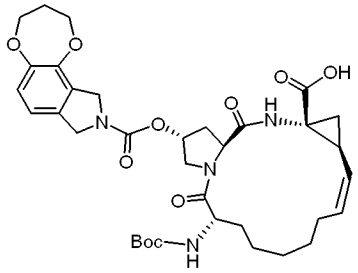
compound **8** was reacted with compounds **VIa-VIf**, respectively, to obtain polyheterocyclic compounds **9**. In anhydrous oxygen-free organic solvents (DCM, DCE, or toluene), an olefin ring-closing metathesis (RCM) reaction was carried out for the diene **9** intermediate in the presence of metathesis catalyst (e.g., Zhan catalyst-1 or Zhan catalyst-1B used in this invention) at 20-80 □ 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** as shown in the following Figure 4-1.



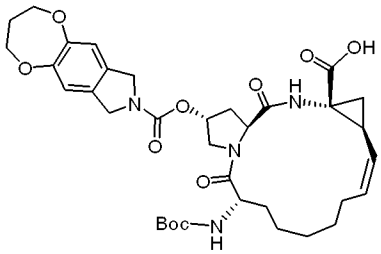
11a



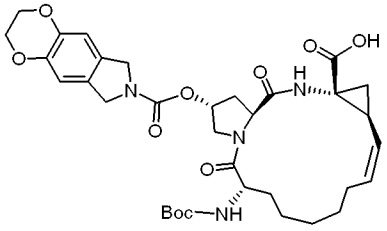
11b



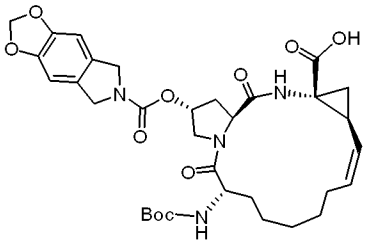
11c



11d



11e



11f

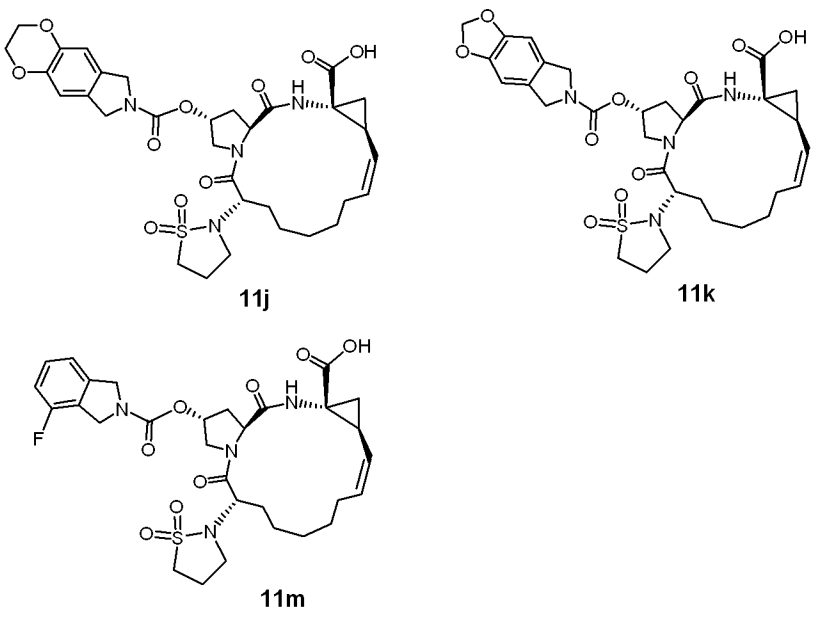
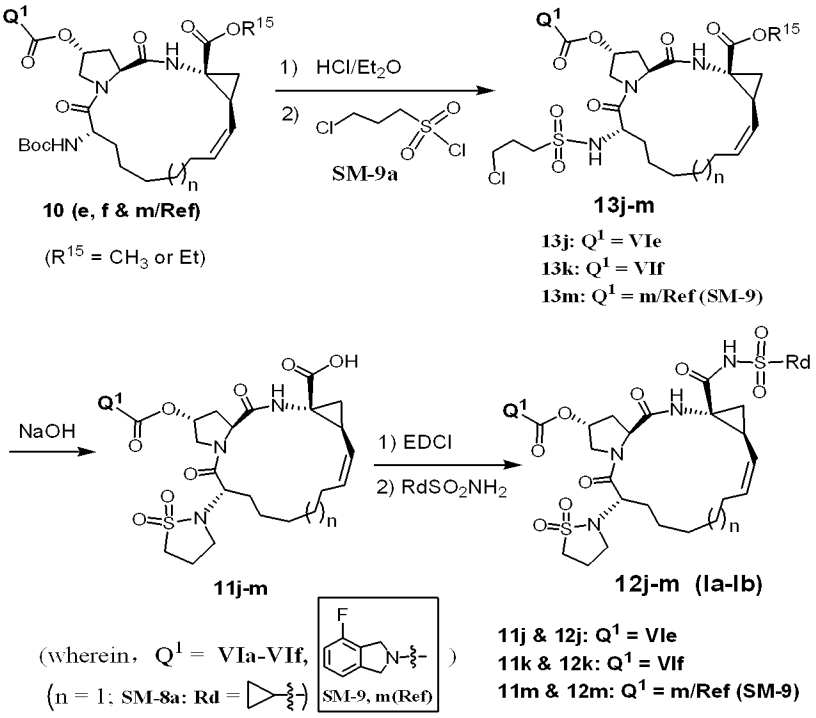


Figure 4-1: Structure of Compounds **11a-11m**

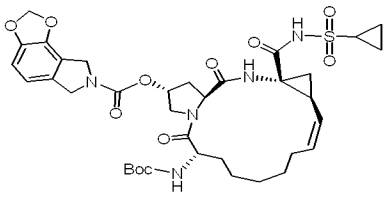
Finally, in the presence of a coupling reagent such as EDCI or HATU, the carboxylic acid product **11** reacted with different kinds of alkylsulfonamide, cycloalkylsulfonamide or arylsulfonamide [$RdS(O)_2NH_2$], respectively, to form a series of novel polyheterocyclic based macrocyclic compounds **Ia-Ib**.

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 cycloalkylsulfonamde products prepared for potency screening.

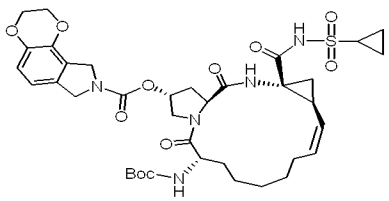
Scheme 6:



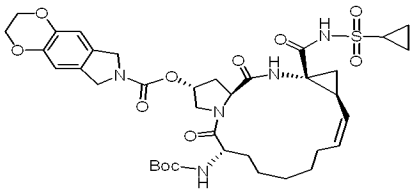
In Scheme 6 above, the compound **10c-d** prepared in Schemes 4 and 5 were used for deprotection first by removing Boc with HCl acid, followed by amidation with an alkylsulfonyl chloride reagent ($RdSO_2Cl$ or $R^{17}SO_2Cl$, **SM-9)** to obtain an alkylsulfonamide product **13**. In the presence of 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 [$RdS(O)_2NH_2$, **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 $R^{17}SO_2Cl$, **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 R^{16}-Cl (or R^{16}-Br, **SM-10)** to form another kind of new desired products **Ia-Ib (12s-12u)** as shown in Figure 5, wherein, R^{16} is C_1-C_6 alkyl、C_3-C_6 cycloalkyl、C_1-C_6 alkoxycarbonyl、C_3-C_6 cycloalkoxycarbonyl、C_6-C_{10} aryl、C_6-C_{10} arylcarbonyl、C_6-C_{10} aryloxycarbonyl or C_2-C_{10} heterocyclic group.



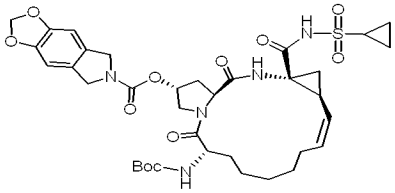
12a



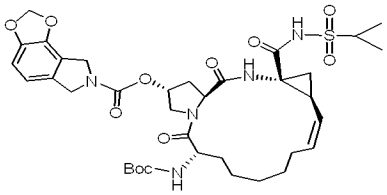
12b



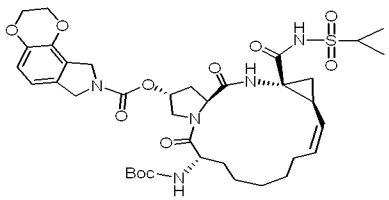
12c



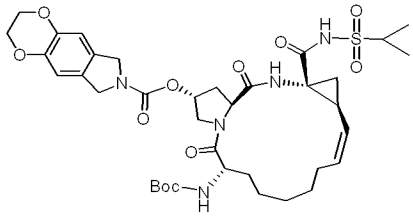
12d



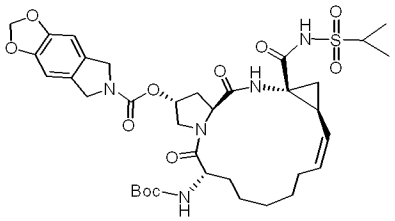
12e



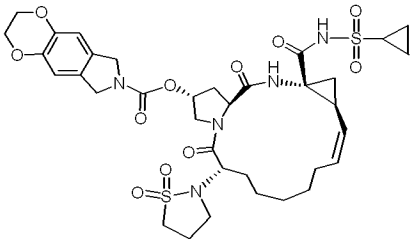
12f



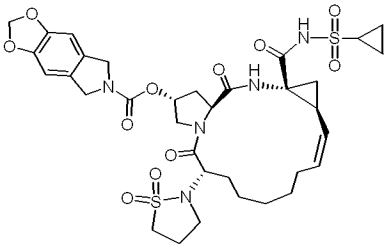
12g



12h



12j



12k

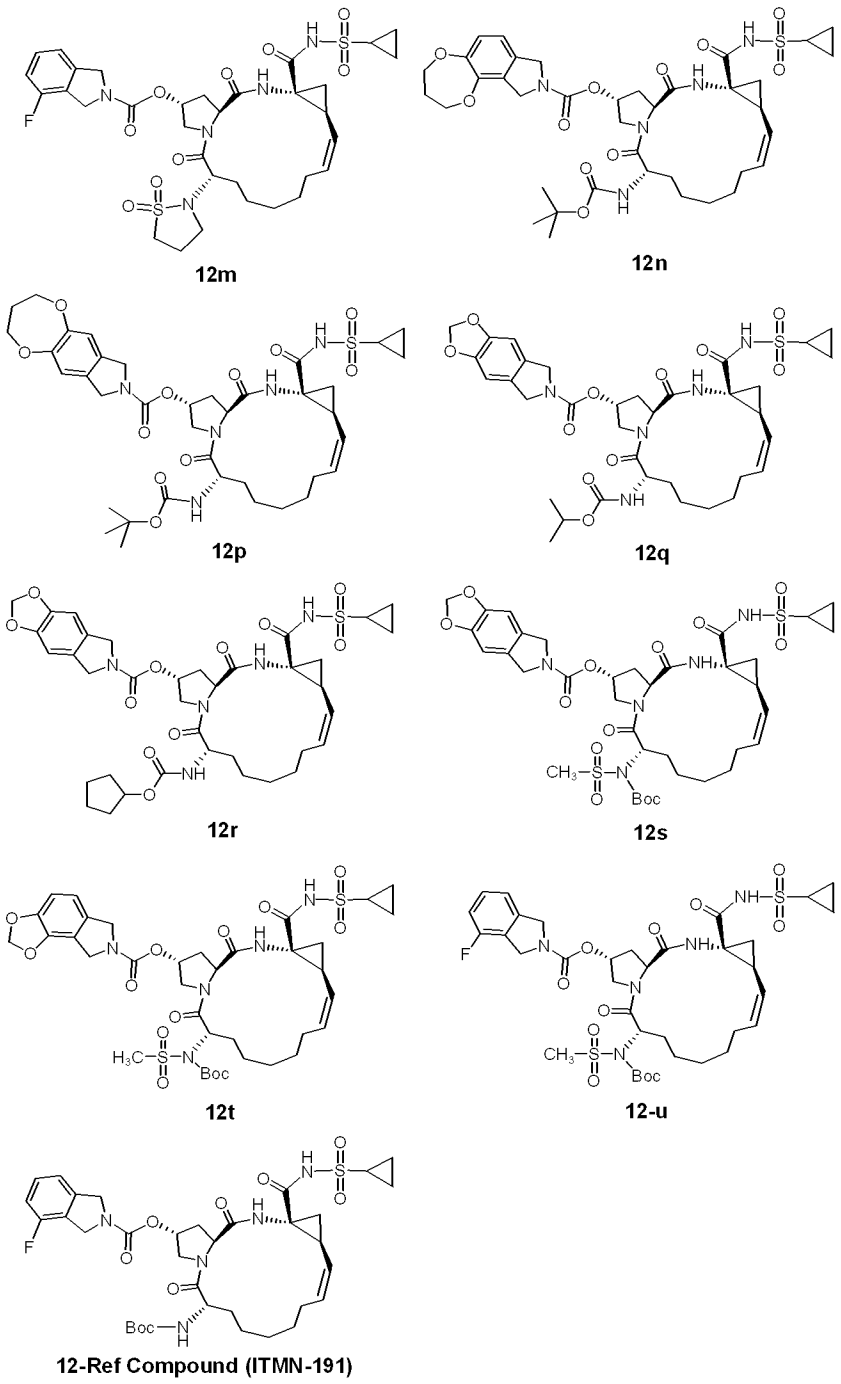
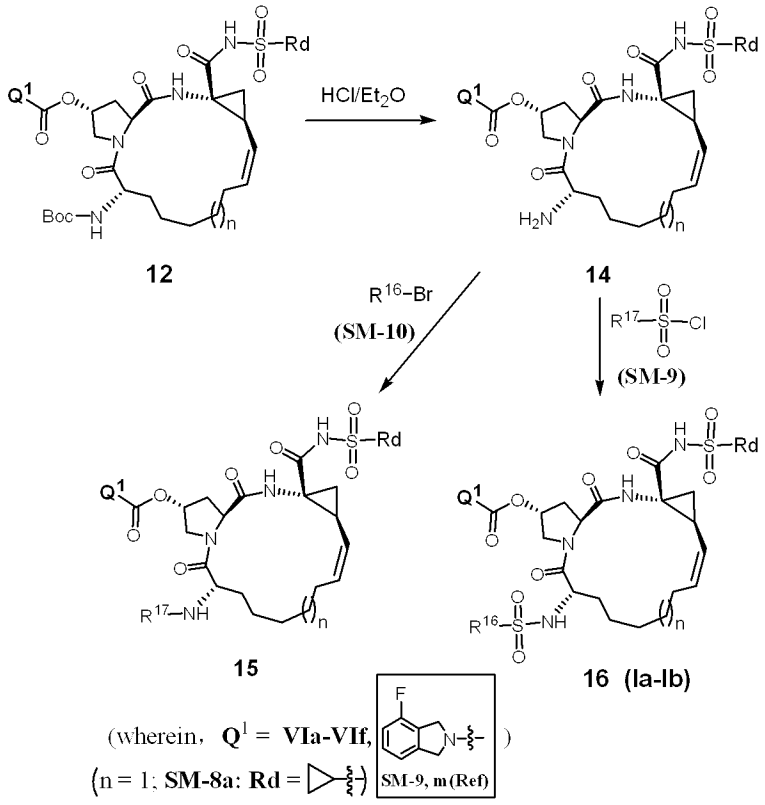


Figure 5: Structure of Compounds **12a-12u** and **12-Ref**

In the following Scheme 7, the product **12** (e.g., **12a-12f** and **12-Ref**) was used for 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 alkoxycarbonyl、C_3-C_6 cycloalkoxycarbonyl、C_6-C_{10} aryl、C_6-C_{10} arylcarbonyl、C_6-C_{10} aryloxycarbonyl or C_2-C_{10} heterocyclic group, which generates more polyheterocyclic compounds **15a-15b** and **16a-16c** shown in Figure 6.

Scheme 7：



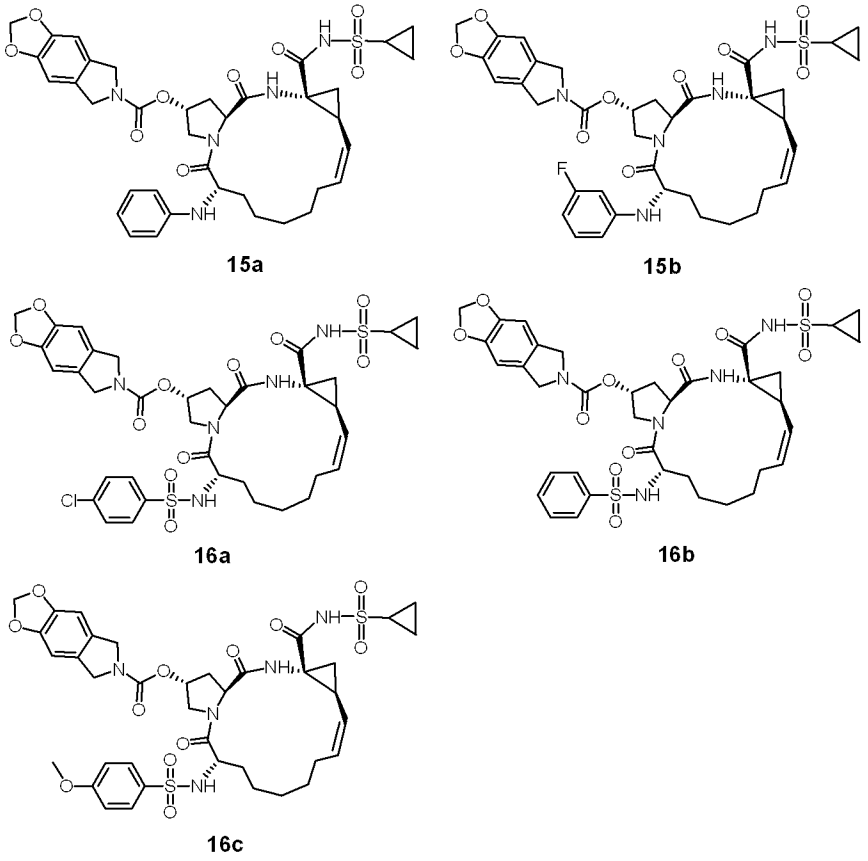
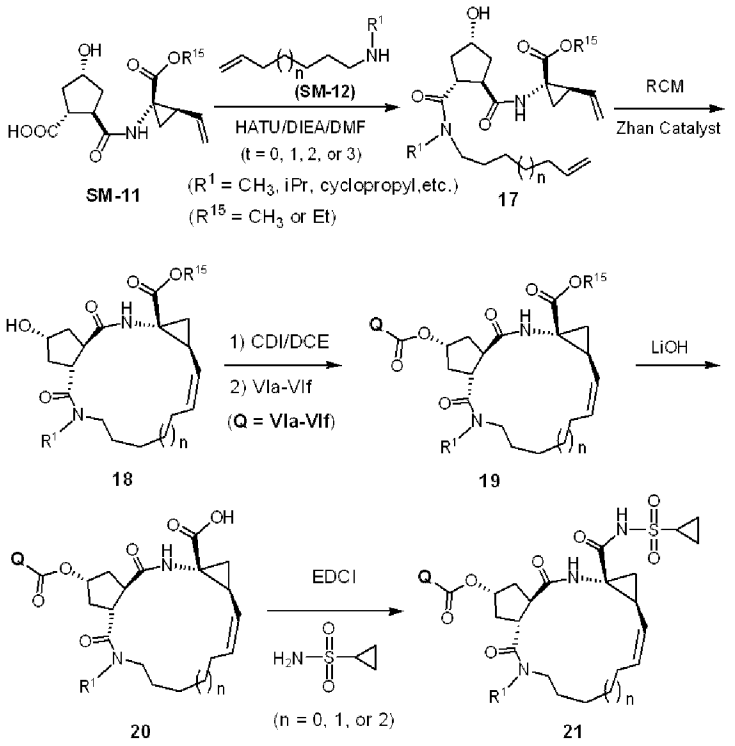


Figure 6: Structure of Compounds **15a-15b**, **16a-16c**

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

Scheme 8**:**



(Ia-Ib; Q = VIa-VIf, respectively)

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-VIf**, 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 [$RdS(O)_2NH_2$], respectively, to form a series of novel polyheterocyclic based macrocyclic compounds **Ia-Ib (21a-21j)**, which structures are shown in the following Figure 7.

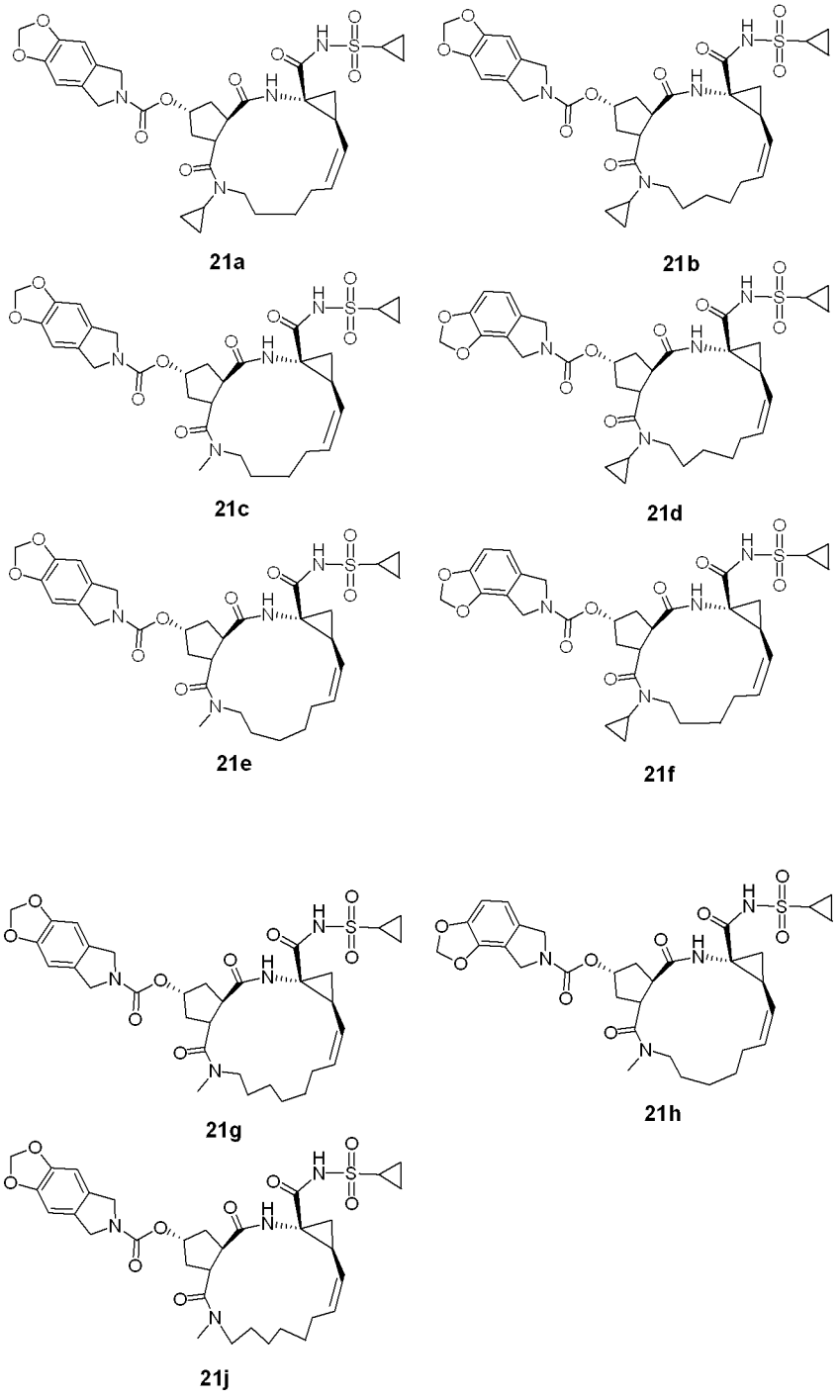
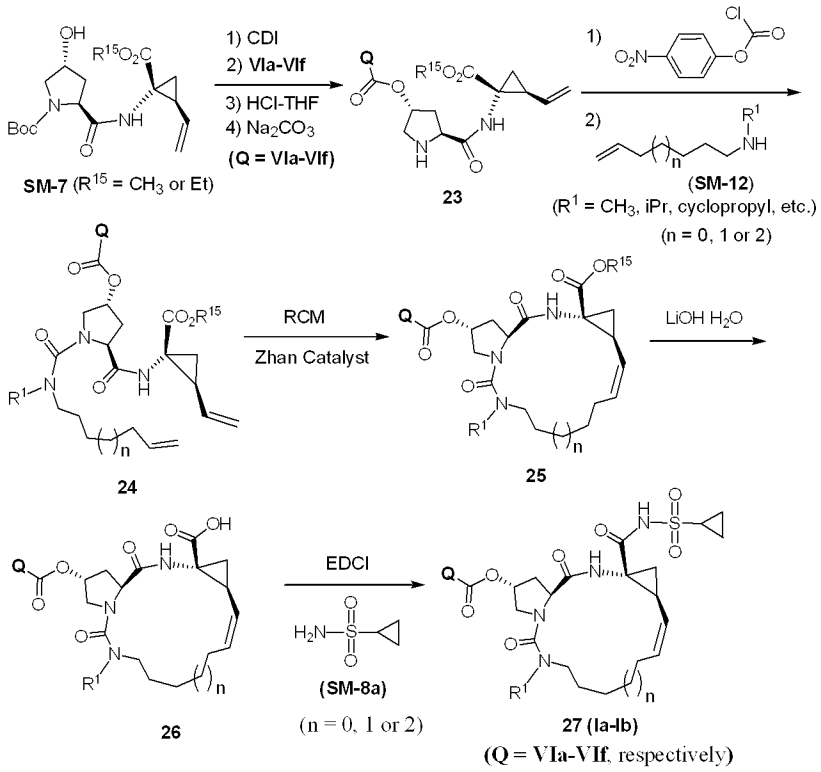


Figure 7: Structure of Compounds **21a-21j**

Scheme 9:



In Scheme 9, in the presence of coupling reagent CDI, **SM-7** was reacted with compounds **VIa-VIf**, 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 [$RdS(O)_2NH_2$], 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.

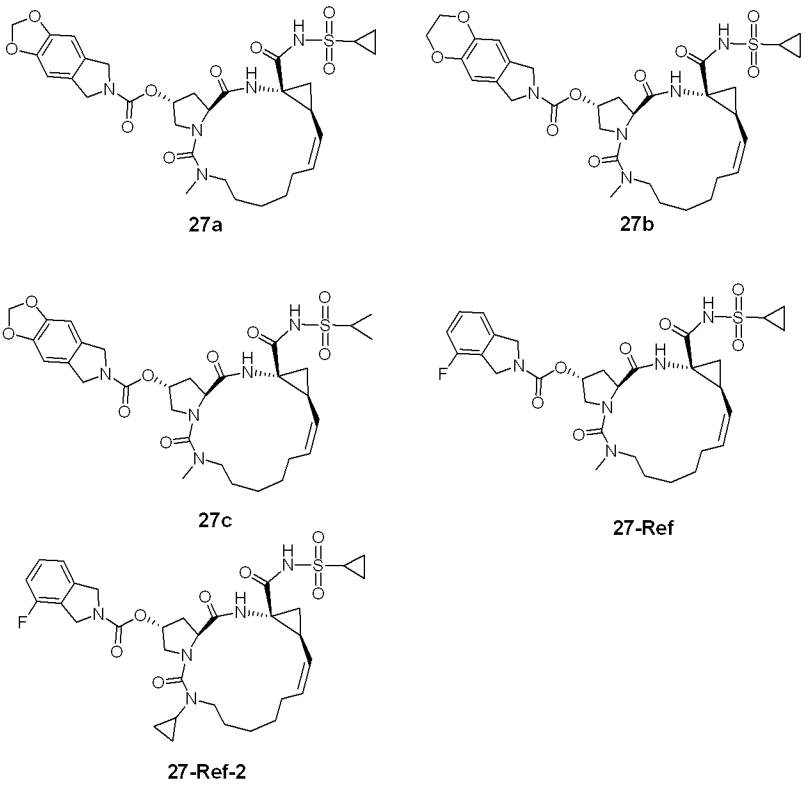
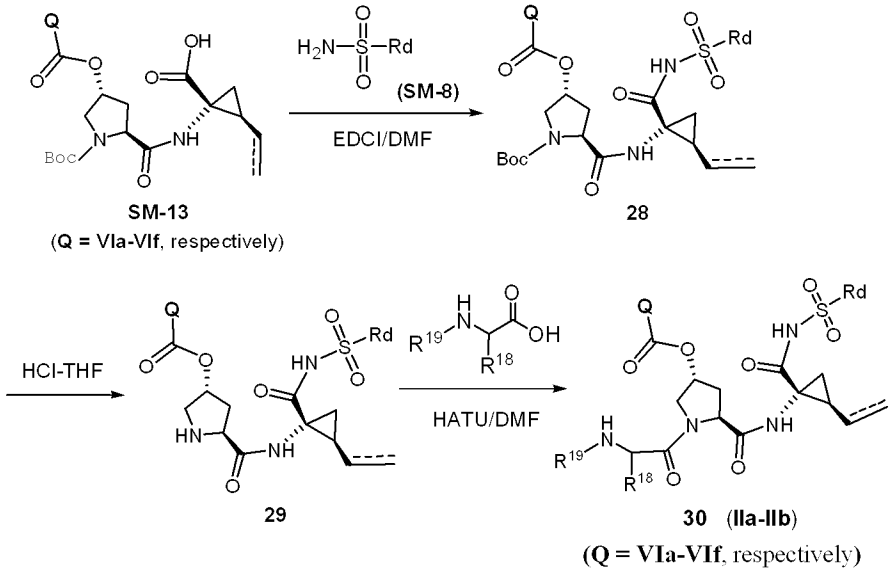


Figure 8: Structure of Compounds **27a-27c** and **27-Ref**

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-VIf** 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 RdS(O) $_2$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 C_1-C_6 alkyl or C_3-C_6 cycloalkyl group, and R^{19} is C_1-C_{20} alkyl, C_1-C_{20} alkylcarbonyl, C_1-C_{20} alkoxycarbonyl, or C_1-C_{20} alkylsulfonamido groups as shown below from compounds **30a-30ar**.

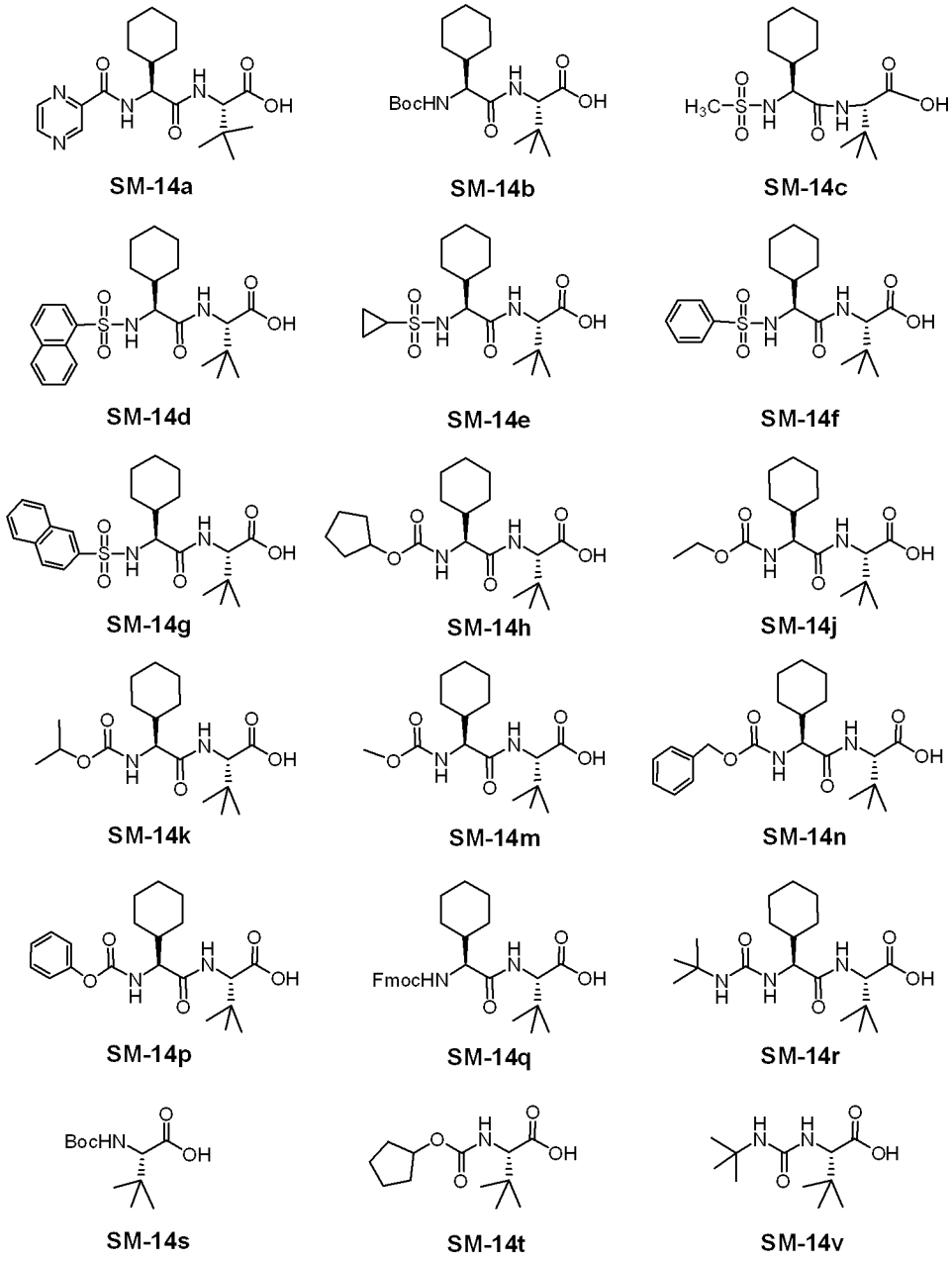
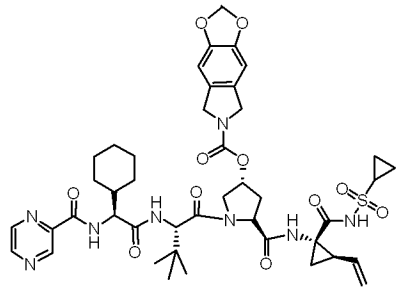
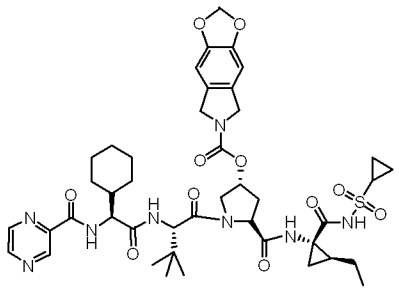


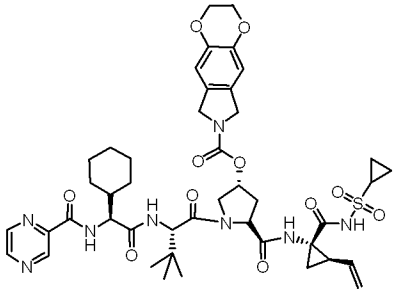
Figure 9: A list of Selected Amino Acid Building Blocks (**SM-14a-SM-14v**)



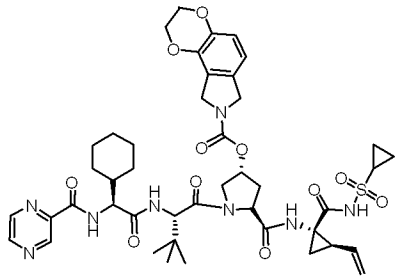
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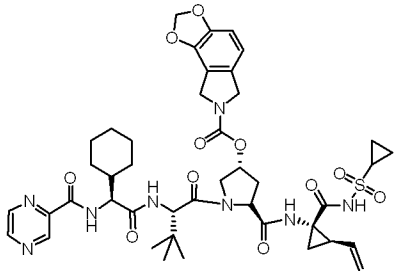
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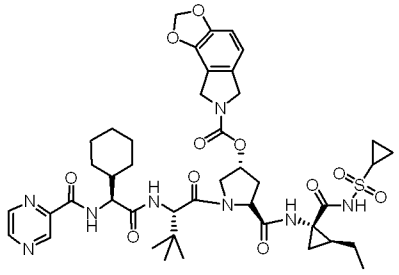
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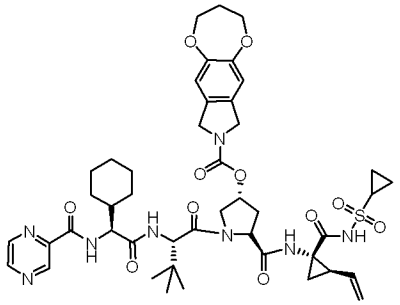
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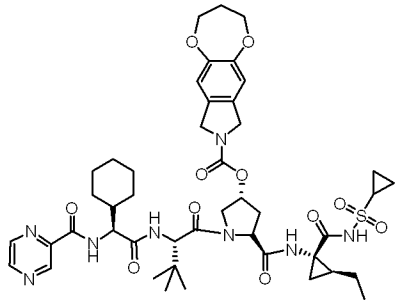
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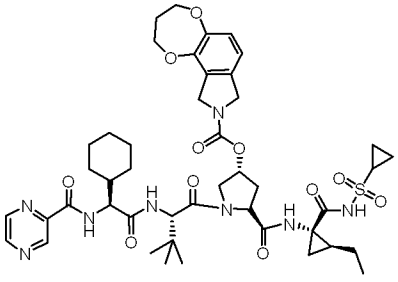
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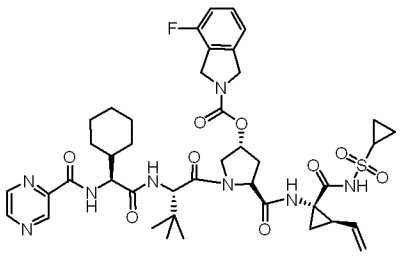
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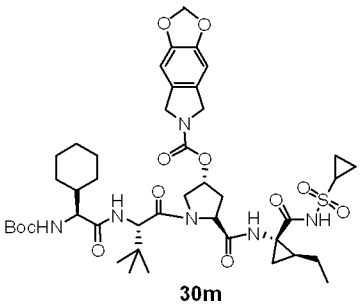
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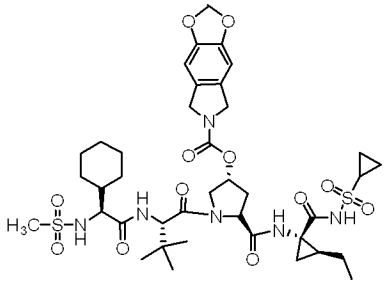
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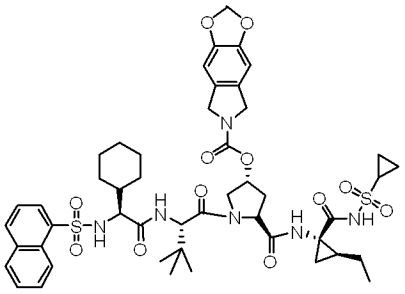
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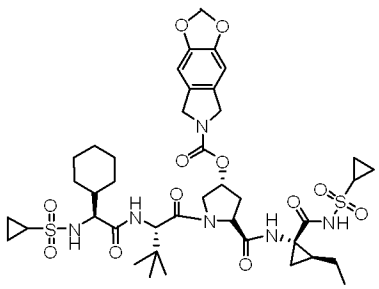
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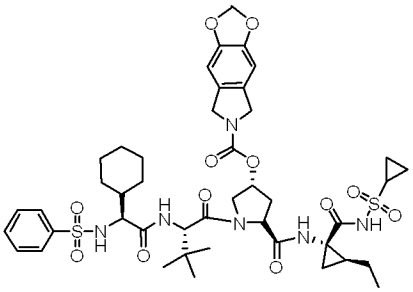
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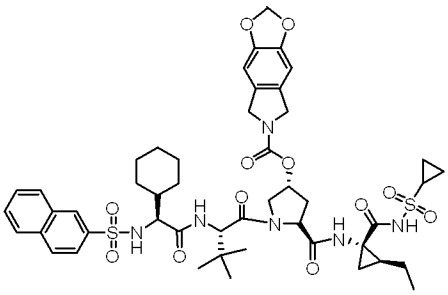
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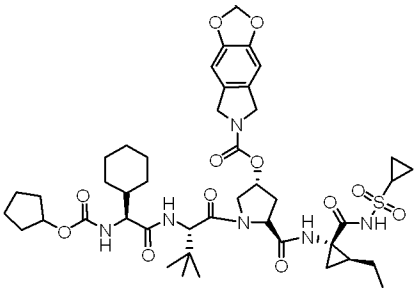
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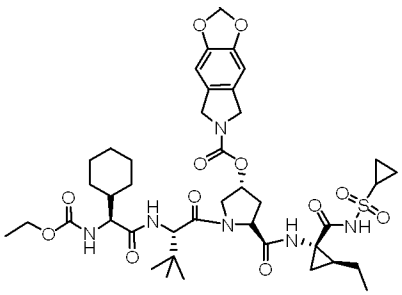
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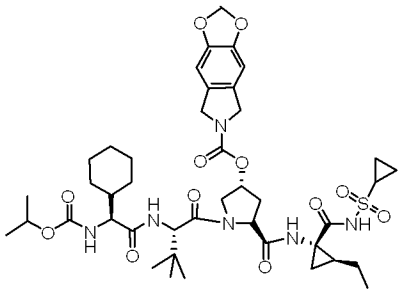
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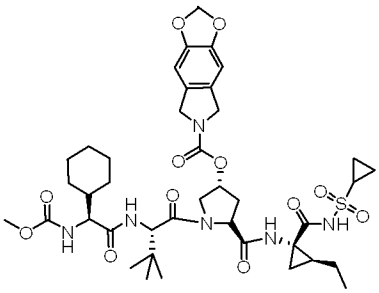
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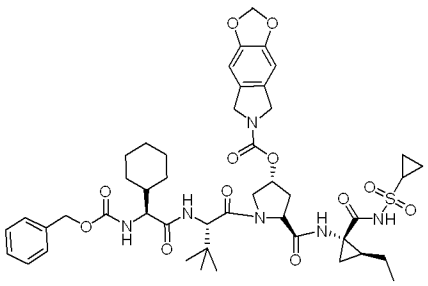
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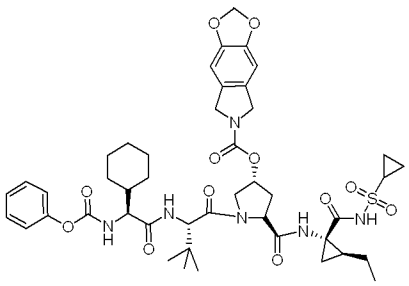
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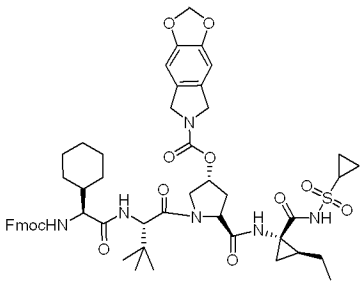
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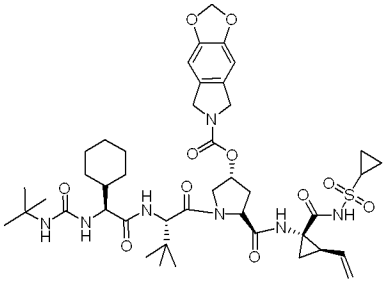
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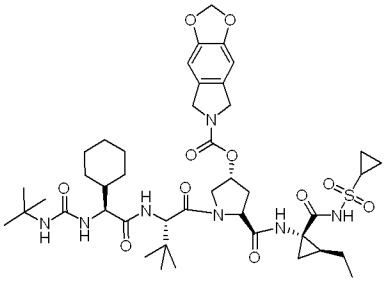
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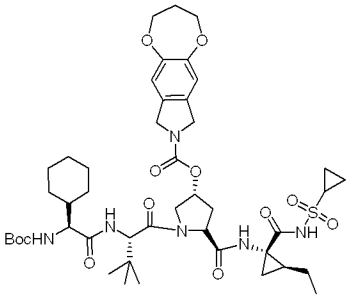
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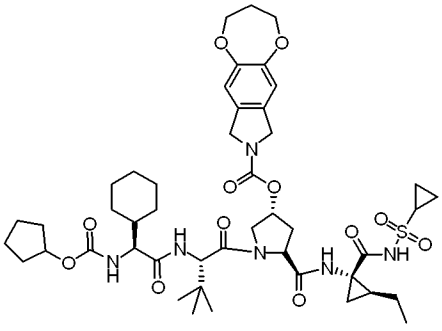
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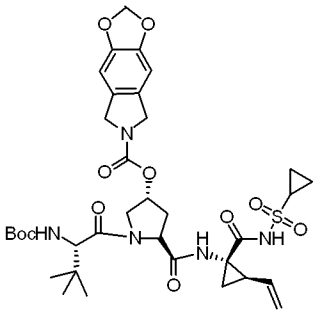
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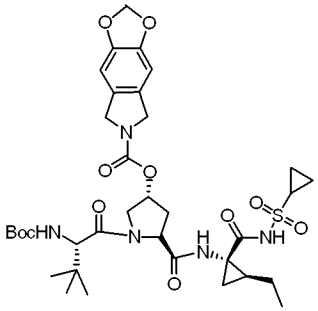
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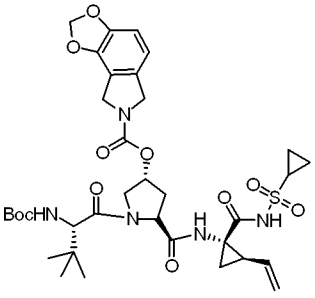
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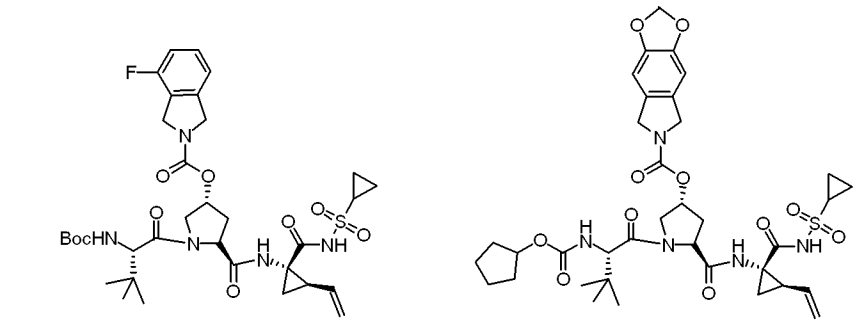
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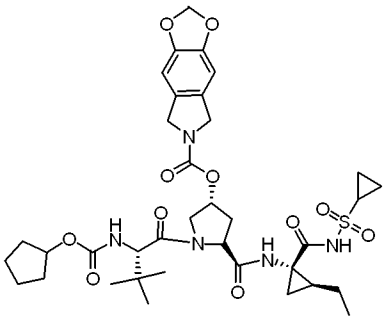


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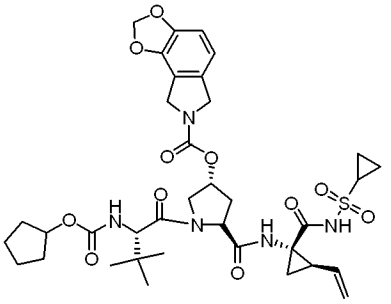


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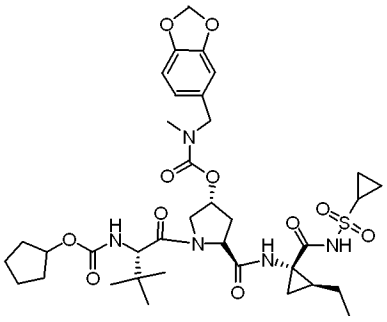
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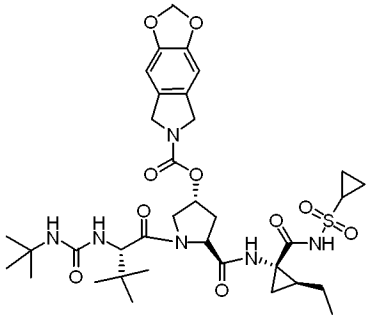
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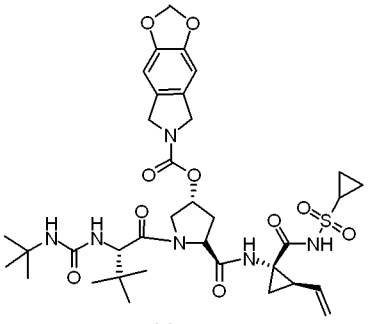
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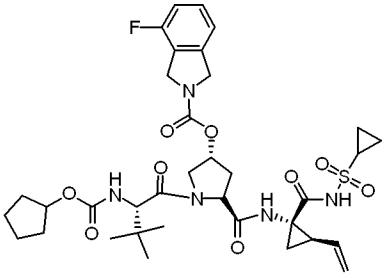
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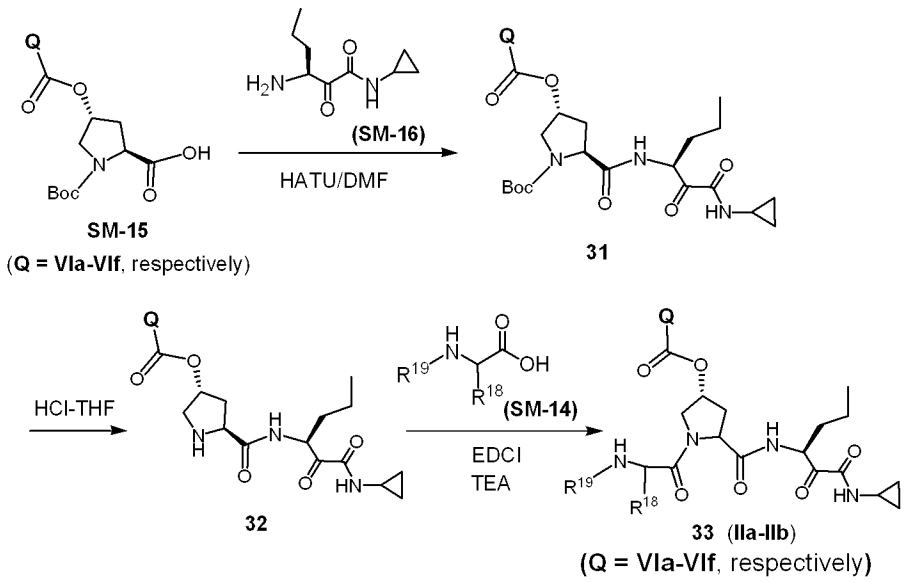
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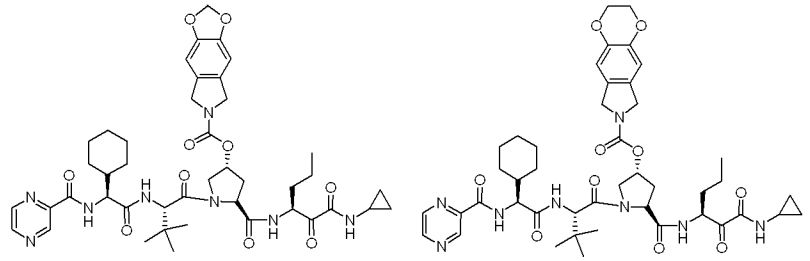
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Figure 10: Structure of Compounds **30a-30ar** and **30-Ref**

Scheme 11:

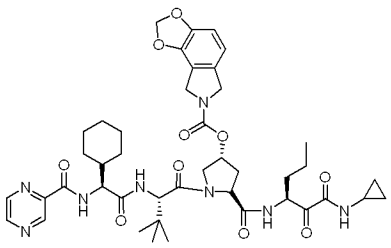


In Scheme 11 above, in the presence of coupling reagent HATU in DMF, an acid **SM-15** was reacted with another amine reagent **SM-16** to form an amide product **31** by amidation, followed by removing Boc protecting group with HCl-THF solution to obtain an amine product **32**. Finally, in the presence 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 Figuren 11, wherein R^{20} and R^{21} each is hydrogen, C_1-C_6 alkyl or C_3-C_6 cycloalkyl group, R^{22} is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl sulfonamido or C_3-C_6 cycloalkyl sulfonamido group.

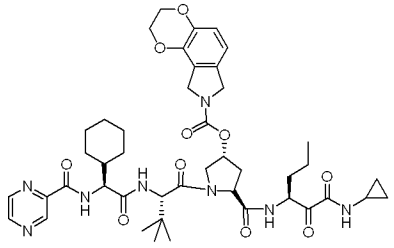


33a

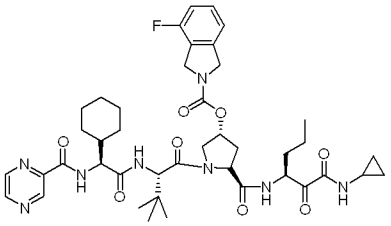
33b



33c



33d



33-Ref

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 andFieser'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, 140μL buffer A, 20μL compounds dissolved in buffer A with different concentration and 20μL HCV NS3-4A protease diluted in buffer A were added into 96-well plate respectively and mixed well. The reaction was initiate with adding 20μL 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. Renila luciferase reporter replicon cells were seeded at a density of 7×10^3 cells/well in 100μl 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 200μl of complete DMEM culture. Following 3 days of incubation, cells were incubated with 100μl fresh culture containing EnduRen™ Live Cell Substrate (Promega) at final concentrations of 60μM 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}): ≥ 200nM labeled "A", active in the range of 30-200nM labeled "B", active range ≤ 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 (EC_{50}: 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, reagnets, 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

DCE: dichloroethane

DMF: N, N-dimethylformamide

DMSO: dimethyl sulfoxide

Et2O: diethyl ether

EA: ethyl acetate

PE: petroleum ether

THF: tetrahydrofuran

TBME: tert-butyl methyl ether

EXAMPLES

General: Infrared (IR) spectra were recorded on a Fourier Transform AVATAR^{TM} 360 E.S.P^{TM} spectrophotometer (Unit: cm^{-1}). Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H 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 ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration, and assignment. ^{19}F and ^{31}P 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 (CF_3CO_2H**:** 0.00 ppm), and the chemical shifts of the phosphorus resonances were determined relative to phosphoric acid as the external standard (H_3PO_4**:** 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 Et_2O 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 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

examples, respectively.

Example 1

Synthesis 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 ℃. 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}H-NMR for the product **VIa** (CDCl3, 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 calculated164.1, founded 164.2.

Example 2

Synthesis 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 ℃. 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%.

^{1}H-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.

Example 3

Synthesis of Ru complex **VIc:**

SM-1 (12g, 0.5mol) and $Br(CH_2)_3Br$ (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 obtained. Total yield for two steps: 47%.

^{1}H-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.

Example 4

Synthesis of Ru complex **VId:**

SM-2 (12g, 0.5mol) and $Br(CH_2)_3Br$ (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 obtained. Total yield for two steps: 41%.

^{1}H-NMR for the product **VId** (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.

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%.

^{1}H-NMR for the product **VIe** (CDCl3, 500MHz): δ^{1}H-NMR (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.

Example 6

Synthesis of compound **VIf**

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 **VIf** was obtained. Total yield for two steps: 51%.

^{1}H-NMR for the product **VIf** ($CDCl_3$, 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

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%.

^{1}H-NMR for the product **4a** ($CDCl_3$, 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.

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%.

^{1}H-NMR for the product **4b** ($CDCl_3$, 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 **VId** (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%.

^{1}H-NMR for the product **4e** ($CDCl_3$, 500MHz): ^{1}H-NMR ($CDCl_3$, 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%.

^{1}H-NMR for the product **4f** ($CDCl_3$, 500MHz): ^{1}H-NMR ($CDCl_3$, 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/Et_2O solvent and stirred at 30 ℃ 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**

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.

Example 15

Synthesis of compound **8**

The raw material **SM-7** (6.5g, 18mmol) was dissolved in HCl/Et_2O solution (4M, 80mL) and stirred at 30 ℃ until completed.

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 product **8** (2.5g), yield 87%.

^{1}H-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), 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 figure 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 9 **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 figure 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 figure 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**

The synthesis of compounds **9d** adopted method II of figure 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 calculated 711.4, founded 711.5.

Example 20

Synthesis of compound **9e**

The synthesis of compounds **9e** adopted method II of figure 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.

Example 21

Synthesis of compound **9f**

The synthesis of compounds **9f** adopted method II of figure 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 **VIf** (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.

Example 22

Synthesis of compound **9-Ref**

Synthesis of compounds **9-Ref** adopted method II of figure 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 **9e** (1.4g), yield 81%.

^{1}H-NMR for the product **9-Ref** ($CDCl_3$, 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 ℃ 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 ℃ 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 25

Synthesis 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 ℃ 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 26

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 ℃ 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 27

Synthesis 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 ℃ 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.

Example 28

Synthesis 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 ℃ 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.

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 ℃ overnight until completed. The reaction mixture was worked out and purified by flash column to obtain the product **10-Ref** (1.4g), yield 71%.

^{1}H-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.

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.

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 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

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, founded 673.3.

Example 34

Synthesis of compound **11e**

The compound **10e** (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 **11e** (418mg), yield 85%, and confirmed by ESI-MS ($M+H^+$): m/z calculated 669.3, founded 669.3.

Example 35

Synthesis 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 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 36

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 ℃. 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 **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 ℃ 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%).

^{1}H-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, founded 673.3.

Example 37

Synthesis 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 ℃. 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 ℃ 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%).

^{1}H-NMR for the product **11k** ($CDCl_3$, 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 ℃. 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 ℃ 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%).

^{1}H-NMR for the product **11m** ($CDCl_3$, 500MHz)**:** δ 7.25 (m, 1H); 7.06-6.95 (m, 2H); 5.71 (q,

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 calculated 633.2, founded 633.3.

Example 39

Synthesis of compound **11-Ref**

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

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%.

^{1}H-NMR for the product **11-Ref** ($CDCl_3$, 500MHz)**:** δ 7.16 (m, 1H), 6.96-7.07 (m, 2H), 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

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, 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%).

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

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, 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 (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 column to obtain the product **12b** (53mg; Yield: 51%).

^{1}H-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), 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 (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 column to obtain the product **12c** (47mg; Yield: 42%).

^{1}H-NMR for the product **12c** ($CDCl_3$, 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.

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 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 **12d** (65mg; Yield: 67%).

^{1}H-NMR for the product **12d** ($CDCl_3$, 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.

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 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 **12e** (53mg; Yield: 49%).

^{1}H-NMR for the product **12e** ($CDCl_3$, 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.

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 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 **12f** (50mg; Yield: 46%).

^{1}H-NMR for the product **12f** ($CDCl_3$, 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

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

Example 46

Synthesis of compound **12g**

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 temperature overnight until completed. The reaction mixture was worked out to obtain the white solid product **12g** (45mg; Yield: 38%).

^{1}H-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), 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

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 (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%).

^{1}H-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.

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. 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%).

^{1}H-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 (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 (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%).

^{1}H-NMR for the product **12k** ($CDCl_3$, 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.

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.

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 **12m** (61mg; Yield: 52%).

^{1}H-NMR for the product **12m** ($CDCl_3$, 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.

Example 51

Synthesis of compound **12n**

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 (0.36mmol, **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%).

^{1}H-NMR for the product **12n** ($CDCl_3$, 500MHz)**:** δ10.27 (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 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 **12p** (65mg; Yield: 67%).

^{1}H-NMR for the product **12p** ($CDCl_3$, 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-Et_2O (2N) and stirred at 30℃ 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%.

^{1}H-NMR for the product **12q** ($CDCl_3$, 500MHz): δ10.27 (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.

Example 54

Synthesis of compound **12r**

Compound **12d** (0.18mmol) was dissolved in 20mL HCl-Et_2O (2N) and stirred at 30℃ until completed to obtain de-Boc product, followed by reacting with another reagent iPrOC(O)Cl (1.2eq) to obtain the product **12r**. yield: 76%.

^{1}H-NMR for the product **12r** ($CDCl_3$, 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.

Example 55

Synthesis 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 calculated 770.3, founded 770.4.

Example 56

Synthesis of compound **12t**

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.

Example 57

Synthesis 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.

Example 58

Synthesis 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 overnigh 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 **12-Ref** (62mg; Yield: 53%).

^{1}H-NMR for the product **12-Ref** (CDCl3, 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.

Example 59

Synthesis of compound **15a**

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 calculated734.3, founded 734.4.

Example 60

Synthesis 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.

Example 61

Synthesis 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.

Example 62

Synthesis 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.

Example 63

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

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

Example 64

Synthesis of compound **17**

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 ($M+H^+$): 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 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**

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

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**

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

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.

^{1}H-NMR for the product **21e** ($CDCl_3$, 500MHz): δ 10.60 (s, 1H), 7.10 (s, 1H), 6.61-6.74 (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

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** was obtained. Confirmed by ESI-MS ($M+H^+$): m/z calculated 669.3, founded669.5.

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 obtained.

^{1}H-NMR for the product **27a** ($CDCl_3$, 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), 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 7-47 for preparation of **12a-12h** to prepare **27b**. After purification, 83mg of product **27b** was obtained.

^{1}H-NMR for the product **27b** ($CDCl_3$, 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), 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 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 74

Synthesis 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.

^{1}H-NMR for the product **21e** ($CDCl_3$, 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 75

Synthesis 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 76

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℃ 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.

^{1}H-NMR for the product **30a** ($CDCl_3$, 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

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.

^{1}H-NMR for the product **30b** ($CDCl_3$, 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

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.

^{1}H-NMR for the product **30c** ($CDCl_3$, 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

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.

^{1}H-NMR for the product **30d** ($CDCl_3$, 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.

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.

^{1}H-NMR for the product **30e** ($CDCl_3$, 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

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.

^{1}H-NMR for the product **30f** ($CDCl_3$, 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), 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**

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

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.

^{1}H-NMR for the product **30h** ($CDCl_3$, 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, 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.

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.

^{1}H-NMR for the product **30j** ($CDCl_3$, 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.

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.

^{1}H-NMR for the product **30k** ($CDCl_3$, 500MHz): δ10.36 (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

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.

^{1}H-NMR for the product **30m** ($CDCl_3$, 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**

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}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**

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}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

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.

^{1}H-NMR for the product **30r** ($CDCl_3$, 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.

^{1}H-NMR for the product **30s** ($CDCl_3$, 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.

^{1}H-NMR for the product **30t** ($CDCl_3$, 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.

^{1}H-NMR for the product **30v** ($CDCl_3$, 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.

^{1}H-NMR for the product **30w** ($CDCl_3$, 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 95

Synthesis 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.

^{1}H-NMR for the product **30x** ($CDCl_3$, 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, founded 845.4

Example 96

Synthesis of compound **30y**

The synthetic procedure was carried out as the same as in Example 76 for preparation of 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 97

Synthesis of compound **30z**

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 98

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.

^{1}H-NMR for the product **30aa** ($CDCl_3$, 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

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.

^{1}H-NMR for the product **30ab** ($CDCl_3$, 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

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.

^{1}H-NMR for the product **30ac** ($CDCl_3$, 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 [$(M+H)^+$]:

m/z calculated 886.4, founded 886.5.

Example 101

Synthesis of compound **30ad**

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.

^{1}H-NMR for the product **30ad** ($CDCl_3$, 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), 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 102

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.

^{1}H-NMR for the product **30ae** ($CDCl_3$, 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), 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

Example 103

Synthesis 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.

^{1}H-NMR for the product **30af** ($CDCl_3$, 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.

^{1}H-NMR for the product **30ah** ($CDCl_3$, 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**

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}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), 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**

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

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}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), 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 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**

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}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), 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**

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}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 (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 compound **30-Ref**. After purification, 37mg of product **30-Ref** was obtained.

^{1}H-NMR for the product **30-Ref** ($CDCl_3$, 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, 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 250mL flask reactor，followed by adding coupling reagent EDCI (1.3eq) to keep the amidation at 55℃ 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.

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.

^{1}H-NMR for the product **33a** ($CDCl_3$, 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), 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**

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.

^{1}H-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, 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

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.

^{1}H-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 (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

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.

^{1}H-NMR for the product **33d** ($CDCl_3$, 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). ESI-MS [$(M+H)^+$]: m/z calculated 859.4, founded 859.5.

Example 118

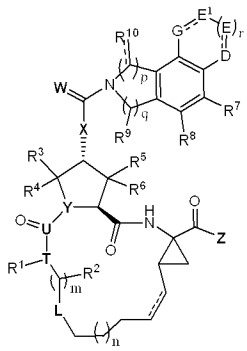
Synthesis of compound **33-Ref**

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.

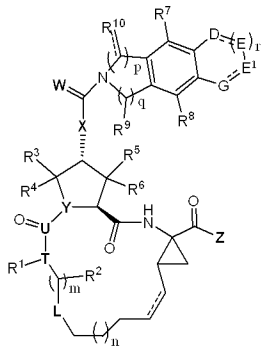
^{1}H-NMR for the product **33-Ref** ($CDCl_3$, 500MHz): δ 9.28 (m, 1H), 8.75 (s, 1H), 8.57 (m, 2H), 7.71 (m, 1H), 7.07 (m, 1H), 6.97-7.00 (m, 2H), 6.63 (m, 1H), 5.92 (m, 1H), 5.41 (s, 1H), 5.30-5.33 (m, 1H), 5.13-5.15 (m, 2H), 4.75 (m, 3H), 4.65-4.68 (m, 1H), 4.59 (m, 1H), 4.47-4.51 (m, 1H), 4.38-4.42 (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.

What is claimed is:

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



Ia



Ib

stereoisomers, solvates, hydrates, tautomers, esterification or amidation prodrugs, 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, respectively;

wherein when "⋯⋯" 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 hydrogen, oxygen, halogen atom, cyano, 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, or C_2-C_{20} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G is each independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_{20} alkyl, C_3-C_{20} cycloalkyl, C_6-C_{20} aryl, C_1-C_{20} alkoxy, C_1-C_{20} alkylthio, C_1-C_{20} alkoxycarbonyl, C_6-C_{20} aryloxy, C_6-C_{20} aryloxycarbonyl, C_2-C_{20} heterocyclic alkoxycarbonyl, C_2-C_{20} heterocyclic aryl, C_1-C_{20} alkylamino, C_2-C_{20} heterocyclic amino, C_6-C_{20} aryl amino, C_1-C_{20} aminocarbonyl, C_1-C_{20} amido, C_1-C_{20} amidocarbonyl, C_1-C_{20} carbonylamino,

C_1-C_{20} alkylsulfonamido, C_2-C_{20} heterocyclic sulfonamido, C_6-C_{20} arylsulfonamido, or C_1-C_{20} 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)-, C_1-C_{20} alkenyl, C_1-C_{20} alkoxy, C_2-C_{20} heterocyclyl, C_2-C_{20} heterocyclic alkoxy, C_1-C_{20} amino, C_1-C_{20} aminocarbonyl, C_1-C_{20} alkoxycarbonyl, C_6-C_{20} aryl, C_6-C_{20} aryloxy, or C_6-C_{20} 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, E^1, and G above;

Y is nitrogen or CH group;

Z 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} heteroarylamino, 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;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C_1-C_{20} alkyl, C_3-C_{20} cycloalkyl, C_1-C_{20} alkoxy, C_3-C_{20} cycloalkoxy, C_1-C_{20} alkoxycarbonyl, C_1-C_{20} alkylamino, C_3-C_{20} cycloalkylamino, C_2-C_{20} heterocyclic amino, C_6-C_{20} arylamino, C_1-C_{20} alkoxycarbonylamino, C_6-C_{20} aryloxycarbonylamino, C_1-C_{20} alkylsulfonamido, C_3-C_{20} cycloalkylsulfonamido, C_2-C_{20} heterocyclic sulfonamido, C_6-C_{20} arylsulfonamido, and C_1-C_{20} aminosulfonamido group;

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} heterocyclicamino, 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

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.

2. The compound according to claim 1,

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, respectively;

wherein when "⋯⋯" 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 hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C_1-C_{15} alkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} aminocarbonyl, C_1-C_{15} carbonylamino, C_6-C_{15} aryl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, or C_2-C_{15} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_6-C_{15} aryl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, C_2-C_{15} heterocyclic alkoxycarbonyl, C_2-C_{15} heterocyclic aryl, C_1-C_{15} alkylamino, C_2-C_{15} heterocyclic amino, C_6-C_{15} aryl amino, C_1-C_{15} aminocarbonyl, C_1-C_{15} amido, C_1-C_{15} amidocarbonyl, C_1-C_{15} carbonylamino, C_1-C_{15} alkylsulfonamido, C_2-C_{15} heterocyclic sulfonamido, C_6-C_{15} arylsulfonamido, or C_1-C_{15} 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)-, C_1-C_{15} alkenyl, C_1-C_{15} alkoxy, C_2-C_{15} heterocyclyl, C_2-C_{15} heterocyclic alkoxy, C_1-C_{15} amino, C_1-C_{15} aminocarbonyl, C_1-C_{15} alkoxycarbonyl, C_6-C_{15} aryl, C_6-C_{15} aryloxy, or C_6-C_{15} 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, E^1, and G above;

Y is nitrogen or CH group;

Z is hydroxyl, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_1-C_{15} alkoxy, C_3-C_{15} cycloalkoxy, C_1-C_{15} alkylamino, C_3-C_{15} cycloalkylamino , C_2-C_{15} heterocyclic amino, C_6-C_{15} aryl, C_6-C_{15} arylamino, C_4-C_{15} heteroarylamino, C_1-C_{15} alkyl sulfonamido, C_3-C_{15} cycloalkylsulfonamido, C_6-C_{15} arylsulfonamido, C_1-C_{15} alkoxy sulfonamido, C_3-C_{15} cycloalkoxy sulfonamido, C_1-C_{15} alkylamino sulfonamido, C_3-C_{15} cycloalkylamino sulfonamido, C_6-C_{15} arylamino sulfonamido, C_1-C_{15} uramido, C_1-C_{15} thioureido, C_1-C_{15} phosphate, or C_1-C_{15} borate;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_1-C_{15} alkoxy, C_3-C_{15} cycloalkoxy, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} alkylamino, C_3-C_{15} cycloalkylamino, C_2-C_{15} heterocyclic amino, C_6-C_{15} arylamino, C_1-C_{15} alkoxycarbonylamino, C_6-C_{15} aryloxycarbonylamino, C_1-C_{15} alkylsulfonamido, C_3-C_{15} cycloalkylsulfonamido, C_2-C_{15} heterocyclic sulfonamido, C_6-C_{15} arylsulfonamido, and C_1-C_{15} aminosulfonamido group;

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_{15} alkyl, C_3-C_{15} cycloalkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylamino, C_2-C_{15} heterocyclicamino, C_6-C_{15} aryl, C_6-C_{15} arylamino, C_1-C_{15} alkylsulfonamido, C_2-C_{15} heterocyclic sulfonamido, and C_6-C_{15} arylsulfonamido group; and

R^7, R^8 and R^9 are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C_1-C_{15} alkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} aminocarbonyl, C_1-C_{15} carbonylamino, C_6-C_{15} aryl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, and C_2-C_{15} heterocyclic group.

3. The compound according to claim 2,

werein:

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, respectively;

wherein when "⋯⋯" 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 hydrogen, oxygen, halogen atom, cyano, 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, or C_2-C_{12} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{12} aryl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, C_1-C_8 alkoxycarbonyl, C_6-C_{12} aryloxy, C_6-C_{12} aryloxycarbonyl, C_2-C_8 heterocyclic alkoxycarbonyl, C_2-C_{12} heterocyclic aryl, C_1-C_8 alkylamino, C_2-C_8 heterocyclic amino, C_6-C_{12} aryl amino, C_1-C_8 aminocarbonyl, C_1-C_8 amido, C_1-C_8 amidocarbonyl, C_1-C_8 carbonylamino, C_1-C_8 alkylsulfonamido, C_2–C_8 heterocyclic sulfonamido, C_6-C_{12} arylsulfonamido, or C_1-C_8 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)-, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_2-C_8 heterocyclyl, C_2-C_8 heterocyclic alkoxy, C_1-C_8 amino, C_1-C_8 aminocarbonyl, C_1-C_8 alkoxycarbonyl, C_6-C_{12} aryl, C_6-C_{12} aryloxy, or C_6-C_{12} 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, E^1, and G above;

Y is nitrogen or CH group;

Z is hydroxyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, C_1-C_8 alkylamino, C_3-C_8 cycloalkylamino , C_2-C_8 heterocyclic amino, C_6-C_{12} aryl, C_6-C_{12} arylamino, C_4-C_{12} heteroarylamino, C_1-C_8 alkyl sulfonamido, C_3-C_8 cycloalkylsulfonamido, C_6-C_{12} arylsulfonamido, C_1-C_8 alkoxy sulfonamido, C_3-C_8 cycloalkoxy sulfonamido, C_1-C_8 alkylamino sulfonamido, C_3-C_8 cycloalkylamino sulfonamido, C_6-C_{12} arylamino sulfonamido, C_1-C_8 uramido, C_1-C_8 thioureido, C_1-C_8 phosphate, or C_1-C_8 borate;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, C_1-C_8 alkoxycarbonyl, C_1-C_8 alkylamino, C_3-C_8 cycloalkylamino, C_2-C_8 heterocyclic amino, C_6-C_{12} arylamino, C_1-C_8 alkoxycarbonylamino, C_6-C_{12} aryloxycarbonylamino, C_1-C_8 alkylsulfonamido, C_3-C_8 cycloalkylsulfonamido, C_2-C_8 heterocyclic sulfonamido, C_6-C_{12} arylsulfonamido, and C_1-C_8

aminosulfonamido group;

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_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkylamino, C_2-C_8 heterocyclicamino, C_6-C_{12} aryl, C_6-C_{12} arylamino, C_1-C_8 alkylsulfonamido, C_2-C_8 heterocyclic sulfonamido, and C_6-C_{12} arylsulfonamido group; and

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.

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 R^{10} is a single bond, and R^{10} is H;

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;

L is $-CH_2-$;

T is N or CH;

U is carbon;

W and X are each oxygen;

Y is N or CH;

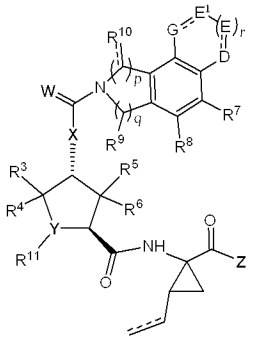
Z is hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfonamido, C_3-C_6 cycloalkylsulfonamido or C_6-C_{10} arylsulfonamido group;

R^1 is hydrogen, C_6-C_{10} arylamino, C_1-C_6 alkoxycarbonylamino, C_2-C_6 heterocyclic amino, C_1-C_6 alkylsulfonamido, or C_6-C_{10} arylsulfonamido; and

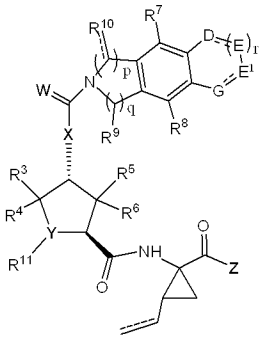
R^2, R^3, R^4, R^5 and R^6 are each H;

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

5. A compound represented by the formula **IIa** and **IIb**:



IIa



IIb

or stereoisomers, solvates, hydrates, tautomers, esterification or amidation prodrugs, pharmaceutically acceptable salt, or mixtures thereof.

wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, 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, or C_2-C_{20} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_{20} alkyl, C_3-C_{20} cycloalkyl, C_6-C_{20} aryl, C_1-C_{20} alkoxy, C_1-C_{20} alkylthio, C_1-C_{20} alkoxycarbonyl, C_6-C_{20} aryloxy, C_6-C_{20} aryloxycarbonyl, C_2-C_{20} heterocyclic alkoxycarbonyl, C_2-C_{20} heterocyclic aryl, C_1-C_{20} alkylamino, C_2-C_{20} heterocyclic amino, C_6-C_{20} aryl amino, C_1-C_{20} aminocarbonyl, C_1-C_{20} amido, C_1-C_{20} amidocarbonyl, C_1-C_{20} carbonylamino,

C_1-C_{20} alkylsulfonamido, C_2-C_{20} heterocyclic sulfonamido, C_6-C_{20} arylsulfonamido, or C_1-C_{20} 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;

Z 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} heteroarylamino, 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;

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} heterocyclicamino, 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

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.

R^{11} 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, or C_3-C_{20} heterocyclicaminosulfonyl group.

6. The compound according to claim 5,

Wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C_1-C_{15} alkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} aminocarbonyl, C_1-C_{15} carbonylamino, C_6-C_{15} aryl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, or C_2-C_{15} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_6-C_{15} aryl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, C_2-C_{15} heterocyclic alkoxycarbonyl, C_2-C_{15} heterocyclic aryl, C_1-C_{15} alkylamino, C_2-C_{15} heterocyclic amino, C_6-C_{15} aryl amino, C_1-C_{15} aminocarbonyl, C_1-C_{15} amido, C_1-C_{15} amidocarbonyl, C_1-C_{15} carbonylamino, C_1-C_{15} alkylsulfonamido, C_2 -C_{15} heterocyclic sulfonamido, C_6-C_{15} arylsulfonamido, or C_1-C_{15} 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;

Z is hydroxyl, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_1-C_{15} alkoxy, C_3-C_{15} cycloalkoxy, C_1-C_{15} alkylamino, C_3-C_{15} cycloalkylamino , C_2-C_{15} heterocyclic amino, C_6-C_{15} aryl, C_6-C_{15} arylamino, C_4-C_{15} heteroarylamino, C_1-C_{15} alkyl sulfonamido, C_3-C_{15} cycloalkylsulfonamido, C_6-C_{15} arylsulfonamido, C_1-C_{15} alkoxy sulfonamido, C_3-C_{15} cycloalkoxy sulfonamido, C_1-C_{15} alkylamino sulfonamido, C_3-C_{15} cycloalkylamino sulfonamido, C_6-C_{15} arylamino sulfonamido, C_1-C_{15} uramido, C_1-C_{15} thioureido, C_1-C_{15} phosphate, or C_1-C_{15} borate;

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_{15} alkyl, C_3-C_{15} cycloalkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylamino, C_2-C_{15} heterocyclicamino, C_6-C_{15} aryl, C_6-C_{15} arylamino, C_1-C_{15} alkylsulfonamido, C_2-C_{15} heterocyclic sulfonamido, and C_6-C_{15} arylsulfonamido group; and

R^7, R^8 and R^9 are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C_1-C_{15} alkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} aminocarbonyl, C_1-C_{15} carbonylamino, C_6-C_{15} aryl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, and C_2-C_{15} heterocyclic group.

R^{11} is H, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_6-C_{15} aryl, C_4-C_{15} heteroaryl, C_1-C_{15} alkylcarbonyl, C_1-C_{15} alkoxycarbonyl, C_6-C_{15} aryloxycarbonyl, C_1-C_{15} alkylaminocarbonyl, C_6-C_{15} arylsulfonyl, C_1-C_{15} alkylaminosulfonyl, C_3-C_{15} cycloalkylaminosulfonyl, C_6-C_{15} arylaminosulfonyl, or C_3-C_{15} heterocyclicaminosulfonyl group.

7. The compound according to claim 6,

wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, 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, or C_2-C_{12} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{12} aryl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, C_1-C_8 alkoxycarbonyl, C_6-C_{12} aryloxy, C_6-C_{12} aryloxycarbonyl, C_2-C_8 heterocyclic alkoxycarbonyl, C_2-C_{12} heterocyclic aryl, C_1-C_8 alkylamino, C_2-C_8 heterocyclic amino, C_6-C_{12} aryl amino, C_1-C_8 aminocarbonyl, C_1-C_8 amido, C_1-C_8 amidocarbonyl, C_1-C_8 carbonylamino, C_1-C_8 alkylsulfonamido, C_2–C_8 heterocyclic sulfonamido, C_6-C_{12} arylsulfonamido, or C_1-C_8 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;

Z is hydroxyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, C_1-C_8 alkylamino, C_3-C_8 cycloalkylamino , C_2-C_8 heterocyclic amino, C_6-C_{12} aryl, C_6-C_{12} arylamino, C_4-C_{12} heteroarylamino, C_1-C_8 alkyl sulfonamido, C_3-C_8 cycloalkylsulfonamido, C_6-C_{12}

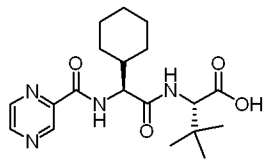
arylsulfonamido, C_1-C_8 alkoxy sulfonamido, C_3-C_8 cycloalkoxy sulfonamido, C_1-C_8 alkylamino sulfonamido, C_3-C_8 cycloalkylamino sulfonamido, C_6-C_{12} arylamino sulfonamido, C_1-C_8 uramido, C_1-C_8 thioureido, C_1-C_8 phosphate, or C_1-C_8 borate;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, C_1-C_8 alkoxycarbonyl, C_1-C_8 alkylamino, C_3-C_8 cycloalkylamino, C_2-C_8 heterocyclic amino, C_6-C_{12} arylamino, C_1-C_8 alkoxycarbonylamino, C_6-C_{12} aryloxycarbonylamino, C_1-C_8 alkylsulfonamido, C_3-C_8 cycloalkylsulfonamido, C_2-C_8 heterocyclic sulfonamido, C_6-C_{12} arylsulfonamido, and C_1-C_8 aminosulfonamido group;

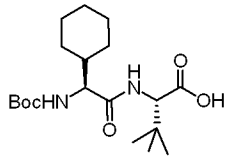
R^3, R^4, R^5 and R^6 are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, nitro, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkylamino, C_2-C_8 heterocyclicamino, C_6-C_{12} aryl, C_6-C_{12} arylamino, C_1-C_8 alkylsulfonamido, C_2-C_8 heterocyclic sulfonamido, and C_6-C_{12} arylsulfonamido group; and

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.

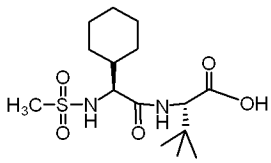
8. The compound according to claims 5-7, wherein R^{11} is H, C_1-C_8 alkyl, C_1-C_8 alkylcarbonyl, C_1-C_8 alkoxycarbonyl, C_6-C_{12} aryloxycarbonyl, or a group having the formula selected from the following structure **SM-14a** to **SM-14v**:



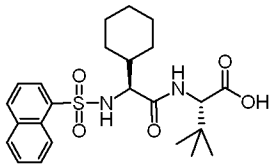
SM-14a



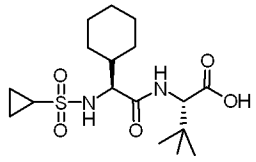
SM-14b



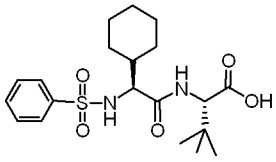
SM-14c



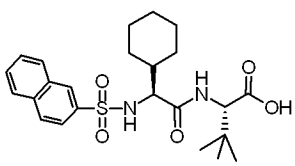
SM-14d



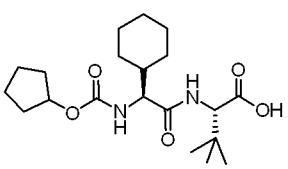
SM-14e



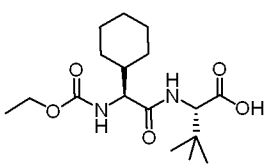
SM-14f



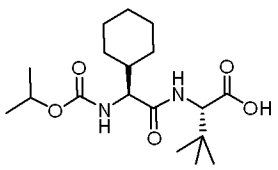
SM-14g



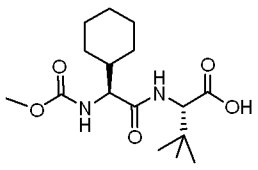
SM-14h



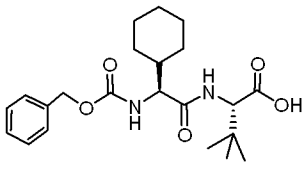
SM-14j



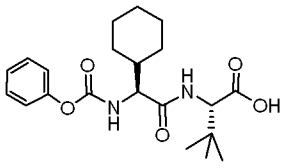
SM-14k



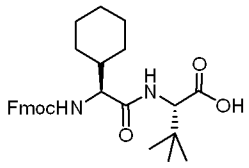
SM-14m



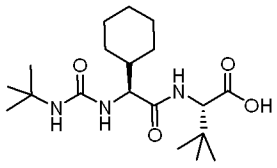
SM-14n



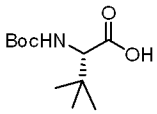
SM-14p



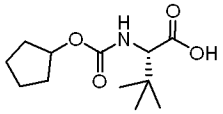
SM-14q



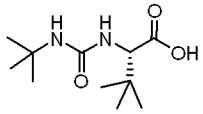
SM-14r



SM-14s



SM-14t



SM-14v

9. The compound according to claim 7,

wherein:

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 is a double bond;

the dashed line "⋯⋯" linked to R^{10} is a single bond, and R^{10} is H;

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;

W and X are each oxygen;

Y is N or CH;

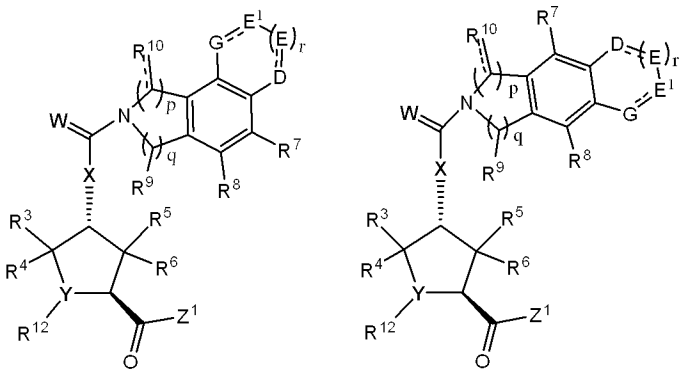
Z is hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfonamido, C_3-C_6 cycloalkylsulfonamido or C_6-C_{10} arylsulfonamido group;

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 alkoxycarbonyl, or a group having the formula selected from the structure **SM-14a** to **SM-14v** of claim 8.

10. A compound represented by the formula **IIIa** or **IIIb**:



IIIa **IIIb**

wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, 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, or C_2-C_{20} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_{20} alkyl, C_3-C_{20} cycloalkyl, C_6-C_{20} aryl, C_1-C_{20} alkoxy, C_1-C_{20} alkylthio, C_1-C_{20} alkoxycarbonyl, C_6-C_{20} aryloxy, C_6-C_{20} aryloxycarbonyl, C_2-C_{20} heterocyclic alkoxycarbonyl, C_2-C_{20} heterocyclic aryl, C_1-C_{20} alkylamino, C_2-C_{20} heterocyclic amino, C_6-C_{20} aryl amino, C_1-C_{20} aminocarbonyl, C_1-C_{20} amido, C_1-C_{20} amidocarbonyl, C_1-C_{20} carbonylamino, C_1-C_{20} alkylsulfonamido, C_2 -C_{20} heterocyclic sulfonamido, C_6-C_{20} arylsulfonamido, or C_1-C_{20} 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;

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} heteroarylamino, 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;

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} heterocyclicamino, 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

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.

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, or C_3-C_{20} heterocyclicaminosulfonyl group.

11. The compound according to claim 10,

wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, trifluoromethyl, C_1-C_{15} alkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} aminocarbonyl, C_1-C_{15} carbonylamino, C_6-C_{15} aryl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, or C_2-C_{15} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_6-C_{15} aryl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, C_2-C_{15} heterocyclic alkoxycarbonyl, C_2-C_{15} heterocyclic aryl, C_1-C_{15} alkylamino, C_2-C_{15} heterocyclic amino, C_6-C_{15} aryl amino, C_1-C_{15} aminocarbonyl, C_1-C_{15} amido, C_1-C_{15} amidocarbonyl, C_1-C_{15} carbonylamino, C_1-C_{15} alkylsulfonamido, C_2-C_{15} heterocyclic sulfonamido, C_6-C_{15} arylsulfonamido, or C_1-C_{15} 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;

Z^1 is hydroxyl, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_1-C_{15} alkoxy, C_3-C_{15} cycloalkoxy, C_1-C_{15} alkylamino, C_3-C_{15} cycloalkylamino , C_2-C_{15} heterocyclic amino, C_6-C_{15} aryl, C_6-C_{15} arylamino, C_4-C_{15} heteroarylamino, C_1-C_{15} alkyl sulfonamido, C_3-C_{15} cycloalkylsulfonamido, C_6-C_{15} arylsulfonamido, C_1-C_{15} alkoxy sulfonamido, C_3-C_{15} cycloalkoxy sulfonamido, C_1-C_{15} alkylamino sulfonamido, C_3-C_{15} cycloalkylamino sulfonamido, C_6-C_{15} arylamino sulfonamido, C_1-C_{15} uramido, C_1-C_{15} thioureido, C_1-C_{15} phosphate, or C_1-C_{15} borate;

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_{15} alkyl, C_3-C_{15} cycloalkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylamino, C_2-C_{15} heterocyclicamino, C_6-C_{15} aryl, C_6-C_{15} arylamino, C_1-C_{15} alkylsulfonamido, C_2-C_{15} heterocyclic sulfonamido, and C_6-C_{15} arylsulfonamido group; and

R^7, R^8 and R^9 are each independently selected from the group consisting of hydrogen, cyano, nitro, trifluoromethyl, C_1-C_{15} alkyl, C_1-C_{15} alkoxy, C_1-C_{15} alkylthio, C_1-C_{15} alkoxycarbonyl, C_1-C_{15} aminocarbonyl, C_1-C_{15} carbonylamino, C_6-C_{15} aryl, C_6-C_{15} aryloxy, C_6-C_{15} aryloxycarbonyl, and C_2-C_{15} heterocyclic group;

R^{12} is H, C_1-C_{15} alkyl, C_3-C_{15} cycloalkyl, C_6-C_{15} aryl, C_4-C_{15} heteroaryl, C_1-C_{15} alkylcarbonyl, C_1-C_{15} alkoxycarbonyl, C_6-C_{15} aryloxycarbonyl, C_1-C_{15} alkylaminocarbonyl, C_6-C_{15} arylsulfonyl, C_1-C_{15} alkylaminosulfonyl, C_3-C_{15} cycloalkylaminosulfonyl, C_6-C_{15} arylaminosulfonyl, or C_3-C_{15} heterocyclicaminosulfonyl group.

12. The compound according to claim 11,

wherein:

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, 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 hydrogen, oxygen, halogen atom, cyano, 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, or C_2-C_{12} heterocyclic group.

wherein when "⋯⋯" is double bond, D, E, E^1 and G each is independently selected from the group consisting of nitrogen N or -C(Rc)- group; and R^{10} is oxygen or sulfur.

Ra, Rb and Rc are each independently selected from the group consisting of hydrogen, halogen atom, cyano, nitro, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_6-C_{12} aryl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, C_1-C_8 alkoxycarbonyl, C_6-C_{12} aryloxy, C_6-C_{12} aryloxycarbonyl, C_2-C_8 heterocyclic alkoxycarbonyl, C_2-C_{12} heterocyclic aryl, C_1-C_8 alkylamino, C_2-C_8 heterocyclic amino, C_6-C_{12} aryl amino, C_1-C_8 aminocarbonyl, C_1-C_8 amido, C_1-C_8 amidocarbonyl, C_1-C_8 carbonylamino, C_1-C_8 alkylsulfonamido, C_2–C_8 heterocyclic sulfonamido, C_6-C_{12} arylsulfonamido, or C_1-C_8 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;

Z^1 is hydroxyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, C_1-C_8 alkylamino, C_3-C_8 cycloalkylamino , C_2-C_8 heterocyclic amino, C_6-C_{12} aryl, C_6-C_{12} arylamino, C_4-C_{12} heteroarylamino, C_1-C_8 alkyl sulfonamido, C_3-C_8 cycloalkylsulfonamido, C_6-C_{12} arylsulfonamido, C_1-C_8 alkoxy sulfonamido, C_3-C_8 cycloalkoxy sulfonamido, C_1-C_8 alkylamino sulfonamido, C_3-C_8 cycloalkylamino sulfonamido, C_6-C_{12} arylamino sulfonamido, C_1-C_8 uramido, C_1-C_8 thioureido, C_1-C_8 phosphate, or C_1-C_8 borate;

R^1 and R^2 are each independently selected from the group consisting of hydrogen, hydroxyl, amino, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, C_1-C_8 alkoxycarbonyl, C_1-C_8 alkylamino, C_3-C_8 cycloalkylamino, C_2-C_8 heterocyclic amino, C_6-C_{12} arylamino, C_1-C_8

alkoxycarbonylamino, C_6-C_{12} aryloxycarbonylamino, C_1-C_8 alkylsulfonamido, C_3-C_8 cycloalkylsulfonamido, C_2-C_8 heterocyclic sulfonamido, C_6-C_{12} arylsulfonamido, and C_1-C_8 aminosulfonamido group;

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_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, C_1-C_8 alkylamino, C_2-C_8 heterocyclicamino, C_6-C_{12} aryl, C_6-C_{12} arylamino, C_1-C_8 alkylsulfonamido, C_2-C_8 heterocyclic sulfonamido, and C_6-C_{12} arylsulfonamido group; and

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;

R^{12} 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_6-C_{12} arylsulfonyl, C_1-C_8 alkylaminosulfonyl, C_3-C_8 cycloalkylaminosulfonyl, C_6-C_{12} arylaminosulfonyl, or C_3-C_8 heterocyclicaminosulfonyl group.

13. The compound according to claim 12,

Wherein:

p = 1;

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;

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;

W and X are each oxygen;

Y is N or CH;

Z^1 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^{12} is H, C_1-C_8 alkyl, C_1-C_6 alkoxycarbonyl, C_6-C_{10} aryloxycarbonyl, or C_6-C_{10} arylsulfonyl group.

14. A pharmaceutical composition comprising one or more compounds of claims 1- 13.

15. A pharmaceutical combination of one or more compounds of claims 1- 13 in a therapeutically effective dose and a second or a third medicament in a therapeutically effective dose.

16. A pharmaceutical combination of any compound of claims 1- 13 and any HIV inhibitor including but not limited to Ritonavir.

17. A pharmaceutical combination of any compound of claims 1- 13 and any hepatitis B virus (HBV) inhibitor including but not limited to Heptodin, Sebivo, Hepsera, Emtriva, Baraclude, or Viread.

18. Use of one or more compounds of claims 1- 13 for the manufacture of a therapeutically effective dose, or by using a combination of one or more of the compounds and a second or a third medicament in a therapeutically effective dose for HCV treatment.

19. Use of a combination of one or more compounds of claims 1- 13 with one or more of the following agent: (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 covered from above (1)-(12), for HCV treatment.