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(71) Applicant: **SUNSHINE LAKE PHARMA CO., LTD.** [CN/CN]; Northern Industrial Area, Songshan Lake, Dongguan, Guangdong 523000 (CN).

(72) Inventors: **ZHANG, Yingjun**; Dongyangguang Hi-tech Park, Zhen An Road No. 368, Shang Sha, Chang An Town, Dongguan, Guangdong 523871 (CN). **XIE, Hongming**; Dongyangguang Hi-tech Park, Zhen An Road No. 368, Shang Sha, Chang An Town, Dongguan, Guangdong 523871 (CN). **FANG, Qinghong**; Dongyangguang Hi-tech Park, Zhen An Road No. 368, Shang Sha, Chang An Town, Dongguan, Guangdong 523871 (CN). **LIU, Zhiqiang**; Dongyangguang Hi-tech Park, Zhen An Road No. 368, Shang Sha, Chang An Town, Dongguan, Guangdong 523871 (CN). **HU, Bailin**; Dongyangguang Hi-tech Park, Zhen An Road No. 368, Shang Sha, Chang An Town, Dongguan, Guangdong 523871 (CN). **ZHANG, Jiancun**; Dongyangguang Hi-tech Park, Zhen An Road No. 368, Shang Sha, Chang An Town, Dongguan, Guangdong 523871 (CN).

(74) Agent: **TSINGYIHUA INTELLECTUAL PROPERTY LLC**; Room 301, Trade Building, Zhaolanyuan, Tsinghua University, Qinghuayuan, Haidian District, Beijing 100084 (CN).

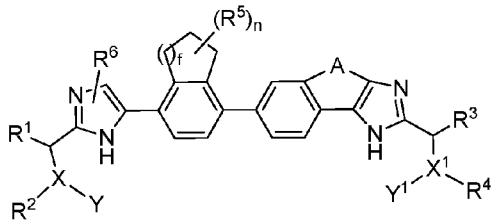
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(54) **Title**: COMPOUNDS AS HEPATITIS C VIRUS INHIBITORS AND PHARMACEUTICAL USES THEREOF



(I)

(57) **Abstract**: The invention provides compounds as hepatitis C virus inhibitors and pharmaceutical uses thereof. Specifically, the invention provides compounds of Formula (I) or a stereoisomer, a tautomer, an enantiomer, an N-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof, which can be used for treating HCV infection or hepatitis C disorders. Furthermore, the invention provides pharmaceutical compositions containing the compound disclosed herein and the methods of using of the compound or pharmaceutical compositions thereof in the treatment of HCV infection or HCV disorders.

WO 2016/141890 A1

Compounds As Hepatitis C Virus inhibitors And Pharmaceutical Uses Thereof

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to Chinese Patent Serial No. 201510108484.6, filed with the State Intellectual Property Office of China on March 12, 2015; and Chinese Patent Serial No. 201510422786.0, filed with the State Intellectual Property Office of China on July 18, 2015, both of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] The present invention belongs to pharmaceutical field, specificially, it relates to compounds and compositions thereof for treating Hepatitis C virus (HCV) infection, uses thereof, and application methods thereof.

BACKGROUND OF THE INVENTION

[0003] HCV is a major human pathogen, infecting an estimated 170 million persons worldwide — roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma. Chronic HCV infection is thus a major worldwide cause of liver-related premature mortality.

[0004] HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins via translation of a single, uninterrupted, open reading frame (ORF).

[0005] Considerable heterogeneity is found within nucleotide and encoded amino acid sequence throughout the HCV genome. At least seven major genotypes have been characterized, and more than 50 subtypes have been described. In HCV infected cells, viral RNA is translated into a polyprotein that is cleaved into ten individual proteins. At the amino terminus are structural proteins, followed by E1 and E2. Additionally, there are six non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B), which play a significant role in the HCV lifecycle (see, for example, Lindenbach et al., *Nature*, 2005, 436, 933-938).

[0006] The major genotypes of HCV differ in their distribution worldwide, and the clinical

significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the possible effect of genotypes on pathogenesis and therapy.

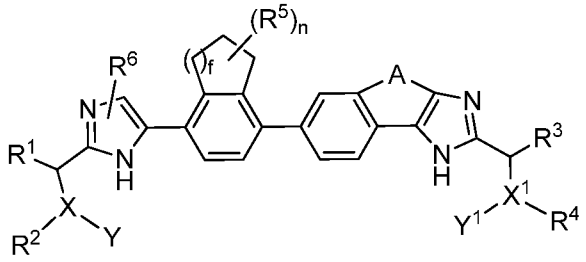
[0007] The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS) proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B) is effected by two viral proteases. The first one is believed to be a metalloprotease and cleaves at the NS2-NS3 junction; the second one is a serine protease within the *N*-terminal region of NS3 (also referred herein as NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, at the remaining NS4A-NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions, acting as a cofactor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficiency at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B (also referred to herein as HCV polymerase) is a RNA-dependent RNA polymerase that is involved in the replication of HCV.

SUMMARY OF THE INVENTION

[0008] The compounds disclosed herein are used for treating HCV-infected patients, and which selectively inhibit HCV viral replication.

[0009] The present invention refers to a method of anti HCV infection. The compounds or composition thereof provided herein have good inhibitory effect on HCV GT1a, GT1b, GT2a, GT3a, GT4b, GT5a, GT6a, and HCVGT1b L31V, GT1b Y93H resistant strains. Therefore, the invention provides durgs as genome-wide HCV inhibitors, which have anti drug-resistance effect and good bioavailability.

[0010] In one aspect, provided herein is a compound having Formula (I) or a stereoisomer, a geometric isomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



(I),

wherein A is $-(CR^7R^{7a})_m-$, $-CR^7=CR^{7a}-$, $-(CH_2)_nO-$, $-N=CR^7-$, $-NR^7-CR^7R^{7a}-$, $-CR^7R^{7a}-NR^7-$, $-O(CH_2)_n-$, $-CR^7=N-$, $-S(CH_2)_n-$, $-(CH_2)_nS-$ or $-NR^{9a}-$;

each of X and X^1 is independently N or CR^{7b};

each of Y and Y^1 is independently H, deuterium, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, $-C(=O)-(CR^8R^{8a})_t-N(R^9)-R^{10}$ or an α-amino acid group; and wherein the α-amino acid group is derived from isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophane, valine, alanine, asparagine, aspartic acid, glutamic acid, glutamine, proline, serine, *p*-tyrosine, arginine, histidine, cysteine, glycine, sarcosine, *N*,*N*-dimethylglycine, homoserine, norvaline, norleucine, ornithine, homocysteine, homophenylalanine, phenylglycine, *o*-tyrosine, *m*-tyrosine or hydroxyproline;

each of R^1, R^2, R^3 and R^4 is independently H, deuterium, alkyl, arylalkyl, cycloalkyl, heterocyclyl, heteroaryl or aryl; or R^1 and R^2, together with the X-CH to which they are attached, optionally form a 3-8 membered heterocyclic ring, 3-8 membered carbocyclic ring, fused bicyclic ring, fused heterobicyclic ring, spiro bicyclic ring or spiro heterobicyclic ring; or R^3 and R^4, together with the X^1-CH to which they are attached, optionally form a 3-8 membered heterocyclic ring, 3-8 membered carbocyclic ring, fused bicyclic ring, fused heterobicyclic ring, spiro bicyclic ring or spiro heterobicyclic ring;

each R^5 and R^6 is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, alkyl, haloalkyl, alkenyl, alkynyl, heterocyclyl, cycloalkyl, mercapto, nitro, aryl, heteroaryl, arylalkyl, alkoxyalkyl, alkoxy, arylamino, heteroarylamino, arylalkylamino, heteroarylalkylamino, heteroaryloxy, heteroarylalkyl, arylalkoxy, heteroarylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylamino, alkylacyl, alkylacyloxy, alkoxyacyl, heterocyclylalkylamino or aryloxy;

each R^7, R^{7a}, R^{7b}, R^8, R^{8a} and R^{9a} is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, deuterated alkyl, alkyl, haloalkyl, alkoxy, alkenyl, alkynyl, heterocyclyl, cycloalkyl, mercapto, nitro, aryl, heteroaryl, arylalkyl, alkoxyalkyl, heteroarylalkyl,

cycloalkylalkyl, heterocyclylalkyl, arylamino, heteroarylamino, arylalkylamino, heteroarylalkylamino, heteroaryloxy, arylalkoxy, heteroarylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylamino, alkyl-OC(=O)-, alkyl-C(=O)-, carbamoyl, alkyl-OS(=O)$_r$-, alkyl-S(=O)$_r$O-, alkyl-OS(=O)$_r$O-, alkyl-S(=O)$_r$-, heterocyclylalkylamino or aryloxy;

each of R^9 and R^{10} is independently H, deuterium, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, alkyl-OC(=O)-, alkyl-C(=O)-, carbamoyl, alkyl-OS(=O)$_r$-, alkyl-S(=O)$_r$O-, alkyl-S(=O)$_r$- or aminosulfonyl;

each f, n and t is independently 0, 1, 2, 3 or 4;

m is 1, 2, 3 or 4;

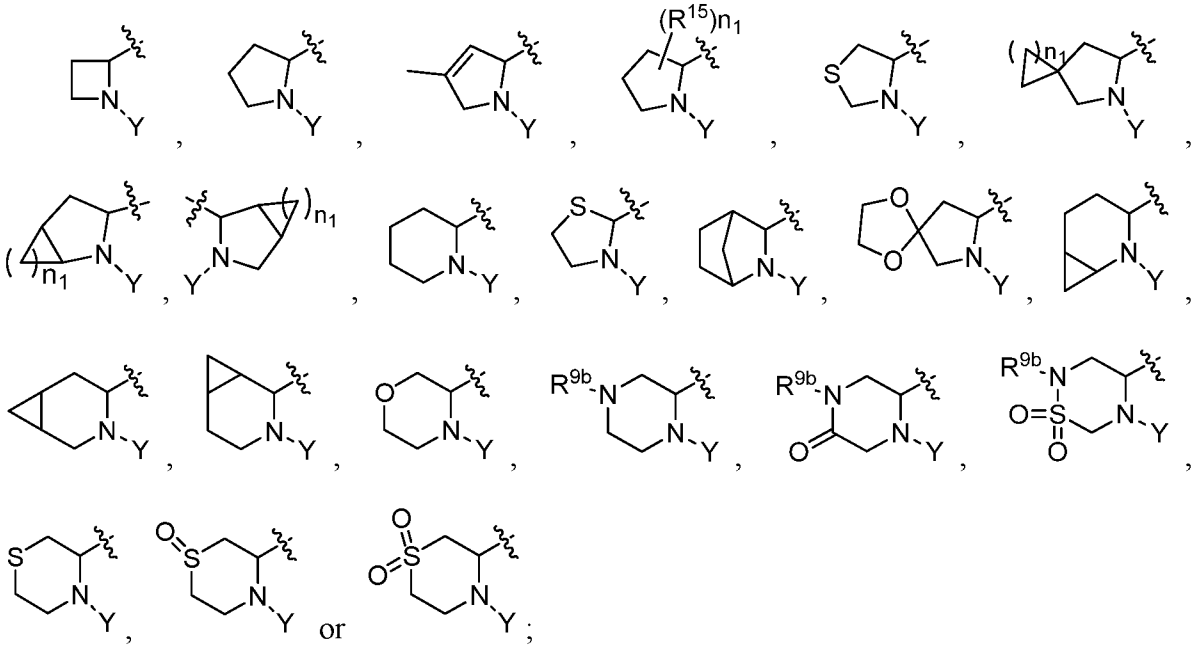
each r is independently 0, 1 or 2; and

wherein each alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, -C(=O)-(CR^{8}R^{8a})$_t$-N(R^9)-R^{10}, α-amino acid group, 3-8 membered heterocyclic ring, 3-8 membered carbocyclic ring, fused bicyclic ring, fused heterobicyclic ring, spiro bicyclic ring, spiro heterobicyclic ring, haloalkyl, alkenyl, alkynyl, alkoxyalkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl, arylamino, heteroarylamino, arylalkylamino, heteroarylalkylamino, aryloxy, heteroaryloxy, arylalkoxy, heteroarylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylamino, alkyl-OC(=O)-, alkyl-C(=O)-, carbamoyl, alkyl-OS(=O)$_r$-, alkyl-S(=O)$_r$O-, alkyl-S(=O)$_r$- and aminosulfonyl is independently and optionally substituted with one, two, three or four substituents selected from hydroxy, deuterium, amino, halogen, cyano, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, mercapto, nitro, aryloxy, arylamino, heteroaryloxy, heteroarylalkyl, oxo (=O), carboxy, hydroxy substituted alkoxy, hydroxy substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-S(=O)$_2$-, hydroxy substituted alkyl-S(=O)-, hydroxy substitued alkyl-S(=O)$_2$- or carboxy substituted alkoxy.

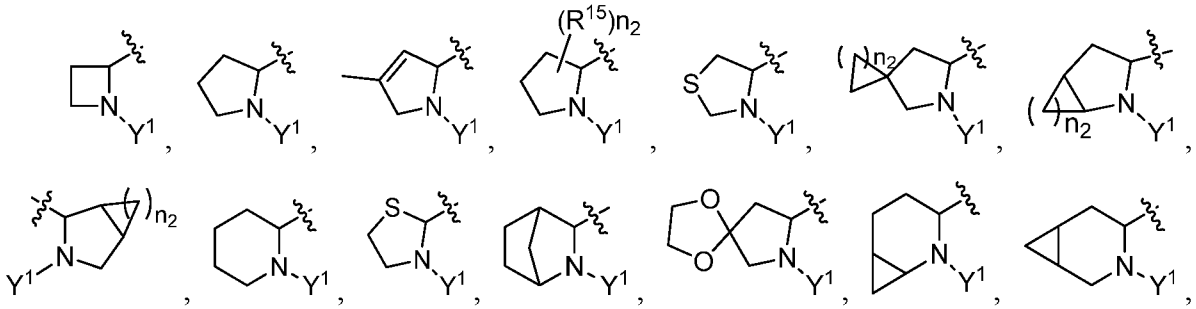
[0011] In certain embodiments, each of R^1, R^2, R^3 and R^4 is independently H, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6}-alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocyclyl, C_{1-9} heteroaryl or C_{6-10} aryl; or R^1 and R^2, together with the X-CH to which they are attached, optionally form a 3-8 membered heterocyclic ring, 3-8 membered carbocyclic ring, C_{5-12} fused bicyclic ring, C_{5-12} fused heterobicyclic ring, C_{5-12} spiro bicyclic ring or C_{5-12} spiro heterobicyclic ring; or R^3 and R^4, together with the X^1-CH

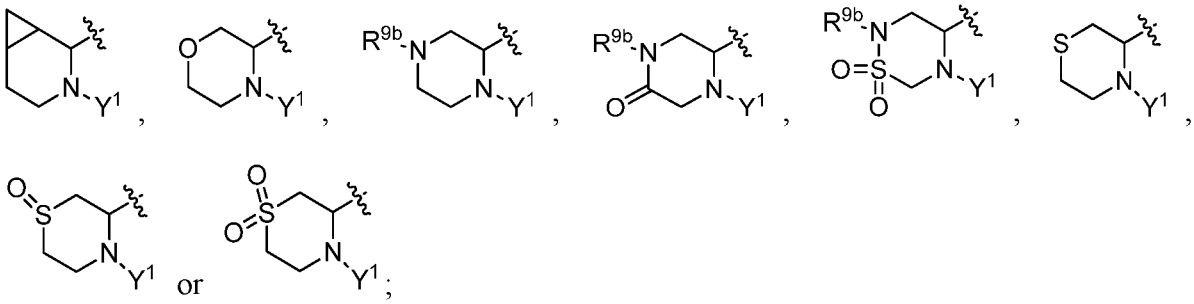
to which they are attached, optionally form a 3-8 membered heterocyclic ring, 3-8 membered carbocyclylic ring, C_{5-12} fused bicyclic ring, C_{5-12} fused heterobicyclic ring, C_{5-12} spiro bicyclic ring or C_{5-12} spiro heterobicyclic ring; and wherein the 3-8 membered heterocyclic ring, 3-8 membered carbocyclic ring, C_{5-12} fused bicyclic ring, C_{5-12} fused heterobicyclic ring, C_{5-12} spiro bicyclic ring or C_{5-12} spiro heterobicyclic ring is independently and optionally substituted with one, two, three or four substituents selected from H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} haloalkoxy-C_{1-6}-alkyl, C_{1-6} alkylamino, C_{1-6} alkylthio, C_{6-10} arylamino, C_{6-10} aryloxy, C_{1-9} heteroaryl, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{2-10} heterocyclyl.

[0012] In certain embodiments, R^1 and R^2, together with Y-X-CH to which they are attached, form one of the following groups:



R^3 and R^4, together with Y^1-X^1-CH to which they are attached, form one of the following groups:





wherein each R^{15} is independently H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} haloalkoxy-C_{1-6}-alkyl, C_{1-6} alkylamino, C_{1-6} alkylthio, C_{6-10} arylamino, C_{6-10} aryloxy, C_{1-9} heteroaryl, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-8} cycloalkyl or C_{2-10} heterocyclyl;

each R^{9b} is independently H, deuterium, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} alkylamino-C_{1-6}-alkyl, C_{1-6} alkylthio-C_{1-6}-alkyl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl, C_{6-10} aryl, C_{2-10} heterocyclyl or C_{3-8} cycloalkyl; and

each n_1 and n_2 is independently 1, 2, 3 or 4.

[0013] In other embodiments, each R^{15} is independently H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} alkoxy-C_{1-3}-alkyl, C_{1-3} haloalkoxy-C_{1-3}-alkyl, C_{1-3} alkylamino, C_{1-3} alkylthio, C_{6-10} arylamino, C_{6-10} aryloxy, C_{1-9} heteroaryl, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-3}-alkyl, C_{3-8} cycloalkyl or C_{2-10} heterocyclyl; and

each R^{9b} is independently H, deuterium, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} aminoalkyl, C_{1-3} alkoxy-C_{1-3}-alkyl, C_{1-3} alkylamino-C_{1-3}-alkyl, C_{1-3} alkylthio-C_{1-3}-alkyl, C_{6-10} aryl-C_{1-3}-alkyl, C_{1-9} heteroaryl, C_{6-10} aryl, C_{2-10} heterocyclyl or C_{3-8} cycloalkyl.

[0014] In other embodiments, each R^{15} is independently H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, methyl, ethyl, propyl, isopropyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, methoxymethyl, difluoromethoxymethyl, trifluoromethoxymethyl, ethoxymethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylamino, ethylamino, phenylamino, phenoxy, pyrrolyl, morpholinyl or piperazinyl; and

each R^{9b} is independently H, deuterium, methyl, ethyl, propyl, isopropyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxymethyl, ethoxymethyl, phenylmethyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[0015] In certain embodiments, each R^7, R^{7a}, R^{7b} and R^{9a} is independently H, deuterium, oxo

(=O), hydroxy, amino, F, Cl, Br, I, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-10} heterocyclyl, C_{3-8} cycloalkyl, mercapto, nitro, C_{6-10} aryl, C_{1-9} heteroaryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6} alkyl, C_{3-8} cycloalkyl-C_{1-6} alkyl, C_{2-10} heterocyclyl-C_{1-6} alkyl, C_{6-10} arylamino, C_{1-9} heteroarylamino, C_{6-10} aryl-C_{1-6}-alkylamino, C_{1-9} heteroaryl-C_{1-6}-alkylamino, C_{1-9} heteroaryloxy, C_{6-10} aryl-C_{1-6}-alkoxy, C_{1-9} heteroaryl-C_{1-6}-alkoxy, C_{2-10} heterocyclyloxy, C_{2-10} heterocyclyl-C_{1-6}-alkoxy, C_{2-10} heterocyclylamino, C_{1-6} alkyl-OC(=O)-, C_{1-6} alkyl-C(=O)-, carbamoyl, C_{1-6} alkyl-OS(=O)$_r$-, C_{1-6} alkyl-S(=O)$_r$O-, C_{1-6} alkyl-OS(=O)$_r$O-, C_{1-6} alkyl-S(=O)$_r$-, C_{2-10} heterocyclyl-C_{1-6}-alkylamino or C_{6-10} aryloxy; and

each r is independently 0, 1 or 2.

[0016] In certain embodiments, each of Y and Y^1 is independently H, deuterium, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl, C_{1-9} heteroaryl, C_{6-10} aryl-C_{1-6}-alkyl or -C(=O)-$(CR^8R^{8a})_t$-N(R^9)-R^{10};

each R^8 and R^{8a} is independently H, deuterium, hydroxy, amino, F, Cl, Br, I, cyano, C_{1-6} alkyl, C_{1-6} deuterated alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-10} heterocyclyl, C_{3-8} cycloalkyl, mercapto, nitro, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-8} cycloalkyl-C_{1-6}-alkyl, C_{2-10} heterocyclyl-C_{1-6}-alkyl, C_{6-10} arylamino, C_{1-9} heteroarylamino, C_{6-10} aryl-C_{1-6}-alkylamino, C_{1-9} heteroaryl-C_{1-6}-alkylamino, C_{1-9} heteroaryloxy, C_{6-10} aryl-C_{1-6}-alkoxy, C_{1-9} heteroaryl-C_{1-6}-alkoxy, C_{2-10} heterocyclyloxy, C_{2-10} heterocyclyl-C_{1-6}-alkoxy, C_{2-10} heterocyclylamino, C_{1-6} alkyl-OC(=O)-, C_{1-6} alkyl-C(=O)-, carbamoyl, C_{1-6} alkyl-OS(=O)$_r$-, C_{1-6} alkyl-S(=O)$_r$O-, C_{1-6} alkyl-OS(=O)$_r$O-, C_{1-6} alkyl-S(=O)$_r$-, C_{2-10} heterocyclyl-C_{1-6}-alkylamino or C_{6-10} aryloxy;

each of R^9 and R^{10} is independently H, deuterium, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl, C_{1-9} heteroaryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-6} alkyl-OC(=O)-, C_{1-6} alkyl-C(=O)-, carbamoyl, C_{1-6} alkyl-OS(=O)$_r$-, C_{1-6} alkyl-S(=O)$_r$O-, C_{1-6} alkyl-S(=O)$_r$- or aminosulfonyl;

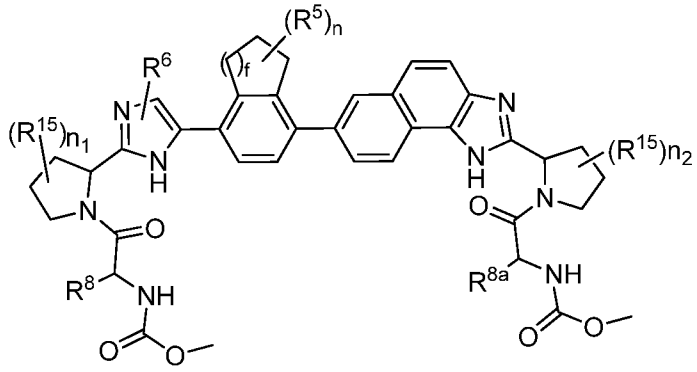
t is 0, 1, 2, 3 or 4; and

each r is independently 0, 1 or 2.

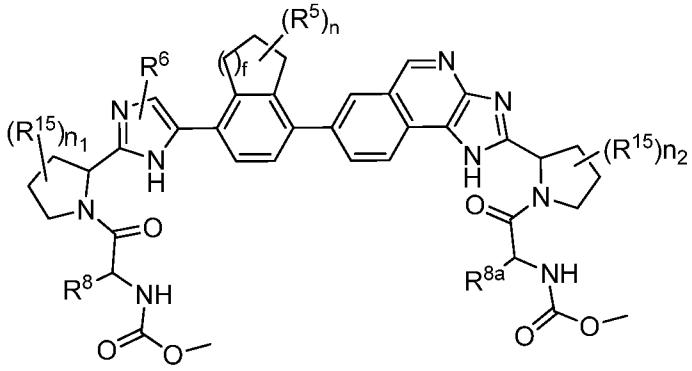
[0017] In certain embodiments, each of R^9 and R^{10} is independently H, deuterium, methyl, ethyl, isopropyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, methyl-OC(=O)-, ethyl-OC(=O)-, propyl-OC(=O)-, isopropyl-OC(=O)-, *t*-butyl-OC(=O)-, methyl-C(=O)-, ethyl-C(=O)-,

isopropyl-C(=O)-, *n*-butyl-C(=O)-, *i*-butyl-C(=O)-, carbamoyl, methylaminoformyl, ethylaminoformyl, methyl-OS(=O)$_2$-, cyclopropyl-OS(=O)$_2$-, methyl-S(=O)$_2$O-, cyclopropyl-S(=O)$_2$O- or aminosulfonyl.

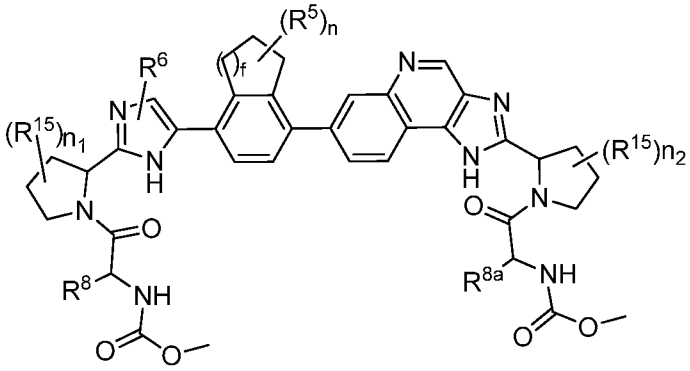
[0018] In certain embodiments, the compound of the invention has Formula (II), (IIa), (IIb) or (III), or a stereoisomer, a geometric isomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



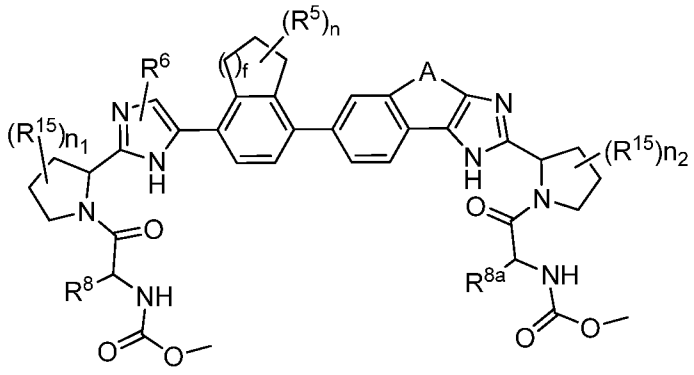
(II),



(IIa),



(IIb) or



(III),

wherein A is -O-, -S-, -NH-, $-CH_2-S-$, $-CH_2-O-$, $-CH_2-NH-$, $-O-CH_2-$, $-NH-CH_2-$, $-S-CH_2-$ or $-CH_2-CH_2-$;

each R^{15} is independently H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} alkoxy-C_{1-3}-alkyl, C_{1-3} haloalkoxy-C_{1-3}-alkyl, C_{1-3} alkylamino, C_{1-3} alkylthio, C_{6-10} arylamino, C_{6-10} aryloxy, C_{1-9} heteroaryl, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-3}-alkyl, C_{3-8} cycloalkyl or C_{2-10} heterocyclyl; and

each n_1 and n_2 is independently 1, 2, 3 or 4.

[0019] In other embodiments, each R^8 and R^{8a} is independently H, deuterium, hydroxy, amino, F, Cl, Br, I, cyano, C_{1-6} alkyl, C_{1-6} deuterated alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-10} heterocyclyl, C_{3-8} cycloalkyl, mercapto, nitro, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-8} cycloalkyl-C_{1-6}-alkyl, C_{2-10} heterocyclyl-C_{1-6}-alkyl, C_{6-10} arylamino, C_{1-9} heteroarylamino, C_{6-10} aryl-C_{1-6}-alkylamino, C_{1-9} heteroaryl-C_{1-6}-alkylamino, C_{1-9} heteroaryloxy, C_{6-10} aryl-C_{1-6}-alkoxy, C_{1-9} heteroaryl-C_{1-6}-alkoxy, C_{2-10} heterocyclyloxy, C_{2-10} heterocyclyl-C_{1-6}-alkoxy, C_{2-10} heterocyclylamino, C_{1-6} alkyl-OC(=O)-, C_{1-6} alkyl-C(=O)-, carbamoyl, C_{1-6} alkyl-$OS(=O)_r$-, C_{1-6} alkyl-$S(=O)_rO$-, C_{1-6} alkyl-$OS(=O)_rO$-, C_{1-6} alkyl-$S(=O)_r$-, C_{2-10} heterocyclyl-C_{1-6}-alkylamino or C_{6-10} aryloxy.

[0020] In other embodiments, each R^{15} is independently H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, methyl, ethyl, propyl, isopropyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, methoxymethyl, difluoromethoxymethyl, trifluoromethoxymethyl, ethoxymethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylamino, ethylamino, phenylamino, phenoxy, pyrrolyl, morpholinyl or piperazinyl.

[0021] In certain embodiments, each R^5 and R^6 is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-10} heterocyclyl, C_{3-8} cycloalkyl, mercapto, nitro, C_{6-10} aryl, C_{1-9} heteroaryl, C_{6-10} aryl-C_{1-6}-alkyl,

C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} alkoxy, C_{6-10} arylamino, C_{1-9} heteroarylamino, C_{6-10} aryl-C_{1-6}-alkylamino, C_{1-9} heteroaryl-C_{1-6}-alkylamino, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{6-10} aryl-C_{1-6}-alkoxy, C_{1-9} heteroaryl-C_{1-6}-alkoxy, C_{2-10} heterocyclyloxy, C_{2-10} heterocyclyl-C_{1-6}-alkoxy, C_{2-10} heterocyclylamino, C_{1-6} alkylacyl, C_{1-6} alkylacyloxy, C_{1-6} alkoxyacyl, C_{2-10} heterocyclyl-C_{1-6}-alkylamino or C_{6-10} aryloxy.

[0022] In other embodiments, each R^5 and R^6 is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, methyl, ethyl, propyl, isopropyl, *n*-butyl, *t*-butyl, trifluoromethyl, methoxymethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, phenoxy, phenylamino, mercapto or nitro.

[0023] In certain embodiments, each R^8 and R^{8a} is independently H, deuterium, hydroxy, amino, F, Cl, Br, I, cyano, methyl, ethyl, isopropyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, deuterated methyl, deuterated ethyl, deuterated propyl, deuterated isopropoxy, methoxy, ethoxy, isopropoxy, methoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 1-methoxypropyl, 2-methoxypropyl, 3-methoxypropyl, phenyl, pyranyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, trifluoromethyl, vinyl, allyl, ethynyl, morpholinyl, mercapto, nitro, phenylmethyl or phenylamino.

[0024] In another aspect, provided herein is a pharmaceutical composition comprising any one of the compounds described above.

[0025] In certain embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

[0026] In other embodiments, the pharmaceutical composition further comprises an anti-HCV agent other than the said compound, wherein the anti-HCV agent is interferon, ribavirin, IL-2, IL-6, IL-12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, imiquimod, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, rimantadine, bavituximab, hepatitis C immunogloblin, Civacir™, boceprevir, telaprevir, erlotinib, daclatasvir, simeprevir, asunaprevir, vaniprevir, faldaprevir, paritaprevir, danoprevir, sovaprevir, grazoprevir, vedroprevir, BZF-961, GS-9256, narlaprevir, ANA975, ombitasvir, EDP239, ravidasvir, velpatasvir, samatasvir, elbasvir, MK-8325, GSK-2336805, PPI-461, ciluprevir, sovaprevir, ACH-1095, VX-985, IDX-375,

VX-500, VX-813, PHX-1766, PHX-2054, IDX-136, IDX-316, modithromycin, VBY-376, TMC-649128, mericitabine, sofosbuvir, INX-189, IDX-184, IDX102, R-1479, UNX-08189, PSI-6130, PSI-938, PSI-879, nesbuvir, HCV-371, VCH-916, lomibuvir, MK-3281, dasabuvir, ABT-072, filibuvir, deleobuvir, tegobuvir, A-837093, JKT-109, Gl-59728, GL-60667, AZD-2795, TMC647055, ledipasvir, odalasvir, ritonavir, furaprevir, setrobuvir, alisporivir, BIT-225, AV-4025, ACH-3422, MK-2748, MK-8325, JNJ-47910382, ABP-560, TD-6450, TVB-2640, ID-12, PPI-383, A-848837, RG-7795, BC-2125, alloferon, nivolumab, WF-10, nitazoxanide, multiferon, nevirapine, ACH-3422, alisporivir, MK-3682, MK-8408, GS-9857, CD-AdNS3, pibrentasvir, RG-101, glecaprevir, BZF-961, INO-8000, MBL-HCV1, CIGB-230, TG-2349, procvax, CB-5300, miravirsen, chronvac-C, MK-1075, ACH-0143422, WS-007, MK-7680, MK-2248, MK-8408, IDX-21459, AV-4025, MK-8876, GSK-2878175, MBX-700, AL-335, JNJ-47910382, AL-704, ABP-560, TD-6450, EDP-239, SB-9200, ITX-5061, ID-12 or a combination thereof; wherein the interferon is interferon α-2b, pegylated interferon α, interferon α-2a, pegylated interferon α-2a, consensus interferon-α, interferon γ or a combination thereof.

[0027] In other embodiments, the anti-HCV agent is used for inhibiting HCV replication process and/or at least a function of a HCV viral protein; and wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral protein comprises metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in the HCV viral replication.

[0028] In another aspect, provided herein is use of the compound or the pharmaceutical composition disclosed herein in the manufacture of a medicament for inhibiting HCV replication process and/or at least a function of a HCV viral protein; wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral protein comprises metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in the HCV viral replication.

[0029] In another aspect, provided herein is use of the compound or the pharmaceutical composition disclosed herein in the manufacture of a medicament for preventing, managing,

treating or lessening the severity of HCV infection or a HCV disorder in a subject.

[0030] In another aspect, provided herein is the compound or the pharmaceutical composition disclosed herein for use in inhibiting HCV replication process and/or at least a function of a HCV viral protein; wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral protein comprises metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in the HCV viral replication.

[0031] In another aspect, provided herein is the compound or the pharmaceutical composition disclosed herein for use in preventing, managing, treating or lessening the severity of HCV infection or a HCV disorder in a subject.

[0032] In another aspect, provided herein is a method of inhibiting HCV replication process and/or at least a function of a HCV viral protein in a subject comprising administering to the subject the compound or the pharmaceutical composition disclosed herein; wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral protein comprises metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in the HCV viral replication.

[0033] In another aspect, provided herein is a method of preventing, managing, treating or lessening the severity of HCV infection or a HCV disorder in a subject, comprising administering to the subject the compound or the pharmaceutical composition disclosed herein.

[0034] In another aspect, provided herein is a method of preparing, separating or purifying the compound of Formula (I), (II), (IIa), (IIb) or (III).

[0035] The foregoing merely summarizes certain aspects disclosed herein and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS AND GENERAL TERMINOLOGY

[0036] Reference will now be made in detail to certain embodiments of the invention, examples

of which are illustrated in the accompanying structures and formulas. The invention is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described herein. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

[0037] It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

[0038] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one skilled in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference in their entirety.

[0039] As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, and *the Handbook of Chemistry and Physics*, 75th Ed. 1994. Additionally, general principles of organic chemistry are described in "*Organic Chemistry*", Thomas Sorrell, University Science Books, Sausalito: 1999, and Smith et al., "*March's Advanced Organic Chemistry*", John Wiley & Sons, New York: 2007, the entire contents of which are hereby incorporated by reference.

[0040] The grammatical articles "a", "an" and "the", as used herein, are intended to include "at least one" or "one or more" unless otherwise indicated herein or clearly contradicted by the context. Thus, the articles are used herein to refer to one or more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example, "a component" means one or more components, and thus, possibly, more than one component is contemplated and may be employed or used in an implementation of the described embodiments.

[0041] As used herein, the term "subject" refers to an animal. Typically the animal is a

mammal. A subject also refers to for example, primates (*e.g.*, humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

[0042] As used herein, "patient" refers to a human (including adults and children) or other animal. In one embodiment, "patient" refers to a human.

[0043] The term "comprise" is an open expression, it means comprising the contents disclosed herein, but don't exclude other contents.

[0044] "In certain embodiments", or "In other embodiments" used before the technical feature of the invention refers that the technical feature defined herein can optionally combine with other technical feature derived from other "In certain embodiments", or "In other embodiments" to form a complete technical feature.

[0045] "Stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. Stereoisomers include enantiomer, diastereomers, conformer (rotamer), geometric (cis/trans) isomer, atropisomer, etc.

[0046] "Chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

[0047] "Enantiomers" refers to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0048] "Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.* melting points, boling points, spectral properties or biological activities. Mixture of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography such as HPLC.

[0049] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "*Stereochemistry of Organic Compounds*", John Wiley & Sons, Inc., New York, 1994.

[0050] Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes

D and *L*, or *R* and *S*, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. A specific stereoisomer may be referred to as an enantiomer, and a mixture of such stereoisomers is called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process.

[0051] Any asymmetric atom (*e.g.,* carbon or the like) of the compound(s) disclosed herein can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R*,*S*)-configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration.

[0052] Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible stereoisomers or as mixtures thereof, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be *E* or *Z* configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a *cis*- or *trans*-configuration.

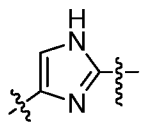
[0053] Any resulting mixtures of stereoisomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric isomers, enantiomers, diastereomers, for example, by chromatography and/or fractional crystallization.

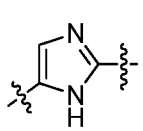
[0054] Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by methods known to those skilled in the art, *e.g.,* by separation of the diastereomeric salts thereof. Racemic products can also be resolved by chiral chromatography, *e.g.,* high performance liquid chromatography (HPLC) using a chiral adsorbent. Preferred enantiomers can also be prepared by asymmetric syntheses. See, for example, Jacques, et al., *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); *Principles of*

Asymmetric Synthesis (2nd Ed. Robert E. Gawley, Jeffrey Aubé, Elsevier, Oxford, UK, 2012); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972); Chiral Separation Techniques: *A Practical Approach* (Subramanian, G. Ed., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2007).

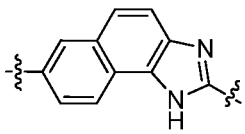
[0055] The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. Where tautomerization is possible (*e.g.* in solution), a chemical equilibrium of tautomers can be reached. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. The specific example of phenol-keto tautomerisms is pyridin-4-ol and pyridin-4(1*H*)-one tautomerism. Unless otherwise stated, all tautomeric forms of the compounds disclosed herein are within the scope of the invention.

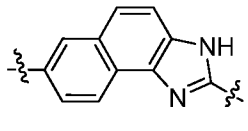
[0056] Annular tautomerism is a type of prototropic tautomerism wherein a proton can occupy two or more positions of a heterocyclic system. Both isomers coexsit in a balanced system at a relatively high rate of conversion to each other, for example, 1*H*- and 3*H*-imidazole; 1*H*-,2*H*- and 4*H*-1,2,4-triazole; 1*H*- and 2*H*-isoindole. The structural fragments refered herein, for example, Aa and Ab, or, Ba and Bb are annular tautomers. Because of coexist of the two isomers, for breif description, the invention only describes the structure of one of the annular tautomers at anywhere, that denotes the invention also describes the other structure of the annular tautomers. For example, though the invention only provides the compound having the fragment Aa, the tautomer of the compound having the frament Ab is also been provided at the same time; though the invention only provides the compound having the fragment Ba, the tautomer of the compound having the frament Bb is also been provided at the same time.


Aa


Ab

and


Ba


Bb

[0057] As described herein, compounds disclosed herein may optionally be substituted with one or more substituents, such as are illustrated generally below, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted". In general, the term "substituted" refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group. When more than one position in a given structure can be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position. When a substituent is defined by using "independently selected from..." means that the substituent is independent from each other, each selection of subsituent can be identical or different.

[0058] Furthermore, what need to be explained is that the phrase "each…is independently", "each…and…is independently", and "each of…and…is independently", unless otherwise stated, should be broadly understood. The specific options expressed by the same symbol are independent of each other in different groups; or the specific options expressed by the same symbol are independent of each other in same groups.

[0059] At various places in the present specification, substituents of compounds disclosed herein are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl.

[0060] At various places in the present specification, linking substituents are described. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists "alkyl" or "aryl" then it is understood that the "alkyl" or "aryl" represents a linking alkylene group or arylene group, respectively.

[0061] The term "alkyl" or "alkyl group" refers to a saturated linear or branched-chain monovalent hydrocarbon group of 1-20 carbon atoms, wherein the alkyl group is optionally substituted with one or more substituents described herein. Unless otherwise stated, the alkyl

group contains 1-20 carbon atoms. In some embodiments, the alkyl group contains 1-12 carbon atoms. In other embodiments, the alkyl group contains 1-6 carbon atoms. In still other embodiments, the alkyl group contains 1-4 carbon atoms. In yet other embodiments, the alkyl group contains 1-3 carbon atoms.

[0062] Some non-limiting examples of the alkyl group include, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), *n*-propyl (*n*-Pr, $-CH_2CH_2CH_3$), isopropyl (*i*-Pr, $-CH(CH_3)_2$), *n*-butyl (*n*-Bu, $-CH_2CH_2CH_2CH_3$), isobutyl (*i*-Bu, $-CH_2CH(CH_3)_2$), *sec*-butyl (*s*-Bu, $-CH(CH_3)CH_2CH_3$), *tert*-butyl (*t*-Bu, $-C(CH_3)_3$), *n*-pentyl ($-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-l-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-l-butyl ($-CH_2CH(CH_3)CH_2CH_3$), *n*-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, *n*-heptyl and *n*-octyl, *etc*.

[0063] The term "haloalkyl", or "haloalkoxy" refer to alkyl, or alkoxy, as the case may be, substituted with one or more halogen atoms. Some non-limiting examples of "haloalkyl" or "haloalkoxy" groups include trifluoromethyl, trifluoromethoxy, and the like.

[0064] The term "hydroxyalkyl" or "hydroxy substituted alkyl" refers to an alkyl group substituted with one or more hydroxy groups, wherein the alkyl is as defined herein. Some non-limiting examples include hydroxymethyl, hydroxyethyl, 1,2-dihydroxyethyl, and the like.

[0065] The term "aminoalkyl" or "amino substituted alkyl" refers to an alkyl group substituted with one or more amino groups, wherein the alkyl is as defined herein.

[0066] The term "alkoxy" refers to an alkyl group, as previously defined, attached to the parent molecular moiety via an oxygen atom. Unless otherwise specified, the alkoxy group contains 1-12 carbon atoms. In one embodiment, the alkoxy group contains 1-6 carbon atoms. In other embodiment, the alkoxy group contains 1-4 carbon atoms. In still other embodiment, the alkoxy group contains 1-3 carbon atoms. The alkoxy group may be optionally substituted with one or more substituents disclosed herein.

[0067] The term "alkoxyalkyl" refers to an alkoxy group attached to the rest of the molecule via an alkyl group, wherein the alkoxy and alkyl are as defined herein. Examples of alkoxyalkyl include, but are not limited to, methoxymethyl, methoxyethyl, 2-methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, 1-propoxymethyl, 2-propoxyethyl, 1-butoxymethyl, 2-methyl-1-propoxyethyl, 2-butoxymethyl, and the like.

[0068] The term "alkylacyl" or "alkoxyacyl" refers to an alkyl group or an alkoxy group, as previously defined, attached to the parent molecular moiety via acyl group, wherein the alkyl, alkoxy and acyl are as defined herein. In some embodiments, examples of these groups are, alkyl-OC(=O)-, alkyl-$OS(=O)_r$-, alkyl-C(=O)-, alkyl-$S(=O)_r$-.

[0069] The term "alkylacyloxy" or "alkoxyacyloxy" refers to an alkyl group or an alkoxy group, as previously defined, attached to the parent molecular moiety via acyloxy group, wherein the alkyl, alkoxy and acyloxy are as defined herein. In some embodiments, examples of these groups are, alkyl-C(=O)O-, alkyl-OC(=O)O-, alkyl-$S(=O)_rO$-, alkyl-$OS(=O)_rO$-.

[0070] The term "acyl" refers to the rest of the monovalent group of organic oxy-acid or inorganic oxy-acid when losing hydroxy group, and denotes R-M(=O)-. Generally, the M atom of acyl group is carbon and sulfur. The term "acyloxy" refers to an acyl group attached to the parent molecular moiety via oxygen atom, and denotes R-M(=O)O-.

[0071] The term "haloalkoxyalkyl" refers to a haloalkoxy group attached to the rest of the molecule through an alkyl group, wherein the haloalkoxy and alkyl are as defined herein.

[0072] The term "alkylamino" refers to "*N*-alkylamino" and "*N*,*N*-dialkylamino", wherein amino groups are independently substituted with one alkyl radical or two alkyl radicals, respectively. In some embodiments, the alkylamino group is a lower alkylamino group having one or two C_{1-6} alkyl groups attached to nitrogen atom. In other embodiments, the alkylamino group is a lower alkylamino group having one or two C_{1-3} alkyl groups attached to nitrogen atom. Some non-limiting examples of the alkylamino group include monoalkylamino or dialkylamino, such as *N*-methylamino, *N*-ethylamino, *N*,*N*-dimethylamino, *N*,*N*-diethylamino, and the like.

[0073] The term "alkylaminoalkyl" refers to an alkylamino group attached to the rest of the molecule through an alkyl group, wherein the alkylamino and alkyl are as defined herein.

[0074] The term "alkylthio" refers to an alkyl group, as previously defined, attached to the parent molecular moiety via a sulfur atom, wherein the alkyl is as defined herein.

[0075] The term "alkylthioalkyl" refers to an alkylthio group attached to the rest of the molecule via an alkyl group, wherein the alkylthio and alkyl are as defined herein.

[0076] The term "alkenyl" refers to a linear or branched-chain monovalent hydrocarbon radical of 2 to 12 carbon atoms with at least one site of unsaturation, *i.e.*, a carbon-carbon, sp^2 double bond, wherein the alkenyl radical may be optionally substituted with one or more substituents described herein, and includes radicals having "*cis*" and "*trans*" orientations, or alternatively, "*E*" and "*Z*" orientations. In some embodiments, the alkenyl contains 2 to 8 carbon atoms. In other embodiments, the alkenyl contains 2 to 6 carbon atoms. In still other embodiments, the alkenyl contains 2 to 4 carbon atoms. Examples of alkenyl groups include, but are not limited to, ethylenyl or vinyl (-CH=CH_2), allyl (-CH_2CH=CH_2), and the like.

[0077] The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical of 2 to 12 carbon atoms with at least one site of unsaturation, *i.e.*, a carbon-carbon, sp triple bond, wherein the alkynyl radical may be optionally substituted with one or more substituents described herein. In some embodiments, the alkynyl contains 2 to 8 carbon atoms. In other embodiments, the alkynyl contains 2 to 6 carbon atoms. In still other embodiments, the alkynyl contains 2 to 4 carbon atoms. Examples of such groups include, but are not limited to, ethynyl (-C≡CH), propargyl (-CH_2C≡CH), 1-propynyl (-C≡C-CH_3), and the like.

[0078] The term "cycloalkyl" refers to a monovalent or multivalent saturated ring having 3 to 12 carbon atoms as a monocyclic, bicyclic, or tricyclic ring system. In some embodiments, the cycloalkyl group contains 3 to 12 carbon atoms. In other embodiments, the cycloalkyl group contains 3 to 8 carbon atoms. In still other embodiments, the cycloalkyl group contains 3 to 6 carbon atoms.

[0079] The term "cycloalkylalkyl" refers to a cycloalkyl group attached to the rest of the molecule via an alkyl group, wherein the cycloalkyl and alkyl are as defined herein.

[0080] The terms "heterocyclyl" and "heterocycle" as used interchangeably herein refer to a saturated or partially unsaturated monocyclic, bicyclic or tricyclic ring containing 3-12 ring atoms of which at least one ring member is selected from nitrogen, sulfur and oxygen and at least one ring is nonaromatic. Unless otherwise specified, the heterocyclyl group may be carbon or nitrogen linked, and a -CH_2- group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to

N-oxide. Some non-limiting examples of the heterocyclyl group include oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, 1,3-dioxolanyl, dithiolanyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, dioxanyl, dithianyl, thioxanyl, homopiperazinyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, indolinyl, 1,2,3,4-tetrahydroisoquinolyl, 1,3-benzodioxolyl, 2-oxa-5-azabicyclo[2.2.1]hept-5-yl, and the like. Some non-limiting examples of heterocyclyl wherein $-CH_2-$ group is replaced by -C(=O)- moiety include 2-oxopyrrolidinyl, oxo-1,3-thiazolidinyl, 2-piperidinonyl, 3,5-dioxopiperidinyl, pyrimidinedione-yl, and the like. Some non-limited examples of heterocyclyl wherein the ring sulfur atom is oxidized is sulfolanyl, 1,1-dioxo-thiomorpholinyl. The heterocyclyl group may be optionally substituted with one or more substituents disclosed herein.

[0081] In certain embodiments, heterocyclyl may be 3-8 membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 3-8 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 3-8 ring atoms may be carbon or nitrogen linked, and a $-CH_2-$ group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Examples of the heterocyclyl group containing 4-7 ring atoms include, but are not limited to, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, 1,3-dioxolanyl, dithiolanyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, dioxanyl, dithianyl, thioxanyl, homopiperazinyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl and thiazepinyl, and the like. Some non-limiting examples of heterocyclyl wherein $-CH_2-$ group is replaced by -C(=O)- moiety include 2-oxopyrrolidinyl, oxo-1,3-thiazolidinyl, 2-piperidinonyl, 3,5-dioxopiperidinyl, pyrimidinedione-yl, and the like. Some non-limited examples of heterocyclyl wherein the ring sulfur atom is oxidized is sulfolanyl, 1,1-dioxo-thiomorpholinyl. The heterocyclyl group containing 3-8 ring atoms may be optionally

substituted with one or more substituents disclosed herein.

[0082] In other embodiments, heterocyclyl may be 4 membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 4 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 4 ring atoms may be carbon or nitrogen linked, and a $-CH_2-$ group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Some non-limiting examples of the heterocyclyl containing 4 ring atoms include azetidinyl, oxetanyl and thietanyl. The heterocyclyl group containing 4 ring atoms may be optionally substituted with one or more substituents disclosed herein.

[0083] In other embodiments, heterocyclyl may be 5 membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 5 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 5 ring atoms may be carbon or nitrogen linked, and a $-CH_2-$ group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Examples of 5 membered heterocyclyl include, but are not limited to, pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, 1,3-dioxolanyl, dithiolanyl. Some non-limiting examples of heterocyclyl wherein $-CH_2-$ group is replaced by -C(=O)- moiety include 2-oxopyrrolidinyl and oxo-1,3-thiazolidinyl. Some non-limited examples of heterocyclyl wherein the ring sulfur atom is oxidized include sulfolanyl. The heterocyclyl group containing 5 ring atoms may be optionally substituted with one or more substituents disclosed herein.

[0084] In other embodiments, heterocyclyl may be 6 membered heterocyclyl, which refers to a saturated or partially unsaturated monocyclic ring containing 6 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 6 ring atoms may be carbon or nitrogen linked, and a $-CH_2-$ group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Examples of the heterocyclyl group containing 6 ring atoms include, but are not limited to, tetrahydropyranyl,

dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, dioxanyl, dithianyl and thioxanyl. Some non-limiting examples of heterocyclyl wherein -CH_2- group is replaced by -C(=O)- moiety include 2-piperidinonyl, 3,5-dioxopiperidinyl and pyrimidinedionyl. Some non-limited examples of heterocyclyl wherein the ring sulfur atom is oxidized include 1,1-dioxo-thiomorpholinyl. The heterocyclyl group containing 6 ring atoms may be optionally substituted with one or more substituents disclosed herein.

[0085] In still other embodiments, heterocyclyl may be 7-12 membered heterocyclyl, which refers to a saturated or partially unsaturated spiro or fused bicyclyl ring containing 7-12 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur and oxygen. Unless otherwise specified, the heterocyclyl group containing 7-12 ring atoms may be carbon or nitrogen linked, and a -CH_2- group can be optionally replaced by a -C(=O)- group. In which, the sulfur can be optionally oxygenized to *S*-oxide and the nitrogen can be optionally oxygenized to *N*-oxide. Some non-limiting examples of the heterocyclyl containing 7-12 ring atoms include indolinyl, 1,2,3,4-tetrahydroisoquinolyl, 1,3-benzodioxolyl, 2-oxa-5-azabicyclo[2.2.1]hept-5-yl. The heterocyclyl group containing 7-12 ring atoms may be optionally substituted with one or more substituents disclosed herein.

[0086] The term “heterocyclyloxy” or “heterocyclylamino” refers to a heterocyclyl group attached to the rest part of the molecule through oxygen atom or nitrogen atom. Wherein the heterocyclyl group is as defined herein.

[0087] The term “heterocyclylalkyl” refers to an alkyl group substitued with heterocyclyl. The term “heterocyclylalkoxy” refers to an alkoxy group substitued with heterocyclyl, which attached to the rest of molecular through an oxygen atom. The term “heterocyclylalkylamino” refers to an alkylamino group substitued with heterocyclyl, which attached to the rest of molecular through nitrogen atom. Wherein the heterocyclyl group, alkyl group, alkoxy group and alkylamino group are as defined herein. Some non-limiting examples of such groups include pyrrol-2-yl-methyl, morpholin-4-yl-ethyl, morpholin-4-yl-ethoxy, piperazin-4-yl-ethoxy, piperidin-4-yl-ethylamino and the like.

[0088] The term “aryl” refers to monocyclic, bicyclic or tricyclic carbocyclic ring system having a total of six to fourteen ring members, or six to twelve ring members, or six to ten ring members, wherein at least one ring in the system is aromatic, wherein each ring in the system

contains 3 to 7 ring members and that has a single point or multipoint of attachment to the rest of the molecule. The term "aryl" and "aromatic ring" can be used interchangeably herein. Examples of aryl group may include phenyl, naphthyl and anthracene. The aryl group may be optionally and independently substituted with one or more substituents disclosed herein.

[0089] The term "aryloxy" refers to an aryl group, attached to the rest part of the molecule through oxygen atom. Wherein the aryl group is as defined herein.

[0090] The term "arylamino" refers to an amino group substituted with one or two aryl groups, wherein the aryl is as defined herein. Some non-limiting examples of such group included *N*-phenylamino. In some embodiments, the aryl group of the arylamino may be further substituted.

[0091] The term "arylalkyl" refers to an aryl substituted alkyl group, which attached to the rest of the molecule via an alkyl group; the term "arylalkoxy" refers to an aryl substituted alkoxy group, which attached to the rest of the molecule via oxygen atom; the term "arylalkylamino" refers to an aryl substituted alkylamino group, which attached to the rest of the molecule via the nitrogen atom. The aryl, alkyl, alkoxy and alkylamino are as defined herein.

[0092] The term "heteroaryl" refers to monocyclic, bicyclic or tricyclic ring system having a total of five to twelve ring members, or five to ten ring members, or five to six ring members, wherein at least one ring in the system is aromatic, and in which at least one ring member is selected from heteroatom, and wherein each ring in the system contains 5 to 7 ring members and that has a single point or multipoint of attachment to the rest of the molecule. The term "hetreroaryl" and "heteroaromatic ring" or "heteroaromatic compound" can be used interchangeably herein. The heteroaryl group is optionally substituted with one or more substituents disclosed herein. In one embodiment, a 5-10 membered heteroaryl comprises 1, 2, 3 or 4 heteroatoms independently selected from O, S and N. Some non-limiting examples of heteroaryl rings include 2-furanyl, 3-furanyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, *N*-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyridazinyl (*e.g.,* 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, tetrazolyl (*e.g.,* 5-tetrazolyl), triazolyl (*e.g.,* 2-triazolyl and 5-triazolyl), 2-thienyl, 3-thienyl, pyrazolyl (*e.g.,* 2-pyrazolyl), isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl,

1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, pyrazinyl, 1,3,5-triazinyl, and the following bicycles: benzimidazolyl, benzofuryl, benzothiophenyl, indolyl (*e.g.*, 2-indolyl), purinyl, quinolinyl (*e.g.*, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl), and isoquinolinyl (*e.g.*, 1-isoquinolinyl, 3-isoquinolinyl or 4-isoquinolinyl), imidazo[1,2-*a*]pyridyl, pyrazolo[1,5-*a*]pyridyl, pyrazolo[1,5-*a*]pyrimidyl, imidazo[1,2-*b*]pyridazinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl, or [1,2,4]triazolo[1,5-*a*]pyridyl, and the like.

[0093] The term "heteroaryloxy" refers to a heteroaryl group, attached to the rest part of the molecule through oxygen atom. Wherein the heteroaryl group is as defined herein.

[0094] The term "heteroarylamino" refers to an amino group substituted with one or two heteroaryl groups.

[0095] The term "heteroarylalkyl" refers to an heteroaryl substituted alkyl group, which attached to the rest of the molecule via an alkyl group; the term "heteroarylalkoxy" refers to an heteroaryl substituted alkoxy group, which attached to the rest of the molecule via the oxygen atom; the term "heteroarylalkylamino" refers to an heteroaryl substituted alkylamino group, which attached to the rest of the molecule via the nitrogen atom. Wherein the heteroaryl, alkyl, alkoxy and alkylamino are as defined herein.

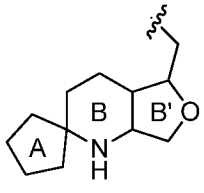
[0096] The term "carbocycle" or "carbocyclyl" as used interchangeably herein refers to a saturated or partially unsaturated monocyclic, bicyclic or tricyclic ring containing 3-12 ring atoms of which at least one ring is nonaromatic. Unless otherwise specified, a $-CH_2-$ group of the "carbocycle" or "carbocyclyl" group can be optionally replaced by a -C(=O)- group. In some embodiments, the carbocyclyl group contains 3 to 8 carbon atoms. In other embodiments, the carbocyclyl group contains 5 carbon atoms. In other embodiments, the carbocyclyl group contains 6 carbon atoms.

[0097] The terms "fused bicycle" and "fused bicyclyl" as used interchangeably herein refer to a monovalent or multivalent saturated or partially unsaturated bridged ring system, which refers to a nonaromatic bicyclic ring system. Such system can comprises independent or conjugated unsaturated units, but the core structure does not comprise aromatic ring or heteroaromatic ring (but aromatic group can be used as substituents of the fused bicyclyl group). In some embodiments, the fused bicyclyl group contains 5 to 12 carbon atoms.

[0098] The term "spiro bicyclyl" or "spiro bicyclic" as used interchangeably herein refers to a monovalent or multivalent saturated or partially unsaturated ring system, wherein a ring originats from a particular annular carbon of another ring. In some embodiments, the spiro bicyclyl group contains 5 to 12 carbon atoms.

[0099] For example, as described below, a saturated bridged ring system (ring B and B') is termed as "fused bicyclic", whereas ring A and ring B share an atom between the two saturated ring system, which terms as a "spirocyclyl" or "spiro bicyclyl".

[00100] When the ring atoms of "fused bicyclyl" or "spiro bicyclyl" contain at least one hetero atom, the "fused bicyclyl" or "spiro bicyclyl" is termed as "fused heterobicyclyl" or "spiro heterobicyclyl", each ring of which may be carbon or nitrogen linked. In some embodiments, the fused heterobicyclyl group or spiro heterobicyclyl group contains 5 to 12 carbon atoms.



(a)

[00101] The term "oxo" refers to that a group is substituted with =O.

[00102] The term "hydroxy" refers to -OH.

[00103] The term "amino" refers to $-NH_2$.

[00104] The term "cyano" refers to -CN.

[00105] The term "mercapto" refers to -SH.

[00106] The term "nitro" refers to $-NO_2$.

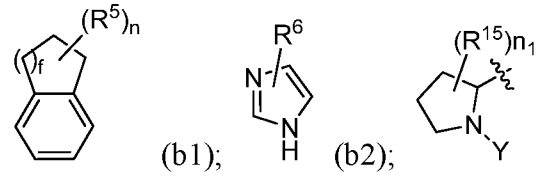
[00107] The term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br) or iodine (I).

[00108] The term "heteroatom" refers to one or more of oxygen, sulfur, nitrogen, phosphorus and silicon, including any oxidized form of nitrogen, sulfur, or phosphorus; the quaternized form of any basic nitrogen; or a substitutable nitrogen of a heterocyclic ring, for example, N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR (as in *N*-substituted pyrrolidinyl).

[00109] The term "n membered", where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6 membered heterocycloalkyl and 1,2,3,4-tetrahydro-naphthalene is an example of a 10 membered carbocyclyl group.

[00110] The term "unsaturated" refers to a moiety having one or more units of unsaturation.

[00111] As described herein, a bond drawn from a substituent to the center of one ring within a ring system (such as Formula (b1), (b2), (b3)) represents substitution of the substituent $(R^5)_n$, R^6 and $(R^{15})_{n1}$ at any substitutable position on the ring.



(b1); (b2); (b3);

[00112] The term "protecting group" or "PG" refers to a substituent that is commonly employed to block or protect a particular functionality while reacting with other functional groups on the compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, *t*-butoxy-carbonyl (BOC, Boc), benzyloxycarbonyl (CBZ, Cbz) and 9-fluorenylmethylenoxy-carbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include $-CH_2CH_2SO_2Ph$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxy-methyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(*p*-nitrophenylsulfonyl)ethyl, 2-(diphenylphosphino)ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see T. W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1991; and P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, 2005.

[00113] The term "prodrug" refers to a compound that is transformed in vivo into a compound of Formula (I), (II), (IIa), (IIb) and (III). Such a transformation can be affected, for example, by hydrolysis of the prodrug form in blood or enzymatic transformation to the parent form in blood or tissue. Prodrugs of the compounds disclosed herein may be, for example, esters. Some common esters which have been utilized as prodrugs are phenyl esters, aliphatic (C_{1-24}) esters, acyloxymethyl esters, carbonates, carbamates and amino acid esters. For example, a compound disclosed herein that contains a hydroxy group may be acylated at this position in its prodrug form. Other prodrug forms include phosphates, such as, those phosphate compounds derived from the phosphonation of a hydroxy group on the parent compound. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of

the A.C.S. Symposium Series, Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, J. Rautio et al., Prodrugs: Design and Clinical Applications, *Nature Review Drug Discovery*, 2008, 7, 255-270, and S. J. Hecker et al., Prodrugs of Phosphates and Phosphonates, *Journal of Medicinal Chemistry*, 2008, 51，2328-2345, all of which are incorporated herein by reference in their entireties.

[00114] A "metabolite" is a product produced through metabolism in the body of a specified compound or salt thereof. The metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein. Such products may result for example from oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzyme cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds disclosed herein, including metabolites produced by contacting a compound disclosed herein with a mammal for a sufficient time period.

[00115] A "pharmaceutically acceptable salts" refers to organic or inorganic salts of a compound disclosed herein. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66: 1-19, which is incorporated herein by reference. Some non-limiting examples of pharmaceutically acceptable and nontoxic salts include salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid and malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, laurylsulfate, malate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, stearate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}$ alkyl$)_4$ salts. This invention

also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, C_{1-8} sulfonate or aryl sulfonate.

[00116] The term "solvate" refers to an association or complex of one or more solvent molecules and a compound disclosed herein. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water.

[00117] As used herein, the term "treat", "treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (*i.e.,* slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treat", "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treat", "treating" or "treatment" refers to modulating the disease or disorder, either physically, (*e.g.,* stabilization of a discernible symptom), physiologically, (*e.g.,* stabilization of a physical parameter), or both. In yet another embodiment, "treat", "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

[00118] Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, *e.g.,* acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, subsalicylate, tartrate, tosylate and trifluoroacetate salts.

[00119] Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

[00120] Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like.

[00121] Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

[00122] Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

[00123] Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

[00124] The pharmaceutically acceptable salts of the present invention can be synthesized from a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, *e.g.*, in "*Remington's Pharmaceutical Sciences*", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "*Handbook of Pharmaceutical Salts: Properties, Selection, and Use*" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

[00125] Furthermore, the compounds disclosed herein, including their salts, can also be obtained in the form of their hydrates, or include other solvents such as ethanol, DMSO, and the like, used

for their crystallization. The compounds of the present invention may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms.

[00126] Any formula given herein is also intended to represent isotopically unenriched forms as well as isotopically enriched forms of the compounds. Any formula given herein is also intended to represent isotopically unenriched forms as well as isotopically enriched forms of the compounds. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chlorine, such as ^{2}H (deuterium, D), ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{18}F, ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I, respectively.

[00127] In another aspect, the compounds of the invention include isotopically enriched compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H, ^{14}C and ^{18}F, or those into which non-radioactive isotopes, such as ^{2}H and ^{13}C are present. Such isotopically enriched compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F-enriched compound may be particularly desirable for PET or SPECT studies. Isotopically-enriched compounds of Formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[00128] Further, substitution with heavier isotopes, particularly deuterium (*i.e.*,^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of Formula (I), (II), (IIa), (IIb) and (III). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term “isotopic enrichment factor” as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such

compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, acetone-d_6, DMSO-d_6.

[00129] In another aspect, provided herein is a compound for preparing the compound of Formula (I), (II), (IIa), (IIb) and (III).

[00130] In another aspect, provided herein is a method of preparing, separating or purifying the compound of Formula (I), (II), (IIa), (IIb) and (III).

[00131] The present invention provides a pharmaceutical composition comprising the compounds disclosed herein and pharmaceutically acceptable carrier, excipient, diluent, adjuvant, solvent or a combination thereof. In some embodiments, the pharmaceutical composition can be liquid, solid, semisolid, gel or spray.

[00132] By "combination" according to the invention, there is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound of the invention and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a cooperative, *e.g.* synergistic effect. The terms "co-administration" or "combined administration" or the like as used herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The term "pharmaceutical combination" as used herein refers to a product obtained from mixing or combining active ingredients, and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, *e.g.*, a compound of the invention and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, *e.g.*

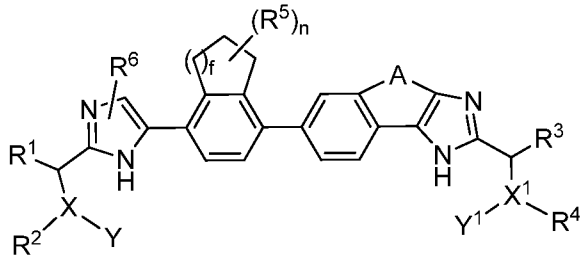
a compound of the invention and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the active ingredients in the body of the patient. The latter also applies to cocktail therapy, *e.g.*, the administration of three or more active ingredients.

[00133] It should be noted that the term of "inhibiting HCV viral protein" should be broadly understood, which comprises inhibiting the expression level of HCV viral protein, inhibiting activity level of HCV viral protein, viral assembly and egress level. The expression level of HCV protein includes but not limited to, translation level of the viral protein, posttranslational modification level of the viral protein, replication level of genetic material in offsprings and so on.

DESCRIPTION OF COMPOUNDS OF THE INVENTION

[00134] The present invention refers to a method of anti HCV infection. The compounds or composition thereof disclosed herein have good inhibitory effect on HCV infection.

[00135] In one aspect, provided herein is a compound having Formula (I) or a stereoisomer, a geometric isomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



(I),

wherein A is $-(CR^7R^{7a})_m-$, $-CR^7=CR^{7a}-$, $-(CH_2)_nO-$, $-N=CR^7-$, $-NR^7-CR^7R^{7a}-$, $-CR^7R^{7a}-NR^7-$, $-O(CH_2)_n-$, $-CR^7=N-$, $-S(CH_2)_n-$, $-(CH_2)_nS-$ or $-NR^{9a}-$;

each of X and X^1 is independently N or CR^{7b};

each of Y and Y^1 is independently H, deuterium, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, $-C(=O)-(CR^8R^{8a})_t-N(R^9)-R^{10}$ or an α-amino acid group; and wherein the α-amino acid group is derived from isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophane, valine, alanine, asparagine, aspartic acid, glutamic acid, glutamine, proline, serine, *p*-tyrosine, arginine, histidine, cysteine, glycine, sarcosine, *N*,*N*-dimethylglycine, homoserine, norvaline, norleucine, ornithine, homocysteine, homophenylalanine, phenylglycine,

o-tyrosine, *m*-tyrosine or hydroxyproline;

each of R^1, R^2, R^3 and R^4 is independently H, deuterium, alkyl, arylalkyl, cycloalkyl, heterocyclyl, heteroaryl or aryl; or R^1 and R^2, together with the X-CH to which they are attached, optionally form a 3-8 membered heterocyclic ring, 3-8 membered carbocyclic ring, fused bicyclic ring, fused heterobicyclic ring, spiro bicyclic ring or spiro heterobicyclic ring; or R^3 and R^4, together with the X^1-CH to which they are attached, optionally form a 3-8 membered heterocyclic ring, 3-8 membered carbocyclic ring, fused bicyclic ring, fused heterobicyclic ring, spiro bicyclic ring or spiro heterobicyclic ring;

each R^5 and R^6 is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, alkyl, haloalkyl, alkenyl, alkynyl, heterocyclyl, cycloalkyl, mercapto, nitro, aryl, heteroaryl, arylalkyl, alkoxyalkyl, alkoxy, arylamino, heteroarylamino, arylalkylamino, heteroarylalkylamino, heteroaryloxy, heteroarylalkyl, arylalkoxy, heteroarylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylamino, alkylacyl, alkylacyloxy, alkoxyacyl, heterocyclylalkylamino or aryloxy;

each R^7, R^{7a}, R^{7b}, R^8, R^{8a} and R^{9a} is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, deuterated alkyl, alkyl, haloalkyl, alkoxy, alkenyl, alkynyl, heterocyclyl, cycloalkyl, mercapto, nitro, aryl, heteroaryl, arylalkyl, alkoxyalkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl, arylamino, heteroarylamino, arylalkylamino, heteroarylalkylamino, heteroaryloxy, arylalkoxy, heteroarylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylamino, alkyl-OC(=O)-, alkyl-C(=O)-, carbamoyl, alkyl-$OS(=O)_r$-, alkyl-$S(=O)_rO$-, alkyl-$OS(=O)_rO$-, alkyl-$S(=O)_r$-, heterocyclylalkylamino or aryloxy;

each of R^9 and R^{10} is independently H, deuterium, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, alkyl-OC(=O)-, alkyl-C(=O)-, carbamoyl, alkyl-$OS(=O)_r$-, alkyl-$S(=O)_rO$-, alkyl-$S(=O)_r$- or aminosulfonyl;

each f, n and t is independently 0, 1, 2, 3 or 4;

m is 1, 2, 3 or 4;

each r is independently 0, 1 or 2; and

wherein each alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, -C(=O)-$(CR^8R^{8a})_t$-$N(R^9)$-R^{10}, α-amino acid group, 3-8 membered heterocyclic ring, 3-8

membered carbocyclic ring, fused bicyclic ring, fused heterobicyclic ring, spiro bicyclic ring, spiro heterobicyclic ring, haloalkyl, alkenyl, alkynyl, alkoxyalkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl, arylamino, heteroarylamino, arylalkylamino, heteroarylalkylamino, aryloxy, heteroaryloxy, arylalkoxy, heteroarylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylamino, alkyl-OC(=O)-, alkyl-C(=O)-, carbamoyl, alkyl-OS(=O)$_r$-, alkyl-S(=O)$_r$O-, alkyl-S(=O)$_r$- and aminosulfonyl is independently and optionally substituted with one, two, three or four substituents selected from hydroxy, deuterium, amino, halogen, cyano, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, mercapto, nitro, aryloxy, arylamino, heteroaryloxy, heteroarylalkyl, oxo (=O), carboxy, hydroxy substituted alkoxy, hydroxy substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-S(=O)$_2$-, hydroxy substituted alkyl-S(=O)-, hydroxy substitued alkyl-S(=O)$_2$- or carboxy substituted alkoxy.

[00136] In certain embodiments, A is -O-, -S-, -NH-, -CH_2-S-, -CH_2-O-, -CH_2-NH-, -O-CH_2-, -NH-CH_2-, -S-CH_2- or -CH_2-CH_2-.

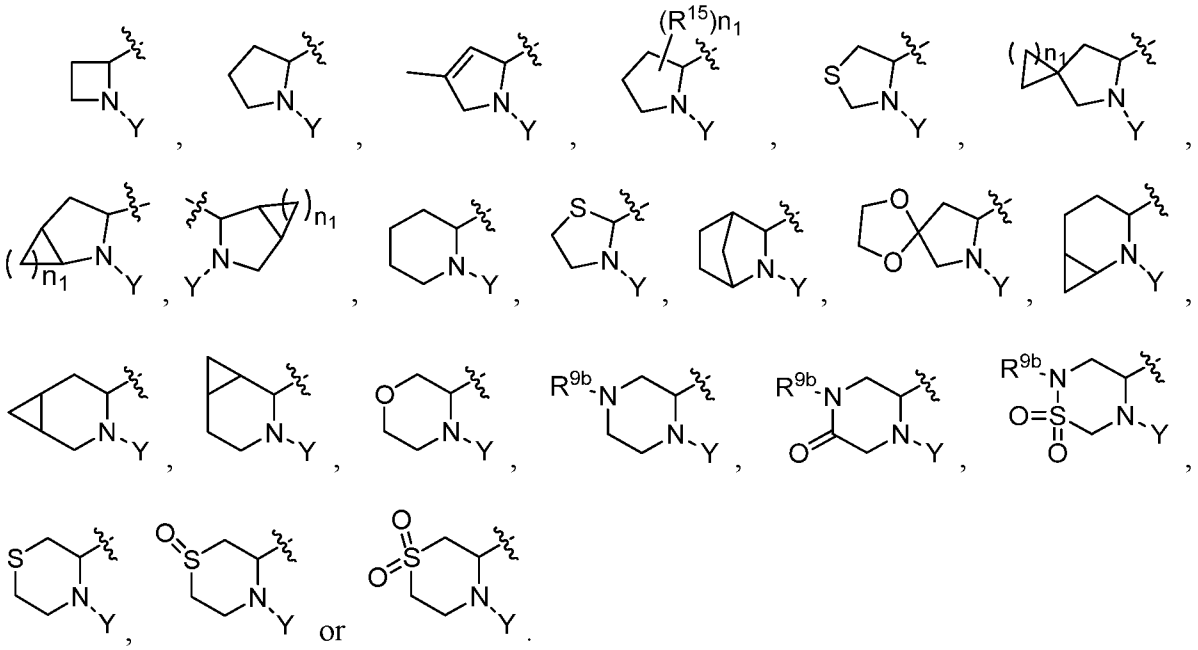
[00137] In certain embodiments, each R^5 and R^6 is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-10} heterocyclyl, C_{3-8} cycloalkyl, mercapto, nitro, C_{6-10} aryl, C_{1-9} heteroaryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} alkoxy, C_{6-10} arylamino, C_{1-9} heteroarylamino, C_{6-10} aryl-C_{1-6}-alkylamino, C_{1-9} heteroaryl-C_{1-6}-alkylamino, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{6-10} aryl-C_{1-6}-alkoxy, C_{1-9} heteroaryl-C_{1-6}-alkoxy, C_{2-10} heterocyclyloxy, C_{2-10} heterocyclyl-C_{1-6}-alkoxy, C_{2-10} heterocyclylamino, C_{1-6} alkylacyl, C_{1-6} alkylacyloxy, C_{1-6} alkoxyacyl, C_{2-10} heterocyclyl-C_{1-6}-alkylamino or C_{6-10} aryloxy.

[00138] In certain embodiments, each R^5 and R^6 is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-8} heterocyclyl, C_{3-8} cycloalkyl, mercapto, nitro, C_{6-10} aryl, C_{1-9} heteroaryl, C_{6-10} aryl-C_{1-3}-alkyl, C_{1-3} alkoxy-C_{1-3}-alkyl, C_{1-3} alkoxy, C_{6-10} arylamino, C_{1-9} heteroarylamino, C_{6-10} aryl-C_{1-3}-alkylamino, C_{1-9} heteroaryl-C_{1-3}-alkylamino, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-3}-alkyl, C_{6-10} aryl-C_{1-3}-alkoxy, C_{1-9} heteroaryl-C_{1-3}-alkoxy, C_{2-8} heterocyclyloxy, C_{2-8} heterocyclyl-C_{1-3}-alkoxy, C_{2-8} heterocyclylamino, C_{1-3} alkylacyl, C_{1-3} alkylacyloxy, C_{1-3} alkoxyacyl, C_{2-8} heterocyclyl-C_{1-3}-alkylamino or C_{6-10} aryloxy.

[00139] In certain embodiments, each R^5 and R^6 is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, methyl, ethyl, propyl, isopropyl, *n*-butyl, *t*-butyl, trifluoromethyl, methoxymethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, phenoxy, phenylamino, mercapto or nitro.

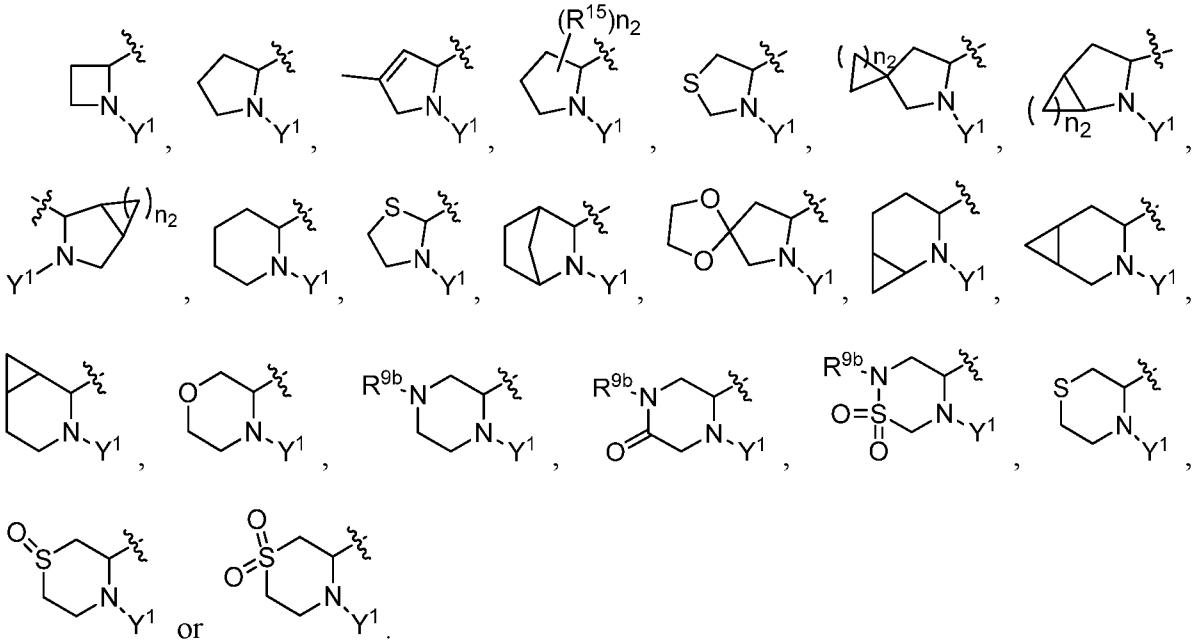
[00140] In certain embodiments, each of R^1, R^2, R^3 and R^4 is independently H, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6}-alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocyclyl, C_{1-9} heteroaryl or C_{6-10} aryl; or R^1 and R^2, together with the X-CH to which they are attached, optionally form a 3-8 membered heterocyclic ring, 3-8 membered carbocyclic ring, C_{5-12} fused bicyclic ring, C_{5-12} fused heterobicyclic ring, C_{5-12} spiro bicyclic ring or C_{5-12} spiro heterobicyclic ring; or R^3 and R^4, together with the X^1-CH to which they are attached, optionally form a 3-8 membered heterocyclic ring, 3-8 membered carbocyclylic ring, C_{5-12} fused bicyclic ring, C_{5-12} fused heterobicyclic ring, C_{5-12} spiro bicyclic ring or C_{5-12} spiro heterobicyclic ring; and wherein the 3-8 membered heterocyclic ring, 3-8 membered carbocyclic ring, C_{5-12} fused bicyclic ring, C_{5-12} fused heterobicyclic ring, C_{5-12} spiro bicyclic ring or C_{5-12} spiro heterobicyclic ring is independently and optionally substituted with one, two, three or four substituents selected from H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} haloalkoxy-C_{1-6}-alkyl, C_{1-6} alkylamino, C_{1-6} alkylthio, C_{6-10} arylamino, C_{6-10} aryloxy, C_{1-9} heteroaryl, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{2-10} heterocyclyl.

[00141] In certain embodiments, R^1 and R^2, together with Y-X-CH to which they are attached, form one of the following groups:



or

[00142] In certain embodiments, R^3 and R^4, together with Y^1-X^1-CH to which they are attached, form one of the following groups:



[00143] In certain embodiments, each R^{15} is independently H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} haloalkoxy-C_{1-6}-alkyl, C_{1-6} alkylamino, C_{1-6} alkylthio, C_{6-10} arylamino, C_{6-10} aryloxy, C_{1-9} heteroaryl, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-8} cycloalkyl or C_{2-10} heterocyclyl.

[00144] In certain embodiments, each R^{15} is independently H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} alkoxy-C_{1-3}-alkyl, C_{1-3} haloalkoxy-C_{1-3}-alkyl, C_{1-3} alkylamino, C_{1-3} alkylthio, C_{6-10} arylamino, C_{6-10} aryloxy, C_{1-9} heteroaryl, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-3}-alkyl, C_{3-8} cycloalkyl or C_{2-10} heterocyclyl.

[00145] In certain embodiments, each R^{15} is independently H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, methyl, ethyl, propyl, isopropyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, methoxymethyl, difluoromethoxymethyl, trifluoromethoxymethyl, ethoxymethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylamino, ethylamino, phenylamino, phenoxy, pyrrolyl, morpholinyl or piperazinyl.

[00146] In certain embodiments, each R^{9b} is independently H, deuterium, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} alkylamino-C_{1-6}-alkyl, C_{1-6} alkylthio-C_{1-6}-alkyl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl, C_{6-10} aryl, C_{2-10} heterocyclyl or C_{3-8} cycloalkyl.

[00147] In certain embodiments, each R^{9b} is independently H, deuterium, C_{1-3} alkyl, C_{1-3}

haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} aminoalkyl, C_{1-3} alkoxy-C_{1-3}-alkyl, C_{1-3} alkylamino-C_{1-3}-alkyl, C_{1-3} alkylthio-C_{1-3}-alkyl, C_{6-10} aryl-C_{1-3}-alkyl, C_{1-9} heteroaryl, C_{6-10} aryl, C_{2-10} heterocyclyl or C_{3-8} cycloalkyl.

[00148] In certain embodiments, each R^{9b} is independently H, deuterium, methyl, ethyl, propyl, isopropyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxymethyl, ethoxymethyl, phenylmethyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[00149] In certain embodiments, each R^{7}, R^{7a}, R^{7b} and R^{9a} is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-10} heterocyclyl, C_{3-8} cycloalkyl, mercapto, nitro, C_{6-10} aryl, C_{1-9} heteroaryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6} alkyl, C_{3-8} cycloalkyl-C_{1-6} alkyl, C_{2-10} heterocyclyl-C_{1-6} alkyl, C_{6-10} arylamino, C_{1-9} heteroarylamino, C_{6-10} aryl-C_{1-6}-alkylamino, C_{1-9} heteroaryl-C_{1-6}-alkylamino, C_{1-9} heteroaryloxy, C_{6-10} aryl-C_{1-6}-alkoxy, C_{1-9} heteroaryl-C_{1-6}-alkoxy, C_{2-10} heterocyclyloxy, C_{2-10} heterocyclyl-C_{1-6}-alkoxy, C_{2-10} heterocyclylamino, C_{1-6} alkyl-OC(=O)-, C_{1-6} alkyl-C(=O)-, carbamoyl, C_{1-6} alkyl-OS(=O)$_r$-, C_{1-6} alkyl-S(=O)$_r$O-, C_{1-6} alkyl-OS(=O)$_r$O-, C_{1-6} alkyl-S(=O)$_r$-, C_{2-10} heterocyclyl-C_{1-6}-alkylamino or C_{6-10} aryloxy; and

each r is independently 0, 1 or 2.

[00150] In certain embodiments, each R^{7}, R^{7a}, R^{7b} and R^{9a} is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-8} heterocyclyl, C_{3-8} cycloalkyl, mercapto, nitro, C_{6-10} aryl, C_{1-9} heteroaryl, C_{6-10} aryl-C_{1-3}-alkyl, C_{1-3} alkoxy-C_{1-3}-alkyl, C_{1-9} heteroaryl-C_{1-3} alkyl, C_{3-8} cycloalkyl-C_{1-3} alkyl, C_{2-8} heterocyclyl-C_{1-3} alkyl, C_{6-10} arylamino, C_{1-9} heteroarylamino, C_{6-10} aryl-C_{1-3}-alkylamino, C_{1-9} heteroaryl-C_{1-3}-alkylamino, C_{1-9} heteroaryloxy, C_{6-10} aryl-C_{1-3}-alkoxy, C_{1-9} heteroaryl-C_{1-3}-alkoxy, C_{2-8} heterocyclyloxy, C_{2-8} heterocyclyl-C_{1-3}-alkoxy, C_{2-8} heterocyclylamino, C_{1-3} alkyl-OC(=O)-, C_{1-3} alkyl-C(=O)-, carbamoyl, C_{1-3} alkyl-OS(=O)$_r$-, C_{1-3} alkyl-S(=O)$_r$O-, C_{1-3} alkyl-OS(=O)$_r$O-, C_{1-3} alkyl-S(=O)$_r$-, C_{2-8} heterocyclyl-C_{1-3}-alkylamino or C_{6-10} aryloxy; and

each r is independently 0, 1 or 2.

[00151] In certain embodiments, each R^{7}, R^{7a}, R^{7b} and R^{9a} is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, methyl, ethyl, vinyl, ethynyl, cyclopropyl or phenyl; and each r is independently 1 or 2.

[00152] In certain embodiments, each of Y and Y^1 is independently H, deuterium, C_{1-6} alkyl, C_{3-8}

cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl, C_{1-9} heteroaryl, C_{6-10} aryl-C_{1-6}-alkyl or -C(=O)-$(CR^8R^{8a})_t$-N(R^9)-R^{10};

[00153] In certain embodiments, each R^8 and R^{8a} is independently H, deuterium, hydroxy, amino, F, Cl, Br, I, cyano, C_{1-6} alkyl, C_{1-6} deuterated alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-10} heterocyclyl, C_{3-8} cycloalkyl, mercapto, nitro, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-8} cycloalkyl-C_{1-6}-alkyl, C_{2-10} heterocyclyl-C_{1-6}-alkyl, C_{6-10} arylamino, C_{1-9} heteroarylamino, C_{6-10} aryl-C_{1-6}-alkylamino, C_{1-9} heteroaryl-C_{1-6}-alkylamino, C_{1-9} heteroaryloxy, C_{6-10} aryl-C_{1-6}-alkoxy, C_{1-9} heteroaryl-C_{1-6}-alkoxy, C_{2-10} heterocyclyloxy, C_{2-10} heterocyclyl-C_{1-6}-alkoxy, C_{2-10} heterocyclylamino, C_{1-6} alkylacyl, C_{1-6} alkylacyloxy, C_{1-6} alkoxyacyl, C_{1-6} alkylsulfonyl, C_{1-6} alkoxysulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfinyloxy, C_{1-6} alkyl-OC(=O)-, C_{1-6} alkyl-C(=O)-, carbamoyl, C_{1-6} alkyl-$OS(=O)_r$-, C_{1-6} alkyl-$S(=O)_rO$-, C_{1-6} alkyl-$OS(=O)_rO$-, C_{1-6} alkyl-$S(=O)_r$-, C_{2-10} heterocyclyl-C_{1-6}-alkylamino or C_{6-10} aryloxy.

[00154] In certain embodiments, each R^8 and R^{8a} is independently H, deuterium, hydroxy, amino, F, Cl, Br, I, cyano, C_{1-4} alkyl, C_{1-4} deuterated alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-8} heterocyclyl, C_{3-8} cycloalkyl, mercapto, nitro, C_{6-10} aryl-C_{1-3}-alkyl, C_{1-3} alkoxy-C_{1-3}-alkyl, C_{1-9} heteroaryl-C_{1-3}-alkyl, C_{3-8} cycloalkyl-C_{1-3}-alkyl, C_{2-8} heterocyclyl-C_{1-3}-alkyl, C_{6-10} arylamino, C_{1-9} heteroarylamino, C_{6-10} aryl-C_{1-3}-alkylamino, C_{1-9} heteroaryl-C_{1-3}-alkylamino, C_{1-9} heteroaryloxy, C_{6-10} aryl-C_{1-3}-alkoxy, C_{1-9} heteroaryl-C_{1-3}-alkoxy, C_{2-8} heterocyclyloxy, C_{2-8} heterocyclyl-C_{1-3}-alkoxy, C_{2-8} heterocyclylamino, C_{1-3} alkylacyl, C_{1-3} alkylacyloxy, C_{1-3} alkoxyacyl, C_{1-3} alkylsulfonyl, C_{1-3} alkoxysulfonyl, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyloxy, C_{1-3} alkylsulfinyloxy, C_{1-4} alkyl-OC(=O)-, C_{1-4} alkyl-C(=O)-, carbamoyl, C_{1-4} alkyl-$OS(=O)_r$-, C_{1-4} alkyl-$S(=O)_rO$-, C_{1-4} alkyl-$OS(=O)_rO$-, C_{1-4} alkyl-$S(=O)_r$-, C_{2-8} heterocyclyl-C_{1-3}-alkylamino or C_{6-10} aryloxy.

[00155] In certain embodiments, each R^8 and R^{8a} is independently H, deuterium, hydroxy, amino, F, Cl, Br, I, cyano, methyl, ethyl, isopropyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, deuterated methyl, deuterated ethyl, deuterated propyl, deuterated isopropoxy, methoxy, ethoxy, isopropoxy, methoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 1-methoxypropyl, 2-methoxypropyl, 3-methoxypropyl, phenyl, pyranyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, trifluoromethyl, vinyl, allyl, ethynyl, morpholinyl, mercapto, nitro, phenylmethyl or

phenylamino.

[00156] In certain embodiments, each of R^9 and R^{10} is independently H, deuterium, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl, C_{1-9} heteroaryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-6} alkyl-OC(=O)-, C_{1-6} alkyl-C(=O)-, carbamoyl, C_{1-6} alkyl-OS(=O)$_r$-, C_{1-6} alkyl-S(=O)$_r$O-, C_{1-6} alkyl-S(=O)$_r$- or aminosulfonyl.

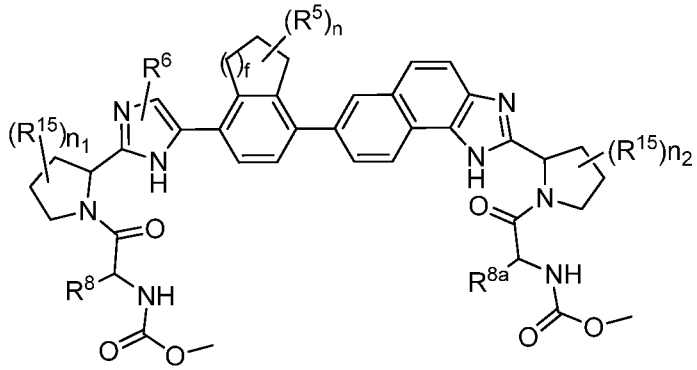
[00157] In certain embodiments, each of R^9 and R^{10} is independently H, deuterium, methyl, ethyl, isopropyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, methyl-OC(=O)-, ethyl-OC(=O)-, propyl-OC(=O)-, isopropyl-OC(=O)-, *t*-butyl-OC(=O)-, methyl-C(=O)-, ethyl-C(=O)-, isopropyl-C(=O)-, *n*-butyl-C(=O)-, *i*-butyl-C(=O)-, carbamoyl, methylaminoformyl, ethylaminoformyl, methyl-OS(=O)$_2$-, cyclopropyl-OS(=O)$_2$-, methyl-S(=O)$_2$O-, cyclopropyl-S(=O)$_2$O- or aminosulfonyl.

[00158] In certain embodiments, t is 0, 1, 2, 3 or 4.

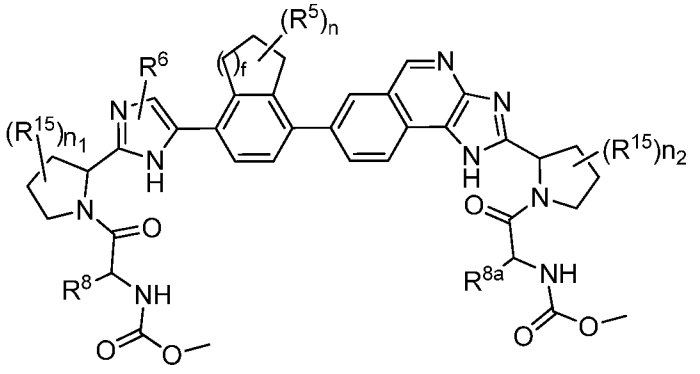
[00159] In certain embodiments, each r is independently 0, 1 or 2.

[00160] In certain embodiments, each n_1 and n_2 is independently 1, 2, 3 or 4.

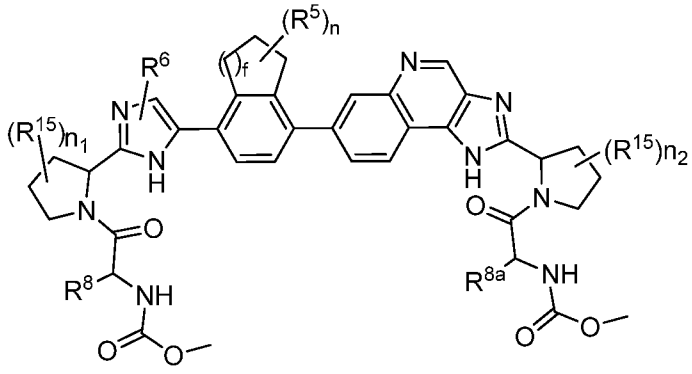
[00161] In certain embodiments, the compound of the invention has Formula (II), (IIa), (IIb) or (III), or a stereoisomer, a geometric isomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



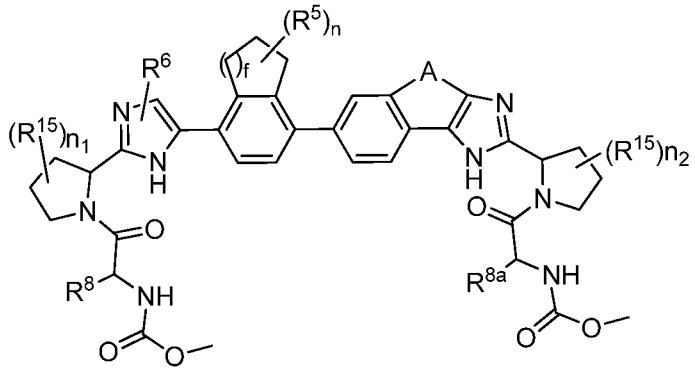
(II),



(IIa),

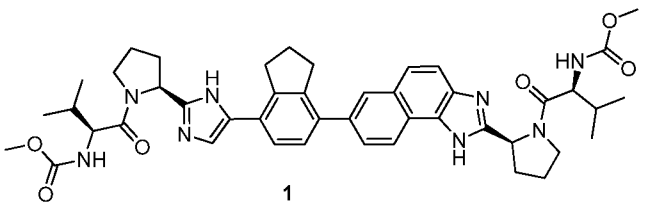


(IIb) or

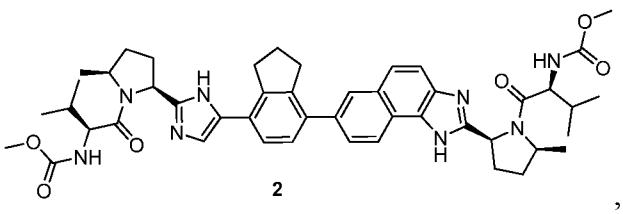


(III).

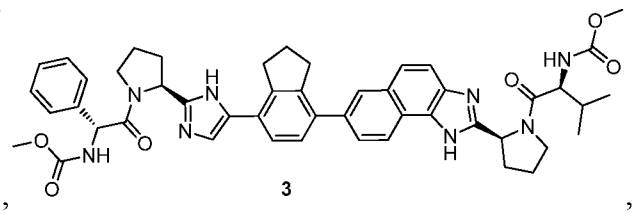
[00162] In certain embodiments, the compound of the invention has one of the following structures, or a stereoisomer, a geometric isomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof:



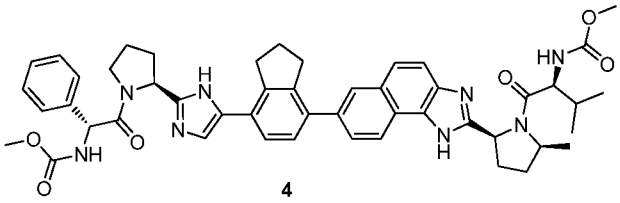
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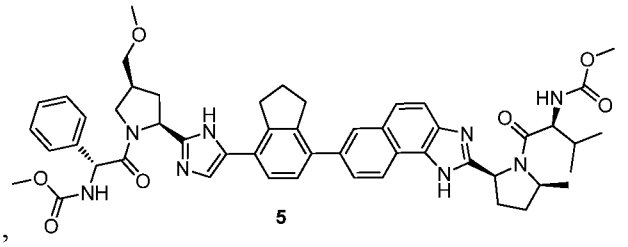
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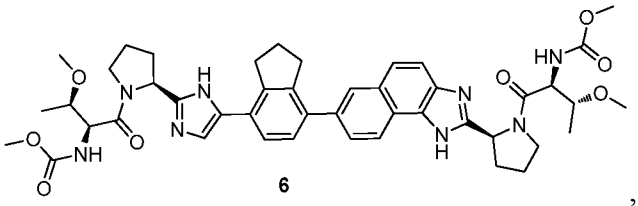
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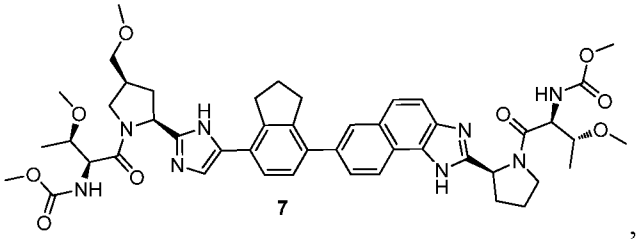
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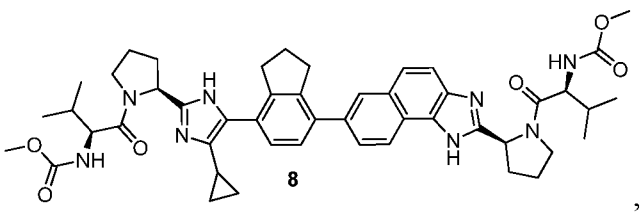
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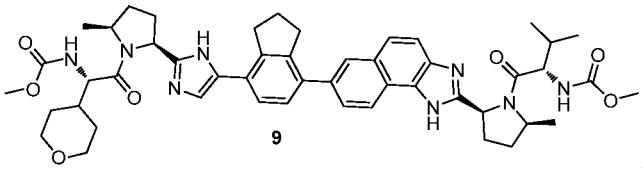
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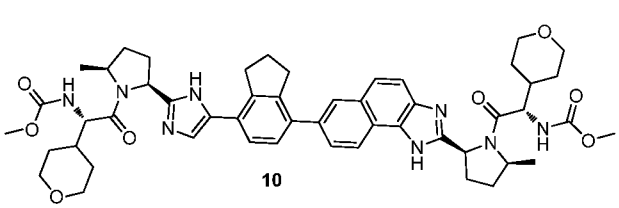
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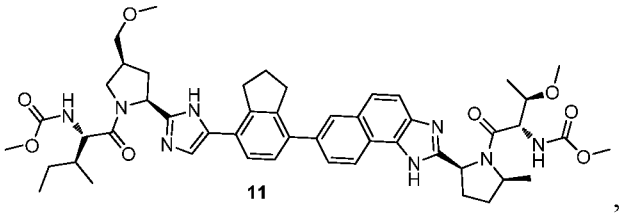
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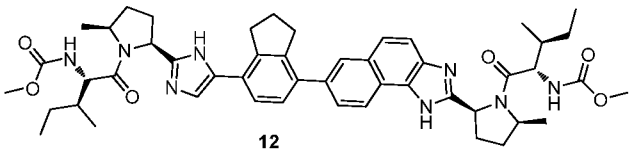
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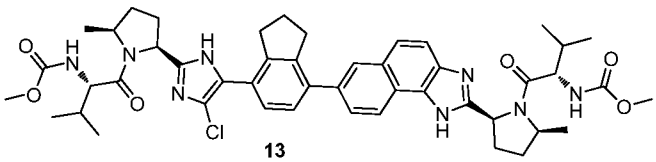
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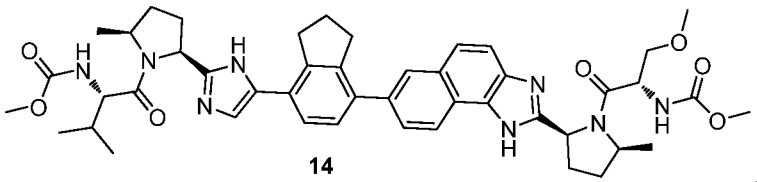
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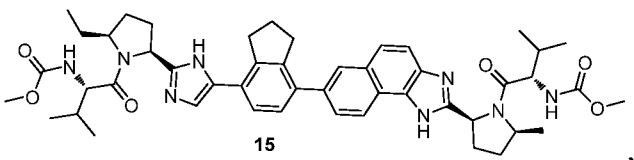
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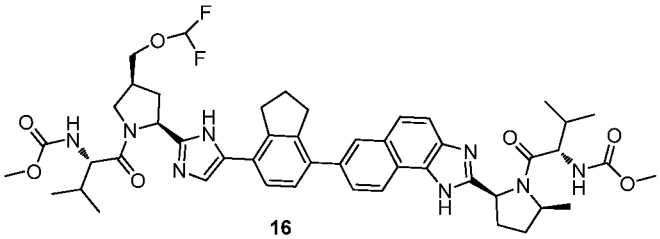
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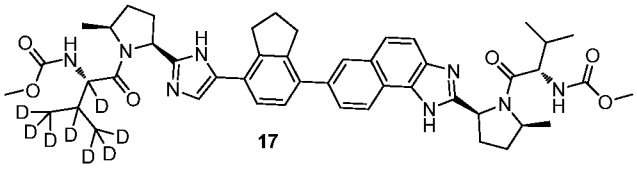
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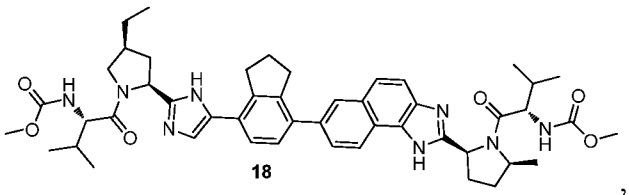
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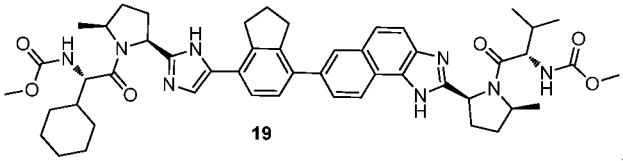
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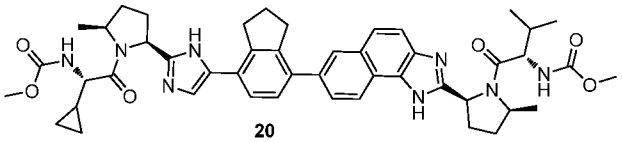
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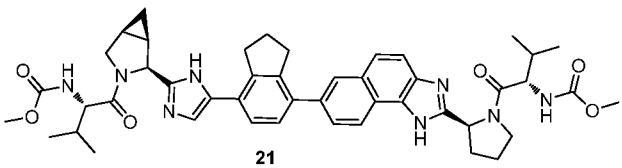
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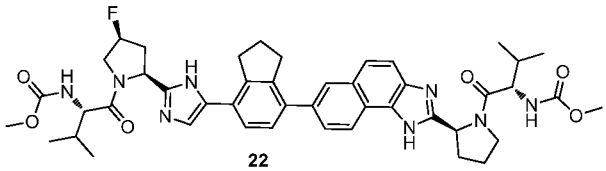
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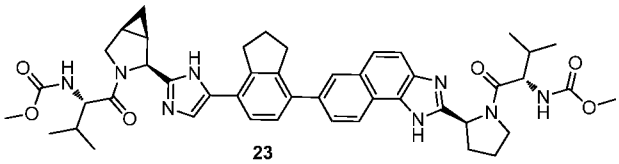
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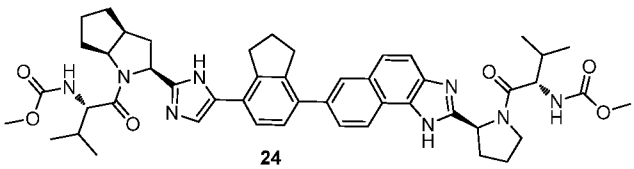
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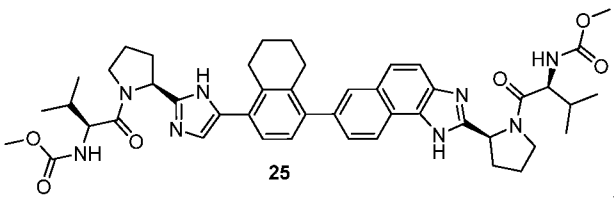
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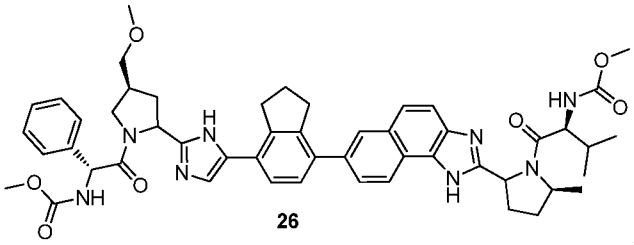
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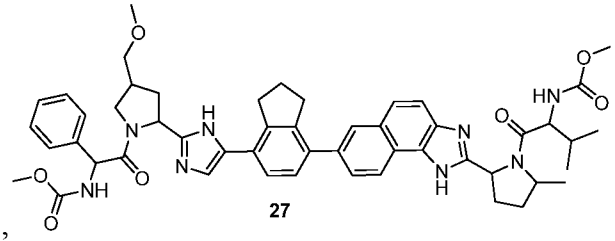


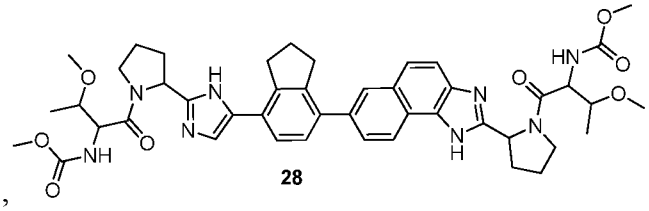
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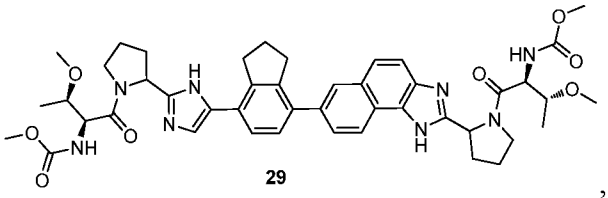


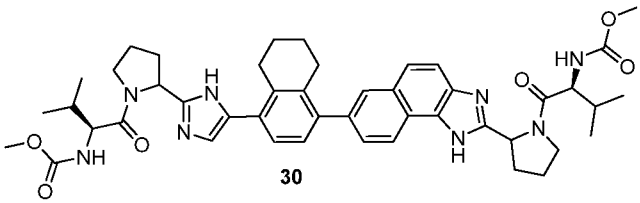
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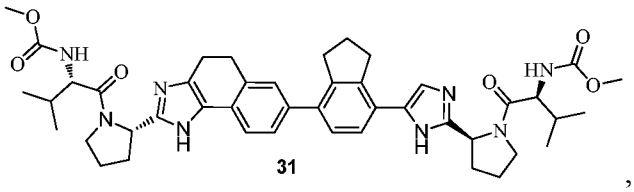

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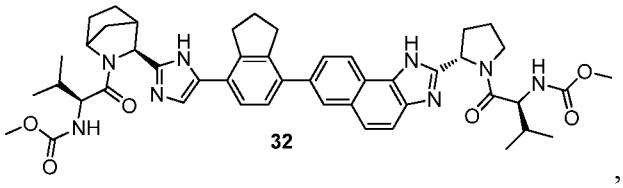

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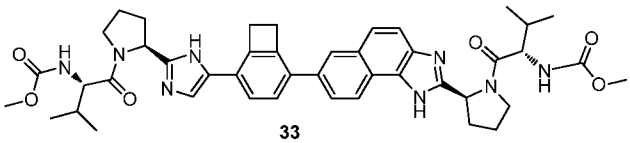

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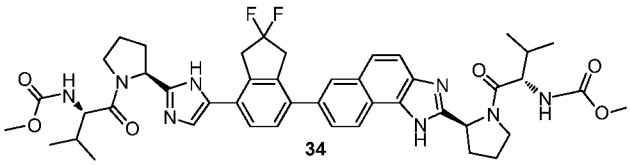

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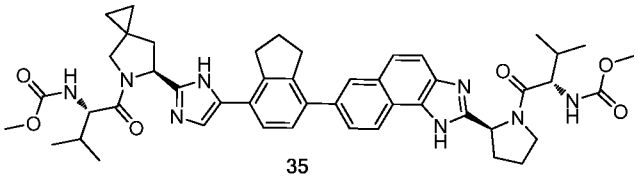

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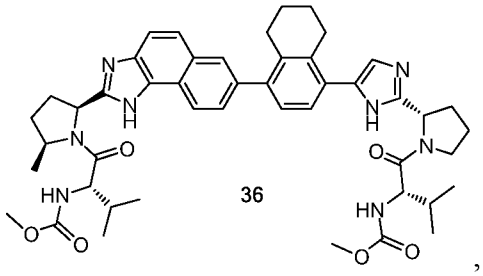

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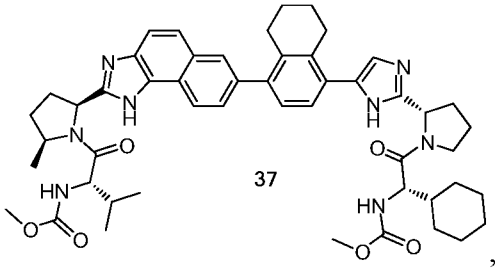

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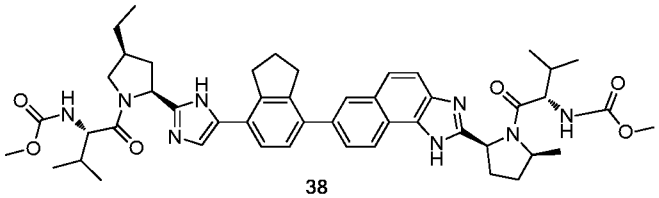
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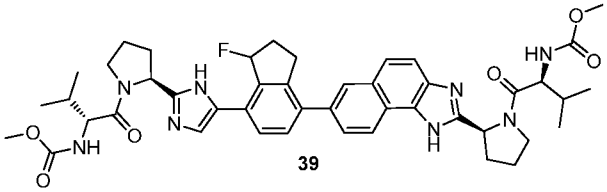
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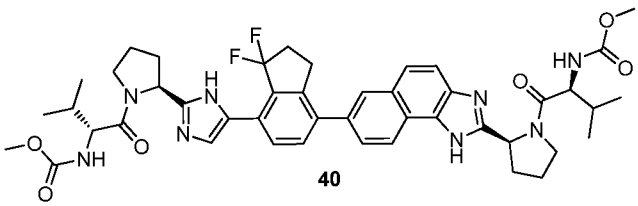
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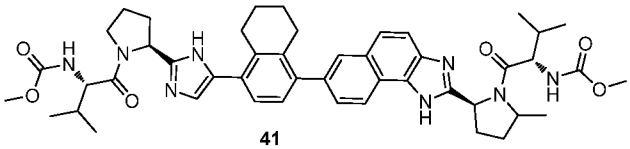
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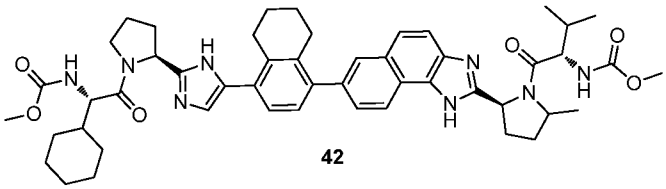
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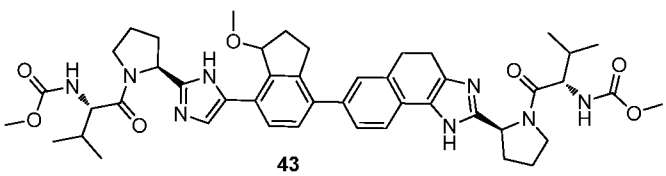
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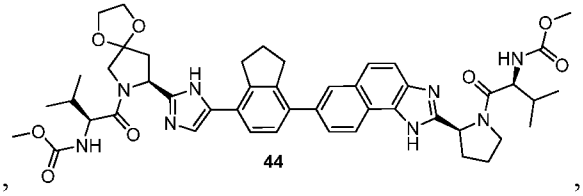
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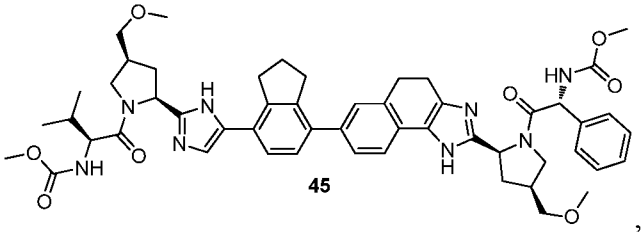
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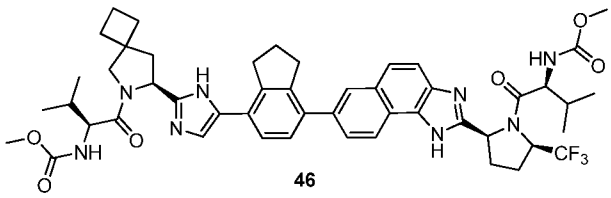
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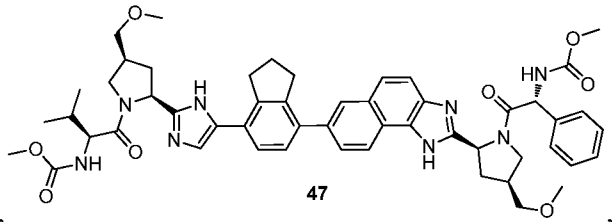
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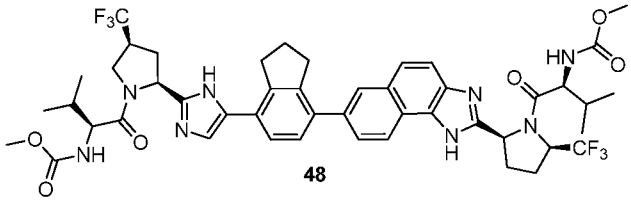
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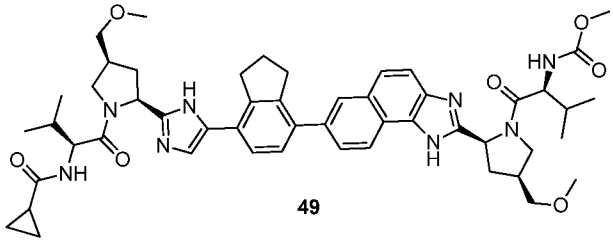
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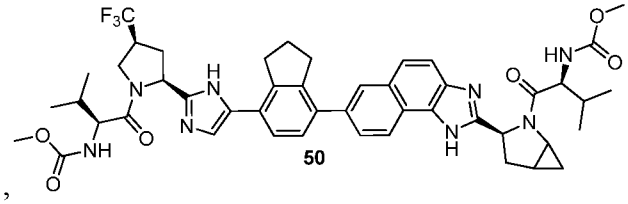
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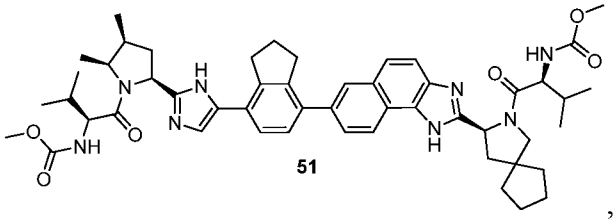

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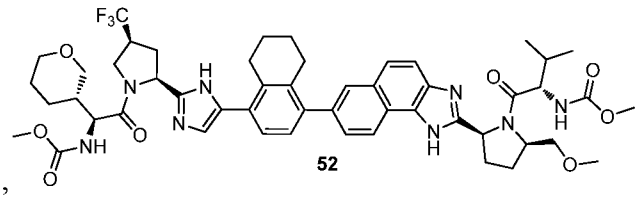

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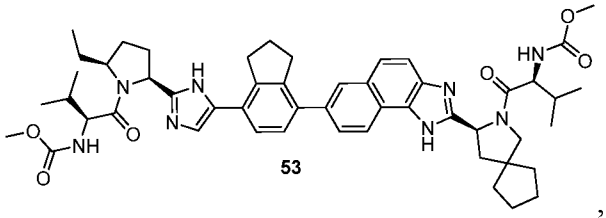

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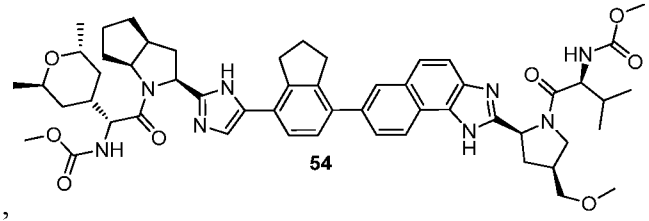

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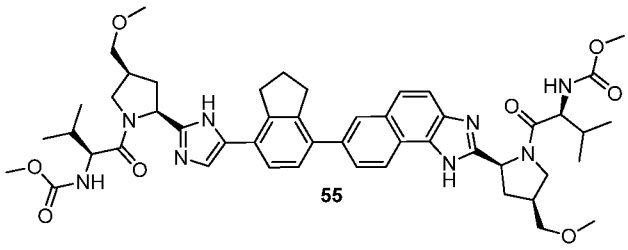

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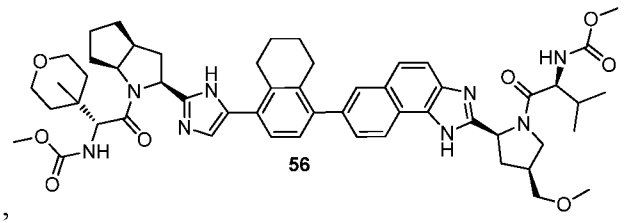

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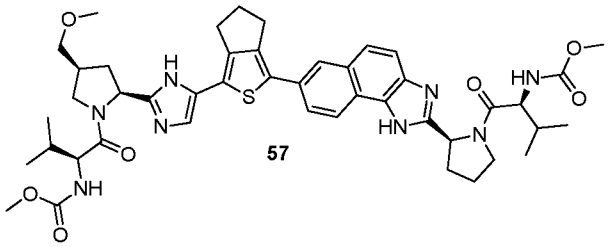
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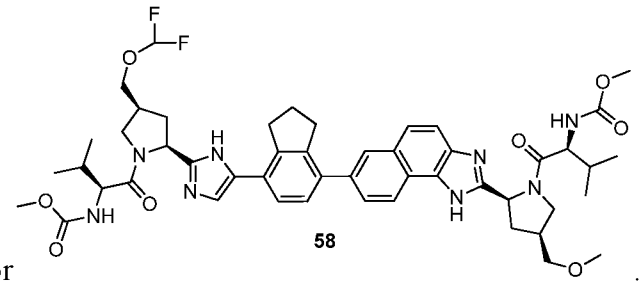
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or .

[00163] The compound of the invention (comprising a compound having Formula (I), (II), (IIa), (IIb) or (III), or a stereoisomer, a geometric isomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof) can be used in the manufacture of a medicament for treatment of acute or chronic HCV infection including that described herein. Further more, the compound of the invention can be used in the manufacture of an anti-HCV medicament. The compound disclosed herein also can be used in the manufacture of a medicament for lessening, prevening, managing or treating diseases mediated by HCV. Thus, the compound of the invention can act as an active ingredient of a pharmaceutical composition, the pharmaceutical composition may comprises the compound of Formula (I), (II), (IIa), (IIb) or (III), and may further comprises at least one pharmaceutically acceptable carrier, adjuvant or diluent.

[00164] In certain embodiments, the salt is a pharmaceutically acceptable salt. The phrase "pharmaceutically acceptable" refers to that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith. The skills in the art could choose "pharmaceutically acceptable" substance or composition based on the other ingredients and the objects for treatment such as human.

[00165] The compounds disclosed herein also include salts of the compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for preparing and/or purifying compounds of Formula (I), (II), (IIa), (IIb) or (III), and/or for separating enantiomers of compounds of Formula (I), (II), (IIa), (IIb) or (III).

[00166] If the compound disclosed herein is a base, the desired salt may be prepared by any

suitable method available in the art, for example, treatment of the free base with an inorganic acid or organic acid, wherein the inorganic acid comprises hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Some non-limiting example of the organic acid include acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid and salicylic acid; a pyranosidyl acid, such as glucuronic acid and galacturonic acid; an alpha-hydroxy acid, such as citric acid and tartaric acid; an amino acid, such as aspartic acid and glutamic acid; an aromatic acid, such as benzoic acid and cinnamic acid; a sulfonic acid, such as *p*-toluenesulfonic acid, ethanesulfonic acid, and the like.

[00167] If the compound disclosed here in is an acid, the desired salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide, or alkaline earth metal hydroxide, and the like. Some non-limiting examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine; ammonia, such as primary, secondary and tertiary amine, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, lithium, and the like.

PHARMACEUTICAL COMPOSITION OF THE COMPOUND OF THE INVENTION, PREPARATIONS AND ADMINISTRATION

[00168] The pharmaceutical composition disclosed herein comprises any one of the compounds of the invention. The pharmaceutical composition further comprises a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof. The pharmaceutical composition can be used for treating HCV infection or a HCV disorder.

[00169] The pharmaceutical composition disclosed herein further comprises anti-HCV agents. The anti-HCV agent may be any other known anti-HCV agent except the compound described herein. Such as interferon, ribavirin, IL-2, IL-6, IL-12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, imiquimod, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, rimantadine, bavituximab, hepatitis C immunogloblin, Civacir™, boceprevir, telaprevir, erlotinib, daclatasvir, simeprevir, asunaprevir, vaniprevir, faldaprevir, paritaprevir, danoprevir, sovaprevir, grazoprevir, vedroprevir, BZF-961, GS-9256, narlaprevir, ANA975, ombitasvir, EDP239, ravidasvir, velpatasvir,

samatasvir, elbasvir, MK-8325, GSK-2336805, PPI-461, ciluprevir, sovaprevir, ACH-1095, VX-985, IDX-375, VX-500, VX-813, PHX-1766, PHX-2054, IDX-136, IDX-316, modithromycin, VBY-376, TMC-649128, mericitabine, sofosbuvir, INX-189, IDX-184, IDX102, R-1479, UNX-08189, PSI-6130, PSI-938, PSI-879, nesbuvir, HCV-371, VCH-916, lomibuvir, MK-3281, dasabuvir, ABT-072, filibuvir, deleobuvir, tegobuvir, A-837093, JKT-109, Gl-59728, GL-60667, AZD-2795, TMC647055, ledipasvir, odalasvir, ritonavir, furaprevir, setrobuvir, alisporivir, BIT-225, AV-4025, ACH-3422, MK-2748, MK-8325, JNJ-47910382, ABP-560, TD-6450, TVB-2640, ID-12, PPI-383, A-848837, RG-7795, BC-2125, alloferon, nivolumab, WF-10, nitazoxanide, multiferon, nevirapine, ACH-3422, alisporivir, MK-3682, MK-8408, GS-9857, CD-AdNS3, pibrentasvir, RG-101, glecaprevir, BZF-961, INO-8000, MBL-HCV1, CIGB-230, TG-2349, procvax, CB-5300, miravirsen, chronvac-C, MK-1075, ACH-0143422, WS-007, MK-7680, MK-2248, MK-8408, IDX-21459, AV-4025, MK-8876, GSK-2878175, MBX-700, AL-335, JNJ-47910382, AL-704, ABP-560, TD-6450, EDP-239, SB-9200, ITX-5061, ID-12 or a combination thereof. In some embodiments, the interferon is interferon α-2b, pegylated interferon α, interferon α-2a, pegylated interferon α-2a, consensus interferon-α, interferon γ or a combination thereof. The pharmaceutical composition futher comprise an HCV inhibitor, wherein the HCV inhibitor inhibits HCV replication process and/or at least a function of a HCV viral protein, and wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral proteins comprise metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in HCV viral replication.

[00170] When it is possible that, for use in therapy, therapeutically effective amounts of the compound of formula (I), (II), (IIa), (IIb) or (III) of the invention, as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. The invention further provides pharmaceutical compositions, which comprise therapeutically effective amounts of compounds of Formula (I), (II), (IIa), (IIb) or (III), or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carrier, diluent or excipient. The term "therapeutically effective amount," as used herein, refers to the total amount of each active component that is

sufficient to show a meaningful patient benefit (*e.g.*, a reduction in viral load). When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously. The compounds of Formula (I), (II), (IIa), (IIb) or (III), and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the present disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of Formula (I), (II), (IIa), (IIb) or (III), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "pharmaceutically acceptable," as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[00171] Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Dosage levels of between about 0.01 and about 250 milligram per kilogram ("mg/kg") body weight per day, preferably between about 0.05 and about 100 mg/kg body weight per day of the compounds of the present disclosure are typical in a monotherapy for the prevention and treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending on the condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Treatment may be initiated with small dosages substantially less than the optimum dose of the

compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

[00172] When the compositions of this disclosure comprise a combination of a compound of the present disclosure and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent are usually present at dosage levels of between about 10 to 150%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen. Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intracutaneous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, intravenous, or intradermal injections or infusions) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). Oral administration and administration by injection are preferred.

[00173] Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solution or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions.

[00174] For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agent can also be present.

[00175] Capsules are maded by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate, or

sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

[00176] Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or β-lactose, corn sweetener, natural and synthetic resin such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, and the like. Lubricants used in these dosage forms include sodium oleate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, betonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitable comminuted, with a diluents or base as described above, and optionally, with a binder such as carboxymethylcellulose, an alginate, gelating, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as betonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage, or solution of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulation, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present disclosure can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

[00177] Oral fluids such as solution, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavor additive such as

peppermint oil or natural sweeteners, or saccharin or other artificial sweeteners, and the like can also be added.

[00178] Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating of embedding particulate material in polymers, wax, or the like.

[00179] The compounds of formula (I), (II), (IIa), (IIb) or (III), and pharmaceutically acceptable salts thereof may also be also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

[00180] The compounds of formula (I), (II), (IIa), (IIb) or (III), and pharmaceutically acceptable salts thereof may also be delivered by the use of monoclonal antibodies as individual carrier to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers may encompass polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidophenol, polyhydroxyethylaspartamidophenol or polyethylene oxide polylysine, substituted by palmitoyl radicals. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, poly(ε-caprolactone), polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

[00181] Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmacol. Res.*, 1986, *3*(6), 318.

[00182] Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, oils or transdermal patch.

[00183] Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

[00184] Pharmaceutical formulations adapted for nasal administration wherein the carrier is a

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

[00185] Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers or insufflators or other devise which suitable for delivering aerosol spray.

[00186] Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

[00187] Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain antioxidants, buffers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

[00188] It should be understood that in addition to ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

USES OF THE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS

[00189] Provided herein is use of the compound or the pharmaceutical composition disclosed herein in the manufacture of a medicament for inhibiting HCV replication process and/or at least a function of a HCV viral protein, and wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral proteins comprise metalloproteinase, non-structural protein NS2, NS3,

NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in HCV viral replication. And any one of the compounds or the pharmaceutical compositions of the invention can be used for treating HCV infection or a HCV disorder.

[00190] Also provided herein is a method, which comprises administering the compound or the pharmaceutical composition disclosed herein, further comprising administering to the patient additional anti-HCV agents. Thus, the compounds or the the pharmaceutical compositions disclosed herein can be combined with additional anti-HCV agents. Wherein the anti-HCV agent is an interferon, ribavirin, IL-2, IL-6, IL-12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, imiquimod, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, rimantadine, bavituximab, hepatitis C immunogloblin, Civacir™, boceprevir, telaprevir, erlotinib, daclatasvir, simeprevir, asunaprevir, vaniprevir, faldaprevir, paritaprevir, danoprevir, sovaprevir, grazoprevir, vedroprevir, BZF-961, GS-9256, narlaprevir, ANA975, ombitasvir, EDP239, ravidasvir, velpatasvir, samatasvir, elbasvir, MK-8325, GSK-2336805, PPI-461, ciluprevir, sovaprevir, ACH-1095, VX-985, IDX-375, VX-500, VX-813, PHX-1766, PHX-2054, IDX-136, IDX-316, modithromycin, VBY-376, TMC-649128, mericitabine, sofosbuvir, INX-189, IDX-184, IDX102, R-1479, UNX-08189, PSI-6130, PSI-938, PSI-879, nesbuvir, HCV-371, VCH-916, lomibuvir, MK-3281, dasabuvir, ABT-072, filibuvir, deleobuvir, tegobuvir, A-837093, JKT-109, Gl-59728, GL-60667, AZD-2795, TMC647055, ledipasvir, odalasvir, ritonavir, furaprevir, setrobuvir, alisporivir, BIT-225, AV-4025, ACH-3422, MK-2748, MK-8325, JNJ-47910382, ABP-560, TD-6450, TVB-2640, ID-12, PPI-383, A-848837, RG-7795, BC-2125, alloferon, nivolumab, WF-10, nitazoxanide, multiferon, nevirapine, ACH-3422, alisporivir, MK-3682, MK-8408, GS-9857, CD-AdNS3, pibrentasvir, RG-101, glecaprevir, BZF-961, INO-8000, MBL-HCV1, CIGB-230, TG-2349, procvax, CB-5300, miravirsen, chronvac-C, MK-1075, ACH-0143422, WS-007, MK-7680, MK-2248, MK-8408, IDX-21459, AV-4025, MK-8876, GSK-2878175, MBX-700, AL-335, JNJ-47910382, AL-704, ABP-560, TD-6450, EDP-239, SB-9200, ITX-5061, ID-12 or a combination thereof. The interferon is interferon α-2b, pegylated interferon α, interferon α-2a, pegylated interferon α-2a, consensus interferon-α, interferon γ or a combination thereof.

[00191] The treatment method that includes administering a compound or composition disclosed

herein can further include administering to the patient an additional anti-HCV agent, wherein the additional anti-HCV drug is administered together with a compound or composition disclosed herein as a single dosage form or separately from the compound or composition as part of a multiple dosage form. The additional anti-HCV agent may be administered at the same time as a compound disclosed herein or at a different time. In the latter case, administration may be staggered by, for example, 6 hours, 12 hours, 1 day, 2 days, 3 days, 1 week, 2 weeks, 3 weeks, 1 month, or 2 months.

[00192] An "effective amount" or "effective dose" of the compound or pharmaceutically acceptable composition is an amount that is effective in treating or lessening the severity of one or more of the aforementioned disorders. The compounds and compositions, according to the method disclosed herein, may be administered using any amount and any route of administration which is effective for treating or lessening the severity of the disorder or disease. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. A compound or composition can also be administered with one or more other therapeutic agents as discussed above.

GENERAL SYNTHETIC PROCEDURES

[00193] Generally, the compounds disclosed herein may be prepared by methods described herein, wherein the substituents are as defined for Formula (I), (II), (IIa), (IIb) or (III) above, except where further noted. The following non-limiting schemes and examples are presented to further exemplify the invention.

[00194] Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare a number of other compounds disclosed herein, and alternative methods for preparing the compounds disclosed herein are deemed to be within the scope disclosed herein. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, *e.g.*, by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds disclosed herein.

[00195] In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company, Inc., Arco Chemical Company and Alfa Chemical Company, and were used without further purification unless otherwise indicated. Common solvents were purchased from commercial suppliers such as Shantou XiLong Chemical Factory, Guangdong Guanghua Reagent Chemical Factory Co. Ltd., Guangzhou Reagent Chemical Factory, Tianjin YuYu Fine Chemical Ltd., Qingdao Tenglong Reagent Chemical Ltd., and Qingdao Ocean Chemical Factory.

[00196] Anhydrous THF, dioxane, toluene, and ether were obtained by refluxing the solvent with sodium. Anhydrous CH_2Cl_2 and $CHCl_3$ were obtained by refluxing the solvent with CaH_2. EtOAc, PE, hexane, *N*,*N*-dimethylacetamide and DMF were treated with anhydrous Na_2SO_4 prior to use.

[00197] The reactions set forth below were done generally under a positive pressure of nitrogen or argon or in anhydrous solvents equipped with a drying tube (unless otherwise stated), and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[00198] Column chromatography was conducted using a silica gel column. Silica gel (300-400 mesh) was purchased from Qingdao Ocean Chemical Factory. ^1H NMR spectra were obtained by using $CDCl_3$, DMSO-d_6, CD_3OD or acetone-d_6 as solvent (reported in ppm), and TMS (0 ppm) or chloroform (7.25 ppm) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, were reported in Hertz (Hz).

[00199] Low-resolution mass spectral (MS) data were determined by an Agilent 6320 Series LC-MS spectrometer equipped with a G1312A binary pump and a G1316A TCC (column was operated at 30 °C). G1329A autosampler and G1315B DAD detector were applied in the analysis, and an ESI source was used in the LC-MS spectrometer.

[00200] Low-resolution mass spectral (MS) data were determined by an Agilent 6120 Series LC-MS spectrometer equipped with a G1311A quaternary pump and a G1316A TCC (column was operated at 30 °C). G1329A autosampler and G1315D DAD detector were applied in the

analysis, and an ESI source was used on the LC-MS spectrometer.

[00201] Both LC-MS spectrometers were equipped with an Agilent Zorbax SB-C18, 2.1 x 30 mm, 5 μm column. Injection volume was decided by the sample concentration. The flow rate was 0.6 mL/min. The HPLC peaks were recorded by UV-Vis wavelength at 210 nm and 254 nm. The mobile phase consisted of 0.1% formic acid in acetonitrile (phase A) and 0.1% formic acid in ultrapure water (phase B). The gradient elution conditions were shown in Table 1:

Table 1

Time (min)	A (CH_3CN, 0.1% HCOOH)	B (H_2O, 0.1% HCOOH)
0-3	5-100	95-0
3-6	100	0
6-6.1	100-5	0-95
6.1-8	5	95

[00202] Purities of compounds were assessed by Agilent 1100 Series high performance liquid chromatography (HPLC) with UV detection at 210 nm and 254 nm (Zorbax SB-C18, 2.1 x 30 mm, 4 μm). The run time was 10 min, and the flow rate was 0.6 mL/min. The elution was performed with a gradient of 5 to 95% phase A (0.1% formic acid in CH_3CN) in phase B (0.1% formic acid in H_2O). Column was operated at 40 °C.

[00203] The following abbreviations are used throughout the specification:

$AlCl_3$ aluminum chloride

AcOK, KOAc potassium acetate

AcOH acetic acid

Ac_2O acetic anhydride

BBr_3 Boron tribromide

BOC, Boc *tert*-butoxycarbonyl

n-$BuNH_2$ *n*-butylamine

$CuBr_2$ Cupric bromide

MeCN, CH_3CN acetonitrile

$CDCl_3$ chloroform-*d*

CH_3COONH_4, NH_4OAc ammonium acetate

CH_3COCl acetyl chloride

DCM, CH_2Cl_2 dichloromethane

DIPEA *N*,*N*-diisopropylethylamine

DMF *N*,*N*-dimethylformamide

DMSO	dimethylsulfoxide
DMSO-d_6	deuterated dimethylsulfoxide
DMAP	4-dimethylaminopyridine
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
EtOH	ethanol
Et_3N	triethylamine
EtOAc, EA	ethyl acetate
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOH/H_2O	the mixture of ethanol and water
Et_3SiH	triethyl silicane
FBS	fetal bovine serum
g	gram
h, hr	hour(s)
H_2O	water
HCl	hydrochloric acid
HCl/EtOAc	a solution of hydrogen chloride in ethyl acetate
H_2SO_4	sulfuric acid
K_2CO_3	potassium carbonate
KNO_3	potassium nitrate
$Na_2S_2O_4$	sodium thiosulfate
Na_2CO_3	sodium carbonate
NH_4F	ammonium fluoride
MnO_2	manganese dioxide
MeOH	methanol
ml, mL	milliliter
mmol	millimole
PE	petroleum ether
Py	pyridine
Pd	palladium
$Pd(dppf)Cl_2$	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)platinum
$Pd(PPh_3)_2Cl_2$	bis(triphenylphosphine)palladium(II) chloride

PBS phosphate buffered saline

rt, r.t room temperature

Selectfluor

Tf trifluoroacetyl

Tf_2O trifluoromethanesulfonic anhydride

TFA, CF_3COOH trifluoroacetic acid

TLC thin layer chromatography

THF tetrahydrofuran

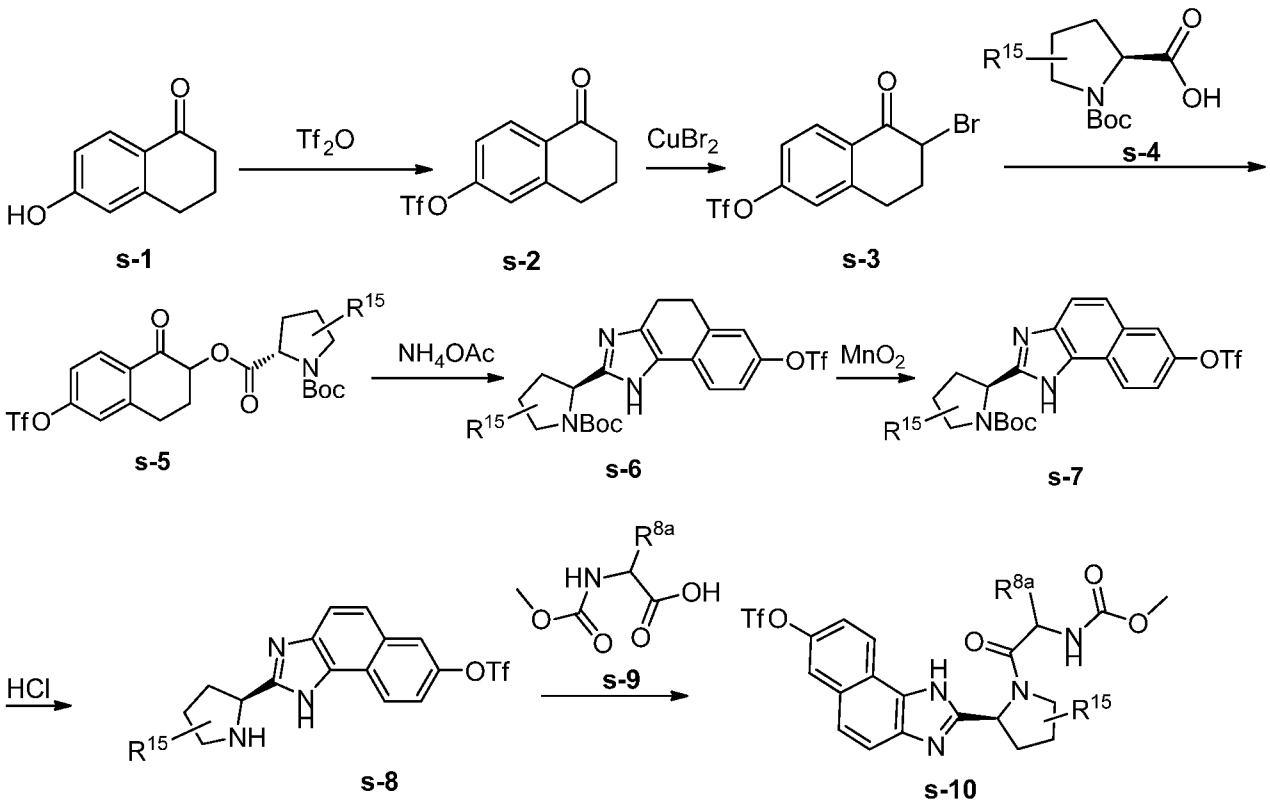
TMSCl trimethylchlorosilane

TMS trimethylsilyl

Scheme

Scheme

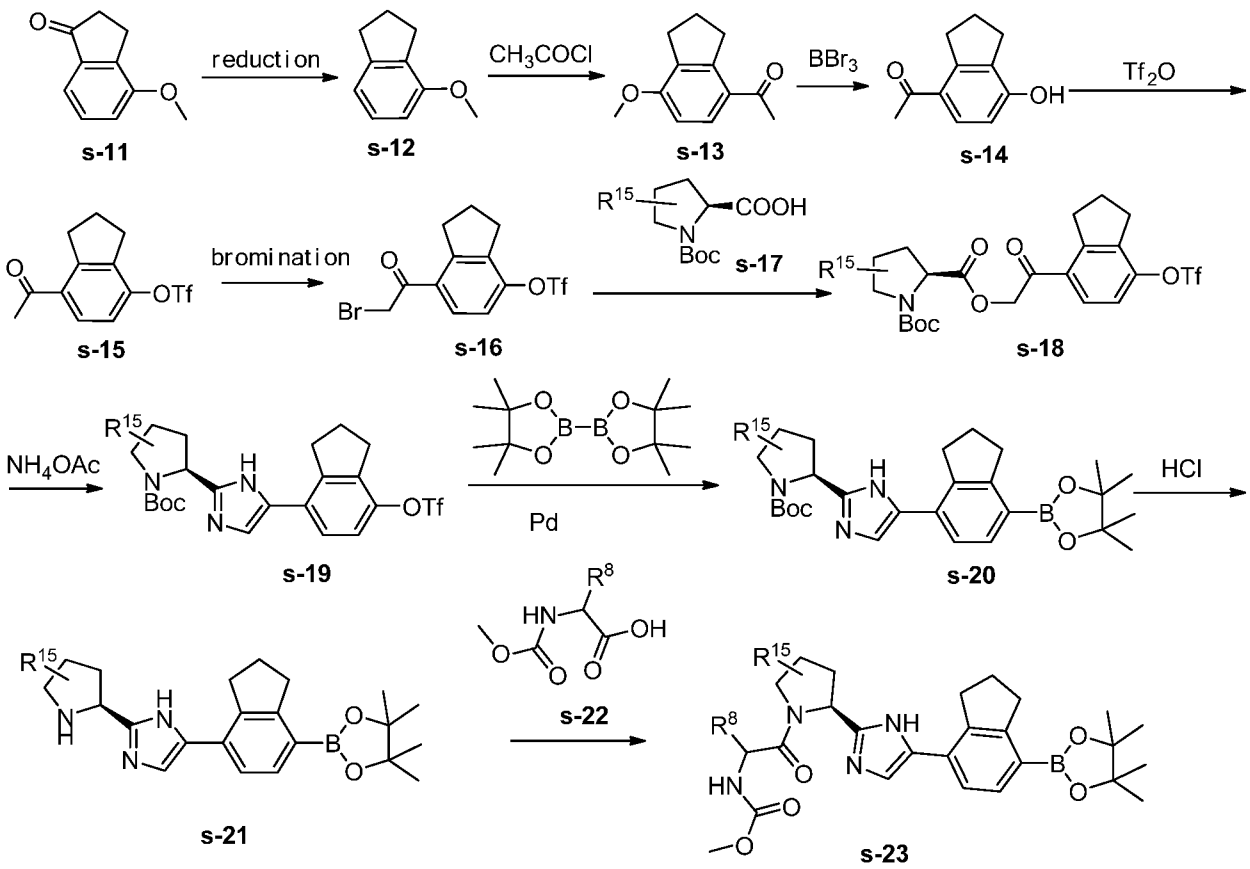
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[00204] Compound **s-10** can be prepared by a general synthetic procedure illustrated in Scheme 1, and wherein R^{15} and R^{8a} are as defined herein. Compound **s-1** can react with trifluoromethanesulfonic anhydride under a base condition to afford compound **s-2**; compound **s-2** can be bromized to afford compound **s-3**; compound **s-3** can react with compound **s-4** under a base condition to afford compound **s-5**; cyclization reaction of compound **s-5** and ammonium

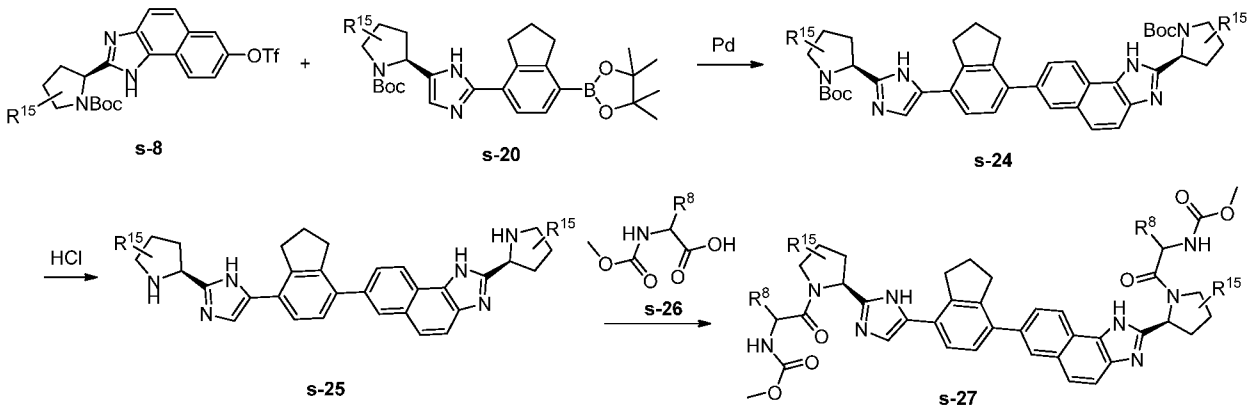
acetate can afford compound **s-6;** compound **s-6** can be oxidized to afford compound **s-7;** deprotection reaction of compound **s-7** can afford compound **s-8**; condensation reaction of compound **s-8** and compound **s-9** can afford compound **s-10**.

Scheme 2



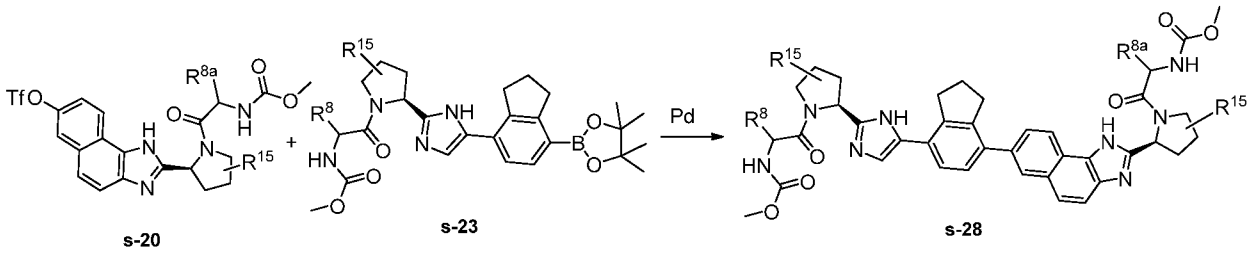
[00205] Compound **s-23** can be prepared by a general synthetic procedure illustrated in Scheme 2, and wherein R^{15} and R^{8} are as defined herein. Compound **s-11** can convert to compound **s-12** in the present of a reductant; compound **s-12** can be acetylized to afford compound **s-13**; demethylation reaction of compound **s-13** can afford compound **s-14;** compound **s-14** can react with trifluoromethanesulfonic anhydride under a base condtion to afford compound **s-15**; compound **s-15** can be bromized to afford compound **s-16**, compound **s-16** can react with compound **s-17** under a base condition to afford compound **s-18**, compound **s-18** can react with ammonium acetate to afford compound **s-19**; compound **s-19** can convert to compound **s-20** in the present of a Pd catalyst; deprotection reaction of compound **s-20** can afford compound **s-21**; compound **s-21** can react with **s-22** to afford **s-23**.

Scheme 3



[00206] Compound **s-27** can be prepared by a general synthetic procedure illustrated in Scheme 3, and wherein R^{15} and R^{8} are as defined herein. Coupling reaction of compound **s-8** and compound **s-20** in the present of a Pd catalyst can afford compound **s-24**; deprotecting reaction of compound **s-24** can afford compound **s-25;** condensation reaction of compound **s-25** and compound **s-26** can afford compound **s-27**.

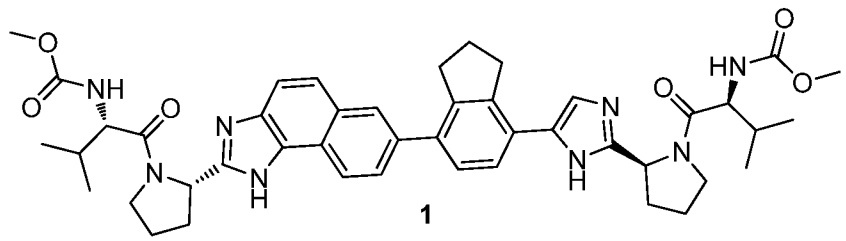
Scheme 4



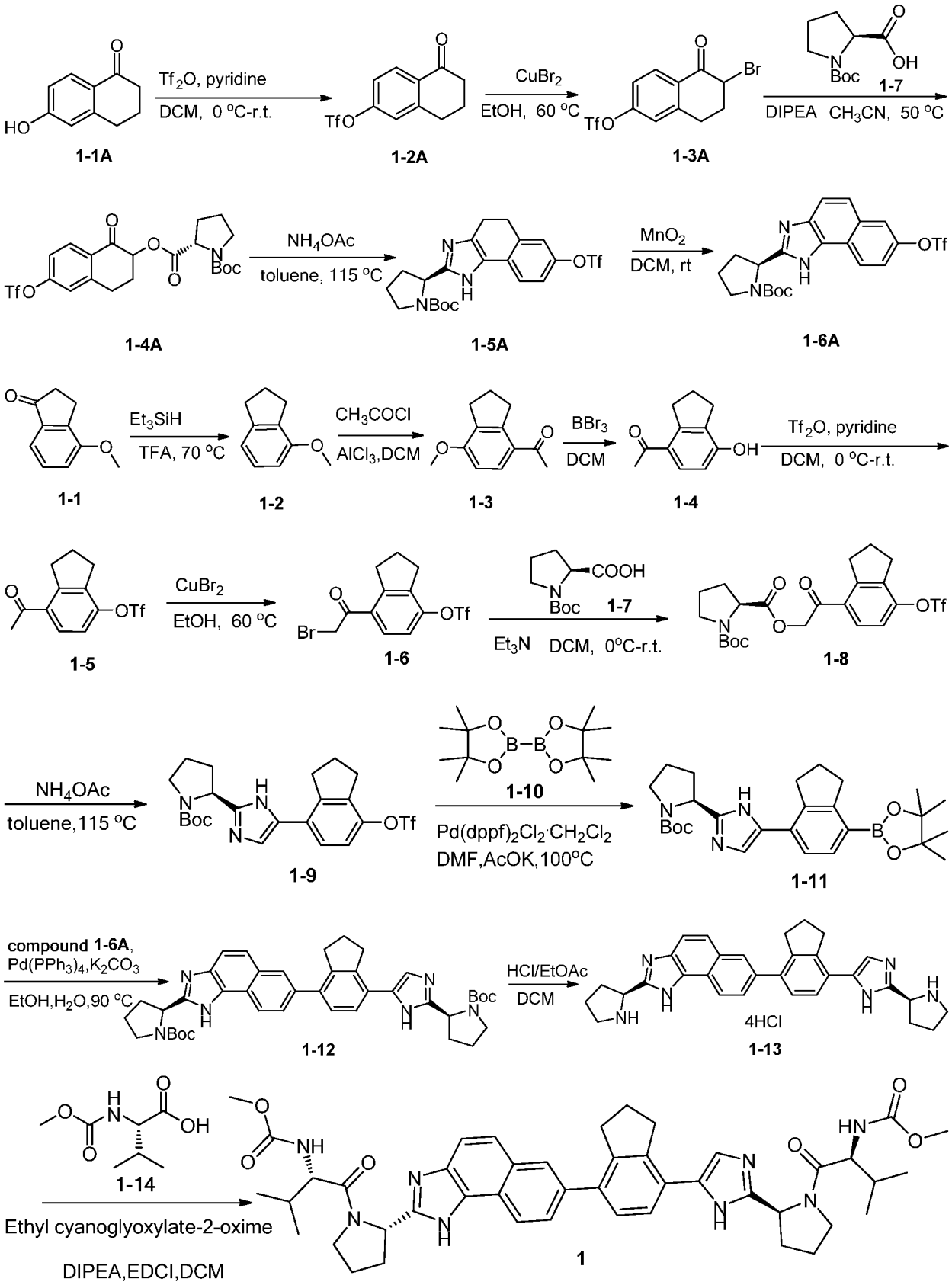
[00207] Compound **s-28** can be prepared by a general synthetic procedure illustrated in Scheme 4, and wherein R^{15}, R^{8} and R^{8a} are as defined herein. Coupling reaction of compound **s-20** and compound **s-23** in the present of a Pd catalyst can afford compound **s-28**.

Example

Example 1



Synthesis route:



Synthesis steps:

Step 1) synthesis of compound **1-2A**

[00208] To a solution of compound **1-1A** (5.0 g, 30.83 mmol) and pyridine (3.0 g, 37.0 mmol) in

DCM (60 mL) was added trifluoromethanesulfonic anhydride (10.44 g, 37.0 mmol) dropwise at 0 °C. After the addition, the mixture was stirred at rt for 8 hours, and then washed with water (30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 10 : 1) to give the title compound (8.5 g, 94.4%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (d, J = 8.7 Hz, 1H), 7.54 (d, J = 2.2 Hz, 1H), 7.44 (dd, J = 8.7, 2.4 Hz, 1H), 3.02 (t, J = 6.0 Hz, 2H), 2.66–2.61 (m, 2H), 2.10–2.03 (m, 2H) ppm.

Step 2) synthesis of compound **1-3A**

[00209] A mixture of compound **1-2A** (3.0 g, 10.2 mmol) and cupric bromide (4.5 g, 20.4 mmol) in EtOH (30 mL) was stirred at 60 °C for 2 hours. After the reaction was completed, the mixture was filtered through a celite pad. The filtrate was concentrated and dissolved in DCM (40 mL × 2), the resulting mixture was washed with water, and then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 6 : 1) to give the title compound as brownish red oil (3.6 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8.7 Hz, 1H), 7.31–7.22 (m, 2H), 4.75 (t, J = 4.1 Hz, 1H), 3.47–3.33 (m, 1H), 2.99 (dt, J = 17.4, 4.2 Hz, 1H), 2.65–2.45 (m, 2H) ppm.

Step 3) synthesis of compound **1-4A**

[00210] A mixture of compound **1-3A** (2.5 g, 6.7 mmol), DIPEA (1.3 g, 10.0 mmol) and acetonitrile (20 mL) was stirred at 50 °C, and then a solution of compound **1-7** (1.6 g, 7.4 mmol) in acetonitrile (10 mL) was added dropwise slowly. After the addition, the mixture was stirred until the reaction was complete. The reaction mixture was concentrated *in vacuo* and diluted with water. The resulting mixture was extracted with EtOAc. The organic layer was dired and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 4 : 1) to give the title compound (3.0 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8.7 Hz, 1H), 7.22 (m, 2H), 5.08 (t, 1H), 4.85 (t, 1H), 3.47 (t, 2H), 3.17 (t, 2H), 2.99 (t, 4H), 2.65 (m, 2H), 1.25 (t, 9H) ppm; MS-ESI, *m/z*: 508.10$[M+H]^+$.

Step 4) synthesis of compound **1-5A**

[00211] A mixture of compound **1-4A** (2.7 g, 5.3 mmol) and ammonium acetate (2.5 g, 31.8 mmol) in toluene (30 mL) was stirred at 115 °C for 12 hours. After the reaction was completed, the mixture was diluted with water (10 mL), and the resulting mixture was extracted with EtOAc

(30 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 6 : 1) to give the title compound as a gray solid (1.8 g, 69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.32 (m, 2H), 5.18 (t, 1H), 3.85 (t, 2H), 3.27 (t, 2H), 2.99 (t, 2H), 2.45 (m, 4H), 1.28 (t, 9H) ppm; MS-ESI, *m/z*: 488.8$[M+H]^+$.

Step 5) synthesis of compound **1-6A**

[00212] To a solution of compound **1-5A** (1.8 g, 3.7 mmol) in DCM (40 mL) was added manganese dioxide (3.2 g, 37 mmol) in portions. The mixure was stirred at rt for 4 days and filtered through a celite pad. The filtrate was washed with water and dried, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 3 : 1) to give the title compound (1.6 g, 88.9%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.52 (m, 2H), 7.32 (m, 2H), 5.18 (t, 1H), 3.37 (t, 2H), 2.59 (t, 2H), 2.35 (m, 2H), 1.26 (t, 9H) ppm; MS-ESI, *m/z*: 485.9$[M+H]^+$.

Step 6) synthesis of compound **1-2**

[00213] A mixture of compound **1-1** (15.0 g, 92.49 mmol), triethylsilane (70.0 g, 601 mmol) and TFA (300 mL) was refluxed in two-neck flask, and the reaction was monitored by TLC. 6 Hours later, the reaction was complete. The mixture was poured into ice-water. The resulting mixture was extracted with EtOAc (100 mL × 2). The combined organic layers were neutralized with aqueous sodium bicarbonate solution and washed with water. The organic layer was dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE) to give the title compound (12.2 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 3.90 (s, 3H), 2.97 (d, J = 15.4, 7.5 Hz, 4H), 2.20–2.11 (m, 2H) ppm.

Step 7) synthesis of compound **1-3**

[00214] To a solution of compound **1-2** (10 g, 67.5 mmol), aluminium chloride (11.7 g, 87.8 mmol) in DCM (80 mL) was added acetylchloride (6.4 g, 82 mmol) dropwise slowly at 0 °C. After the addition, the mixture was stirred at rt for 4 h and poured into ice-water. The resulting mixture was extracted with DCM (60 mL × 2). The combined organic layers were dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : DCM (V : V) = 5 : 1) to give the title compound (8.9 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.73 (d, J = 8.1

Hz, 1H), 3.90 (s, 3H), 2.97 (t, J = 15.4, 7.5 Hz, 4H), 2.20–2.11 (m, 2H) ppm.

Step 8) synthesis of compound **1-4**

[00215] To a solution of compound **1-3** (5.5 g, 29 mmol) in DCM (50 ml) was added boron tribromide (8.7 g, 35 mmol) dropwise slowly at 0 °C. After the addition, the mixture was stirred until the reaction was complete and poured into ice-water. The resulting mixture was extracted with EtOAc (40 mL × 3). The combined organic layers were dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 6 : 1) to give the title compound (2.1 g, 41%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.66 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 3.13 (t, J = 7.5 Hz, 2H), 2.72 (t, J = 7.5 Hz, 2H), 2.44 (s, 3H), 2.01–1.94 (m, 2H) ppm.

Step 9) synthesis of compound **1-5**

[00216] To a solution of compound **1-4** (0.75 g, 4.3 mmol) and pyridine (0.5 g, 6.0 mmol) in DCM (20 mL) was added trifluoromethanesulfonic anhydride (1.3 g, 4.7 mmol) dropwise at 0 °C. After the addition, the mixture was stirred at rt for 4 hours, and the reaction was monitored by TLC. After the reaction was completed, the reaction mixtue was washed with water. The organic layer was dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE) to give the title compound (1.2 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.6 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 3.35 (t, J = 7.5 Hz, 2H), 3.05 (t, J = 7.6 Hz, 2H), 2.61 (s, 3H), 2.23–2.11 (m, 2H) ppm.

Step 10) synthesis of compound **1-6**

[00217] A mixture of compound **1-5** (1.2 g, 3.9 mmol) and cupric bromide (1.7 g, 7.6 mmol) in EtOH (20 mL) was stirred at 60 °C for 2 hours. After the reaction was completed, the mixture was filtered through a celite pad. The filtrate was concentrated and dissolved in DCM (20 mL × 2). The resulting mixture was washed with water, and then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 6 : 1) to give the title compound (1.25 g, 80.5%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.6 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.43 (s, 2H), 3.36 (t, J = 7.6 Hz, 2H), 3.07 (t, J = 7.6 Hz, 2H), 2.29–2.14 (m, 2H) ppm.

Step 11) synthesis of compound **1-8**

[00218] To a solution of compound **1-6** (1.4 g, 3.6 mmol) and compound **1-7** (1.0 g, 4.6 mmol) in DCM (20 mL) was added triethylamine (0.6 g, 6 mmol) dropwise at 0 °C. After the addition,

the mixture was stirred at rt and monitored by TLC. After the reaction was complete, the mixture was washed with water. The organic layer was dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 6 : 1) to give the title compound (1.5 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.6 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 5.13 (s, 1H), 4.43 (s, 2H), 3.36 (t, 2H), 3.16 (t, 2H), 3.07 (t, 4H), 2.29 (m, 4H), 1.36 (t, 9H) ppm; MS-ESI, *m/z*: 522.8$[M+H]^+$.

Step 12) synthesis of compound **1-9**

[00219] A mixture of compound **1-8** (1.1 g, 2.1 mmol) and ammonium acetate (0.81 g, 10.5 mmol) in toluene (20 mL) was stirred at 115 °C for 12 hours. After the reaction was completed, the mixture was diluted with water (10 mL), and the resulting mixture was extracted with EtOAc (30 mL × 2). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 4 : 1) to give the title compound as a gray solid (0.8 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 5.33 (s, 1H), 4.83 (s, 1H), 3.36 (t, 4H), 3.16 (t, 2H), 2.86 (t, 4H), 2.29 (m, 2H), 1.35 (t, 9H) ppm; MS-ESI, *m/z*: 502.8$[M+H]^+$.

Step 13) synthesis of compound **1-11**

[00220] A mixture of compound **1-9** (0.4 g, 0.8 mmol), 4,4,4',4',5,5,5',5'-octamethyl -2,2'-bi-1,3,2-dioxaborolane **1-10** (0.24 g, 0.95 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.07 g, 0.086 mmol) and KOAc (0.23 g, 2.0 mmol) in DMF (20 mL) was stirred at 100 °C under N_2 for 4 hours. The mixture was cooled to rt and diluted with water (10 mL). The resulting mixture was extracted with EtOAc (30 mL × 2). The combined organic layers were washed with water twice and dried, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 4 : 1) to give the title compound (0.3 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 5.33 (s, 1H),4.83 (s, 1H), 3.36 (t, 4H), 3.16 (t, 2H), 2.86 (t, 4H), 2.29 (m, 2H), 1.35 (t, 9H), 1.25 (t, 12H) ppm; MS-ESI, *m/z*: 480.4$[M+H]^+$.

Step 14) synthesis of compound **1-12**

[00221] A mixture of compound **1-11** (0.8 g, 1.7 mmol), compound **1-6A** (0.73 g, 1.5 mmol),

$Pd(PPh_3)_4$ (0.20 g, 0.17 mmol) and K_2CO_3 (0.69 mg, 5.0 mmol) in EtOH/H_2O (30 mL, V: V = 3 : 1) was stirred at 90 °C under N_2 for 3 hours. After the mixture was complete, most of the solvent was removed. The resulting mixture was extracted with DCM (20 mL × 2). The combined organic layers were dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 2 : 1) to give the title compound as a gray solid (0.5 g, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.52 (d, 2H), 7.32 (m, 2H),7.22 (m, 2H), 5.33 (s, 1H), 4.93 (s, 2H), 3.26 (m, 4H), 3.10 (m,4H), 2.76 (m, 4H), 2.19 (m, 6H), 1.25 (m, 9H), 1.29 (m, 9H) ppm; MS-ESI, *m/z*: 689.2$[M+H]^+$.

Step 15) synthesis of compound **1-13**

[00222] To a solution of compound **1-12** (0.5 g, 0.7 mmol) in DCM (15 mL) was added HCl/EtOAc (4 N, 4 mL) dropwise at 0 °C. After the addition, the mixture was stirred at rt for 6 hours. The reaction mixture was concentrated *in vacuo*. The residue was triturated with EtOAc to give a brown solid (0.4 g, 87%).

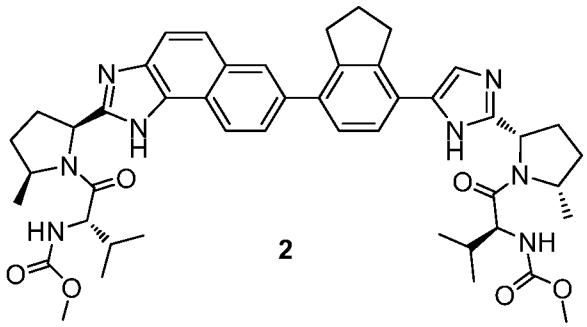
MS-ESI, *m/z*: 489.3$[M+H]^+$.

Step 16) synthesis of compound **1**

[00223] A mixture of compound **1-13** (0.40 g, 0.82 mmol), compound **1-14** (0.316 g, 1.8 mmol), EDCI (0.377 g, 1.97 mmol) and ethyl cyanoglyoxylate-2-oxime (0.07 g, 0.49 mmol) in DCM (10 mL) was stirred at 0 °C, and DIPEA (0.530 g, 4.1 mmol) was added dropwise. After the addition, the mixture was stirred at rt for 2 hours. After the mixture was complete, ammonium hydroxide (2 mL) was added, and the resulting mixture was stirred for 1 hour, then partitioned. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 1) to give the title compound as a gray solid (0.35 g, 53%).

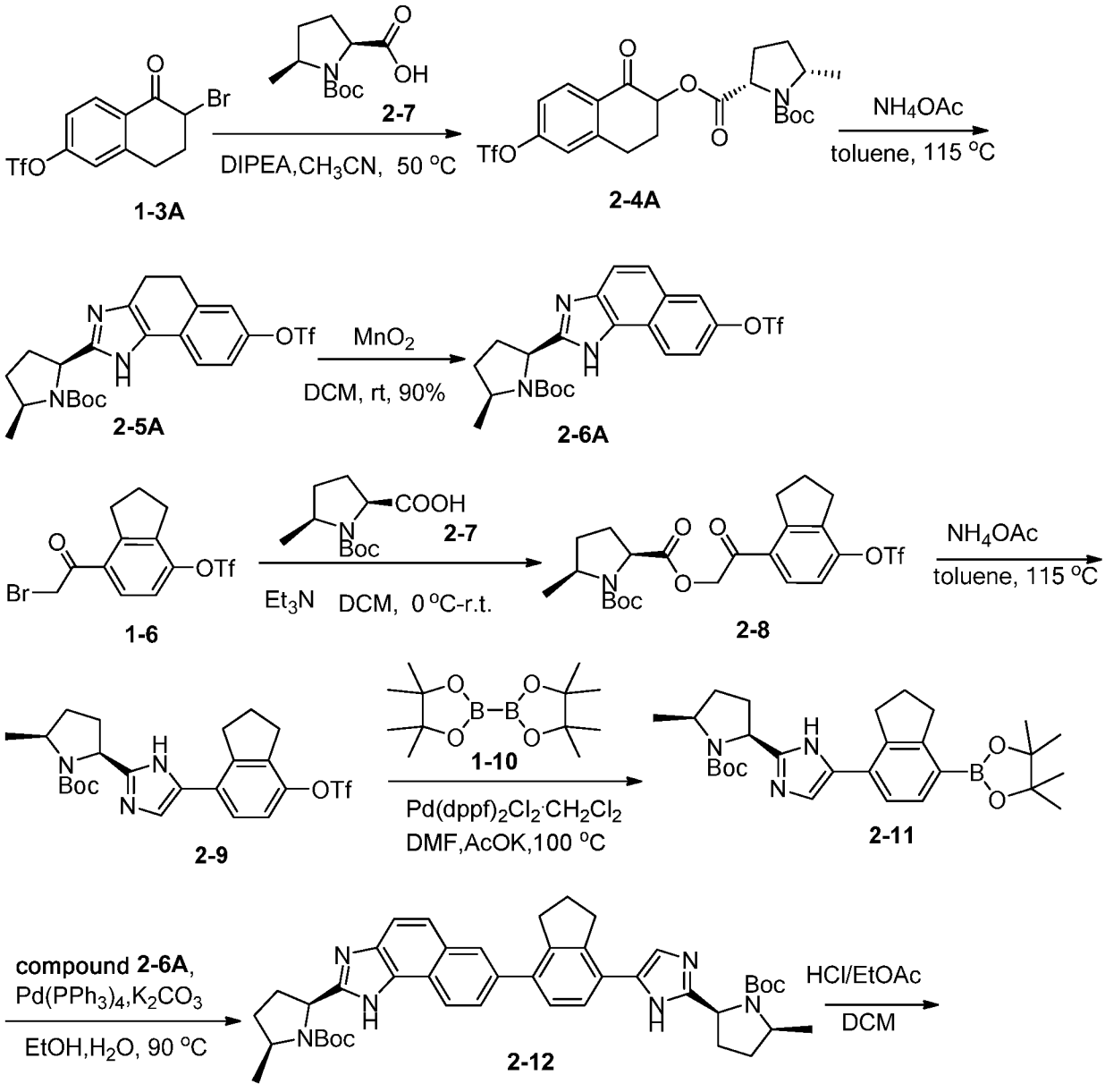
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.62 (d, 2H), 7.36 (m, 2H),7.21 (m, 2H), 5.43 (s, 1H), 5.10 (s, 2H), 3.56 (m, 4H), 3.16 (m,4H), 3.10 (m, 4H), 2.66 (m, 4H), 2.56 (m, 2H), 2.36 (m, 4H), 2.09 (m, 6H), 1.05 (m, 12H) ppm; MS-ESI, *m/z*: 802.7$[M+H]^+$.

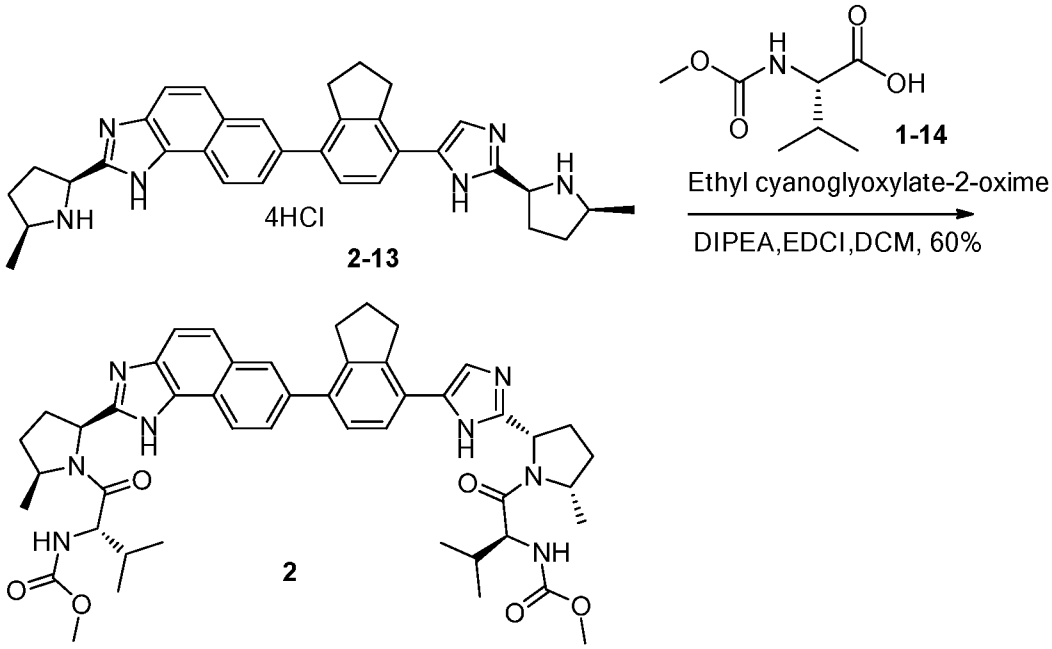
Example 2



2

Synthesis route:





Synthesis steps:

Step 1) synthesis of compound **2-4A**

[00224] A mixture of compound **1-3A** (2.5 g, 6.7 mmol), DIPEA (1.3 g, 10.0 mmol) and acetonitrile (20 mL) was stirred at 50 °C, and then a solution of (2*S*,5*S*)-1-(*tert*-butoxycarbonyl)-5- methylpyrrolidine-2-carboxylic acid **2-7** (1.38 g, 6.04 mmol) in acetonitrile (10 mL) was added dropwise slowly. After the addition, the mixture was stirred until the reaction was complete. The reaction mixture was concentrated *in vacuo* and diluted with water. The resulting mixture was extracted with EtOAc. The organic layer was dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 4 : 1) to give the title compound (1.5 g, 44%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8.7 Hz, 1H), 7.22 (m, 2H), 5.08 (t, 1H), 4.85 (t, 1H), 3.47 (t, 2H), 3.17 (t, 1H), 2.99 (t, 4H), 2.65 (m, 2H), 1.35 (t, 3H), 1.25 (t, 9H) ppm; MS-ESI, *m/z*: 522.1M+H]$^+$.

Step 2) synthesis of compound **2-5A**

[00225] A mixture of compound **2-4A** (1.5 g, 2.9 mmol) and ammonium acetate (1.6 g, 21 mmol) in toluene (30 mL) was stirred at 115 °C for 12 hours. After the reaction was completed, the mixture was diluted with water, and the resulting mixture was extracted with EtOAc (30 mL × 2). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 6 : 1) to give the title compound as a gray solid (1.0 g, 69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.32 (m, 2H), 5.18 (t, 1H), 3.85 (t, 2H),3.27 (t, 1H), 2.99 (t, 2H), 2.45 (m, 4H), 1.35 (t,3H), 1.28 (t, 9H) ppm; MS-ESI, *m/z*: 502.8$[M+H]^+$.

Step 3) synthesis of compound **2-6A**

[00226] To a solution of compound **2-5A** (1.0 g, 2.0 mmol) in DCM (40 mL) was added manganese dioxide (1.7 g, 20 mmol) in portions. The mixure was stirred at rt for 4 days and filtered through a celite pad. The filtrate was washed with water and dried, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 3 : 1) to give the title compound (0.8 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.52 (m, 2H), 7.32 (m, 2H), 5.18 (t, 1H), 3.37 (t, 1H), 2.59 (t, 2H), 2.35 (m, 2H), 1.35 (t, 3H), 1.26 (t, 9H) ppm; MS-ESI, *m/z*: 500.8$[M+H]^+$.

Step 4) synthesis of compound **2-8**

[00227] To a solution of compound **1-6** (2.3 g, 5.95 mmol) and compound **2-7** (1.23 g, 5.36 mmol) in DCM (20 mL) was added triethylamine (0.9 g, 8.9 mmol) dropwise at 0 °C. After the addition, the mixture was stirred at rt and monitored by TLC. After the reaction was complete, the mixture was washed with water (10 mL) and saturated aqueous NaCl. The organic layer was dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 6 : 1)) to give the title compound (1.6 g, 50.3%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.6 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 5.13 (s, 1H), 4.43 (s, 2H), 3.36 (t, 2H), 3.16 (t, 2H), 3.07 (t, 3H), 2.29 (m, 4H), 1.45 (t, 3H), 1.36 (t, 9H) ppm, MS-ESI, *m/z*: 535.8$[M+H]^+$.

Step 5) synthesis of compound **2-9**

[00228] A mixture of compound **2-8** (1.6 g, 3.0 mmol) and ammonium acetate (1.4 g, 18 mmol) in toluene (20 mL) was stirred at 115 °C for 12 hours. After the reaction was complete, the mixture was diluted with water, and the resulting mixture was extracted with EtOAc (30 mL × 2). The combined organic layers were washed with water and dried over anhydrous Na_2SO_4, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 4 : 1) to give the title compound as a gray solid (1.0 g, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 5.33 (s, 1H), 4.83 (s, 1H), 3.36 (t, 4H), 3.16 (t, 1H), 2.86 (t, 4H), 2.29 (m, 2H), 1.39 (t, 3H), 1.35 (t, 9H) ppm; MS-ESI, *m/z*: 516.2$[M+H]^+$.

Step 6) synthesis of compound **2-11**

[00229] A mixture of compound **2-9** (1.0 g, 1.94 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-

bi-1,3,2-dioxaborolane **1-10** (0.6 g, 2.1 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.17 g, 0.19 mmol) and KOAc (0.57 g, 5.82 mmol) in DMF (20 mL) was stirred at 100 °C under N_2 for 4 hours. The mixture was cooled to rt and diluted with water (10 mL). The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with water twice and dried, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 4 : 1) to give the title compound (0.9 g, 90%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 5.33 (s, 1H),4.83 (s, 1H), 3.36 (t, 4H), 3.16 (t, 1H), 2.86 (t, 4H), 2.29 (m, 2H), 1.35 (t, 12H), 1.25 (t, 12H) ppm; MS-ESI, *m/z*: 494.4$[M+H]^+$.

Step 7) synthesis of compound **2-12**

[00230] A mixture of compound **2-11** (1.0 g, 2.0 mmol), compound **2-6A** (0.9 g, 1.8 mmol), $Pd(PPh_3)_4$ (0.23 g, 0.2 mmol) and K_2CO_3 (0.84 mg, 6.1 mmol) in EtOH/H_2O (V : V = 3 : 1, 30 mL) was stirred at 90 °C under N_2 for 3 hours. After the mixture was complete, most of the solvent was removed. The resulting mixture was extracted with DCM (20 mL × 2). The combined organic layers were dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 2 : 1) to give the title compound as a gray solid (1.0 g, 69%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.52 (d, 2H), 7.32 (m, 2H), 7.22 (m, 2H), 5.33 (s, 1H), 4.93 (s, 2H), 3.26 (m, 4H), 3.10 (m, 2H), 2.76 (m, 4H), 2.19 (m, 6H), 1.35 (t, 6H), 1.29 (m, 9H), 1.25 (m, 9H) ppm; MS-ESI, *m/z*:717.8$[M+H]^+$.

Step 8) synthesis of compound **2-13**

[00231] To a solution of compound **2-12** (1.1 g, 1.5 mmol) in DCM (15 mL) was added HCl/EtOAc (4 N, 5 mL) dropwise at 0 °C. After the addition, the mixture was stirred at rt for 6 hours. The reaction mixture was concentrated *in vacuo*. The residue was recrystallized from EtOAc to give a brown solid (0.7 g, 68.6%).

MS-ESI, *m/z*: 517.9 $[M+H]^+$.

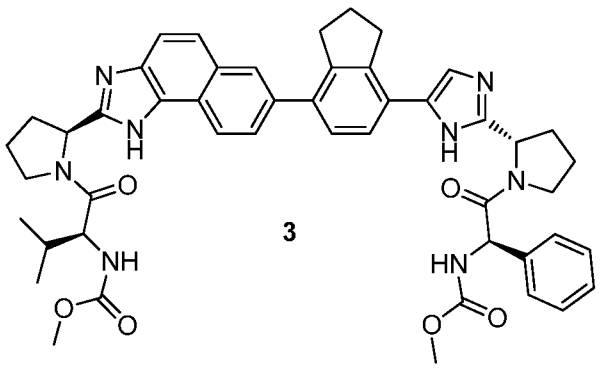
Step 15) synthesis of compound **2**

[00232] A mixture of compound **2-13** (0.60 g, 0.905 mmol), compound **1-14** (0.349 g, 1.99 mmol), EDCI (0.417 g, 2.17 mmol) and ethyl cyanoglyoxylate-2-oxime (0.077 g, 0.543 mmol) in DCM (10 mL) was stirred at 0 °C, and DIPEA (0.585 g, 4.525 mmol) was added. After the addition, the mixture was stirred at rt for 2 hours. After the mixture was complete, ammonium

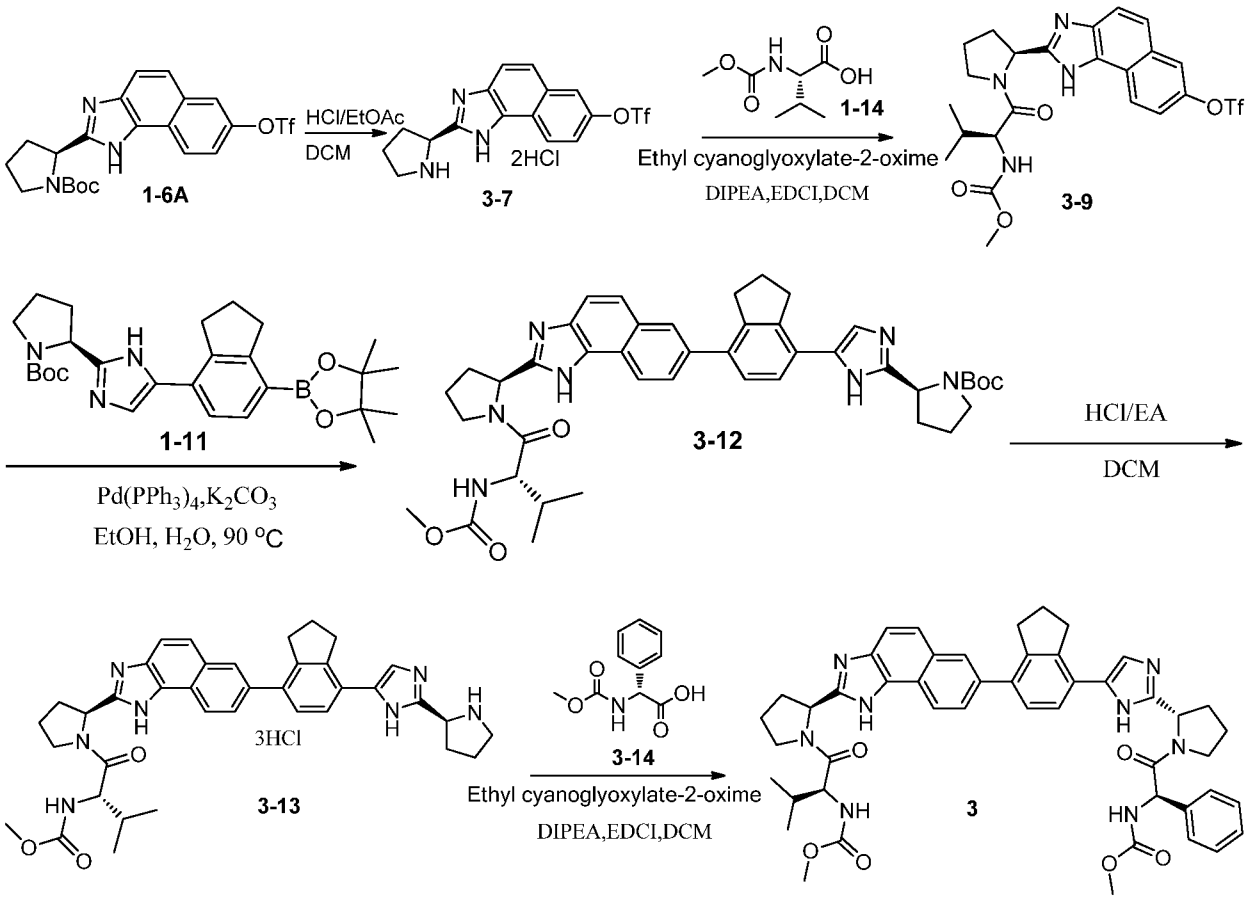
hydroxide (2 mL) was added. The resulting mixture was stirred for 1 hour, then partitioned. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 1) to give the title compound as a gray solid (0.6 g, 79.7%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.62 (d, 2H), 7.36 (m, 2H), 7.21 (m, 2H), 5.43 (s, 1H), 5.10 (s, 2H), 3.56 (m, 4H), 3.16 (m, 4H), 3.10 (m, 4H), 2.66 (m, 2H), 2.36 (m, 4H), 2.09 (m, 6H), 1.35 (m, 6H), 1.05 (m, 12H) ppm; MS-ESI, *m/z*: 832.4 $[M+H]^+$

Example 3



Synthesis route:



Synthesis steps:

Step 1) synthesis of compound **3-7**

[00233] To a solution of compound **1-6A** (1.8 g, 3.7 mmol) in DCM (15 mL) was added HCl/EtOAc (4 N, 6 mL) dropwise at 0 °C. After the addition, the mixture was stirred at rt. After the reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was recrystallized from EtOAc to give a brown solid (0.8 g, 47%).

MS-ESI, *m/z*: 385.8$[M+H]^+$.

Step 2) synthesis of compound **3-9**

[00234] A mixture of compound **3-7** (1.5 g, 3.27 mmol), compound **1-14** (0.687 g, 3.92 mmol), EDCI (0.752 g, 3.92 mmol) and ethyl cyanoglyoxylate-2-oxime (0.186 g, 1.31 mmol) in DCM (10 mL) was stirred at 0 °C, and DIPEA (1.27 g, 9.82 mmol) was added dropwise. After the addition, the mixture was stirred at rt for 2 hours. After the mixture was complete, ammonium hydroxide (2 mL) was added, and the resulting mixture was stirred for 1 hour, then partitioned. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 1) to give the title compound as a gray solid (1.4 g, 79%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.52 (m, 2H), 7.32 (m, 2H), 5.18 (t, 1H), 4.18 (t, 1H), 3.37 (t, 3H), 3.07 (t, 1H), 2.85 (m, 2H), 2.59 (m, 2H), 2.45 (m, 2H), 1.01 (m, 6H) ppm; MS-ESI, *m/z*: 543.2$[M+H]^+$.

Step 3) synthesis of compound **3-12**

[00235] A mixture of compound **1-11** (0.7 g, 1.5 mmol), compound **3-9** (0.873 g, 1.6 mmol), $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol) and K_2CO_3 (0.61 mg, 4.4 mmol) in EtOH/H_2O (V : V = 3 : 1, 30 mL) was stirred at 90 °C under N_2 for 3 hours. After the mixture was complete, most of the solvent was removed. The resulting mixture was extracted with DCM (20 mL × 2). The combined organic layers were dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 2 : 1) to give the title compound as a gray solid (0.8 g, 70%).

^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.62 (d, 2H), 7.36 (m, 2H), 7.21 (m, 2H), 5.43 (s, 1H), 5.10 (s, 2H), 3.56 (m, 4H), 3.16 (m,4H), 3.10 (m, 4H), 2.66 (m, 4H), 2.56 (m, 3H), 2.36 (m, 4H), 2.09 (m, 6H), 1.05 (m, 9H) ppm; MS-ESI, *m/z*: 747.5$[M+H]^+$.

Step 4) synthesis of compound **3-13**

[00236] To a solution of compound **3-12** (0.7 g, 0.9 mmol) in DCM (15 mL) was added HCl/EtOAc (4 N, 4 mL) dropwise at 0 °C. After the addition, the mixture was stirred at rt. After t the reaction was completed, the reaction mixture was concentrated *in vacuo*. The residue was recrystallized from EtOAc to give a brown solid (0.6 g, 89%).

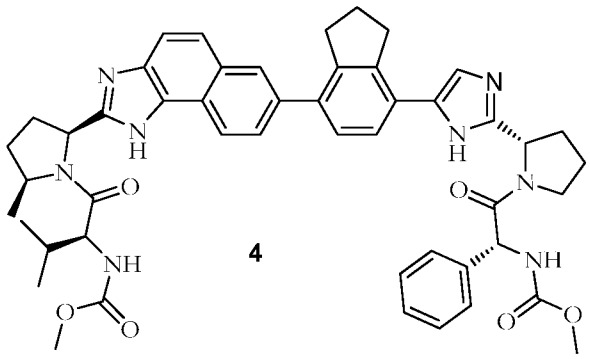
MS-ESI, *m/z*: 647.4[M+H]$^+$.

Step 5) synthesis of compound **3**

[00237] A mixture of compound **3-13** (0.60 g, 0.835 mmol), compound **3-14** (0.21 g, 1.0 mmol), EDCI (0.192 g, 1.0 mmol) and ethyl cyanoglyoxylate-2-oxime (0.048 g, 0.334 mmol) in DCM (10 mL) was stirred at 0 °C, and DIPEA (0.324 g, 2.505 mmol) was added dropwise. After the addition, the mixture was stirred at rt for 2 hours. After the mixture was completed, ammonium hydroxide (2 mL) was added. The resulting mixture was stirred for 1 hour, then partitioned. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 1) to give the title compound as a gray solid (0.45 g, 64%).

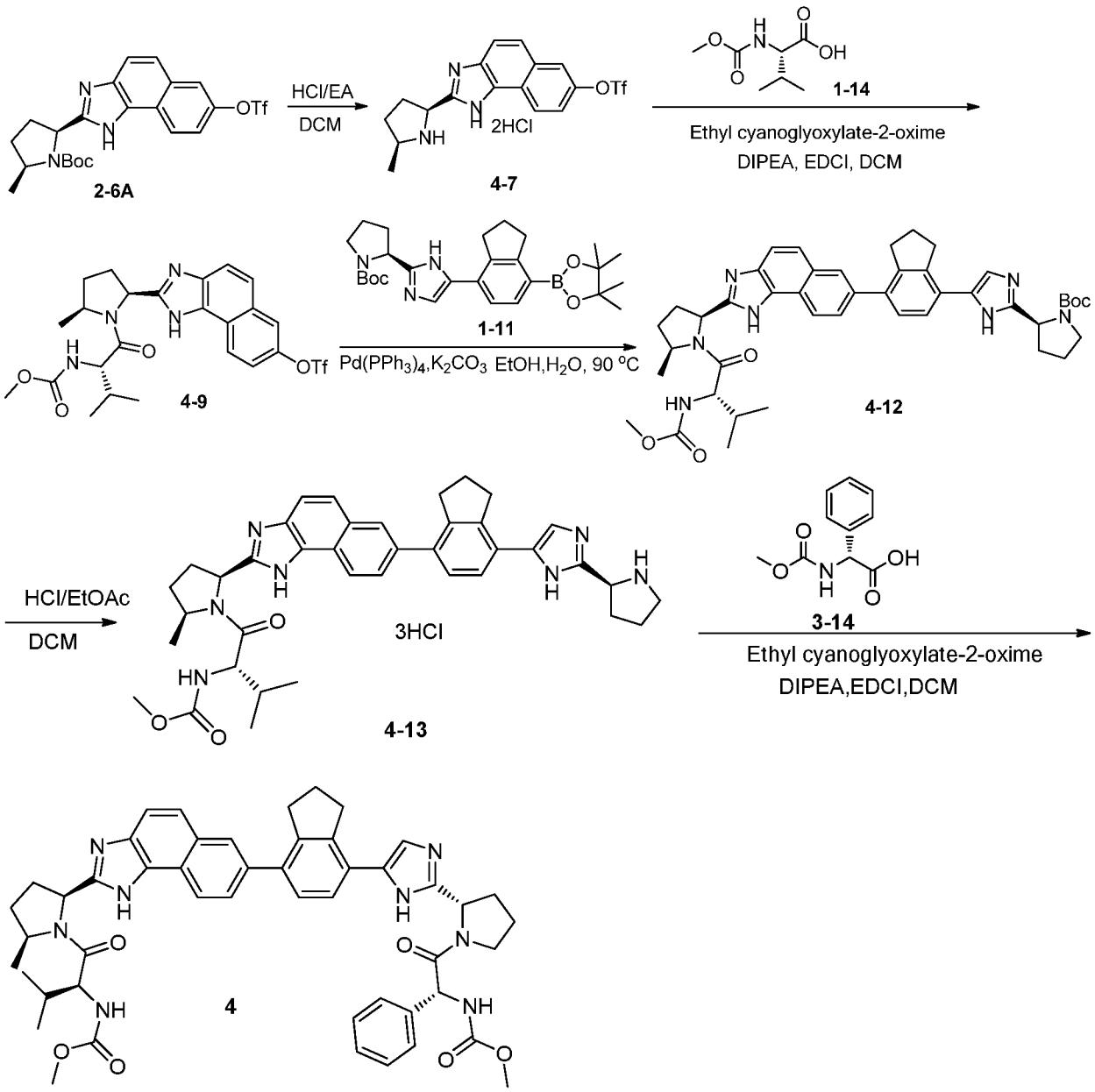
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.62 (d, 4H), 7.36 (m, 4H), 7.21 (m, 3H), 5.43 (s, 2H), 5.10 (s, 2H), 3.56 (m, 4H), 3.16 (m, 4H), 3.10 (m, 4H), 2.66 (m, 4H), 2.36 (m, 4H), 2.09 (m, 6H), 1.05 (m, 6H) ppm; MS-ESI, *m/z*: 837.7[M+H]$^+$.

Example 4



4

Synthesis route:



Synthesis steps:

Step 1) synthesis of compound **4-7**

[00238] To a solution of compound **2-6A** (0.8 g, 2 mmol) in DCM (15 mL) was added HCl/EtOAc (4 N, 4 mL) dropwise at 0 °C. After the addition, the mixture was stirred at rt. After the reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was recrystallized from EtOAc to give a brown solid (0.56 g, 90%).

MS-ESI, *m/z*: 400.2 $[M+H]^+$.

Step 2) synthesis of compound **4-9**

[00239] A mixture of compound **4-7** (0.9 g, 2.3 mmol), compound **1-14** (0.47 g, 2.7 mmol), EDCI (0.52 g, 2.7 mmol) and ethyl cyanoglyoxylate-2-oxime (0.13 g, 0.91 mmol) in DCM (10

mL) was stirred at 0 °C, and DIPEA (0.87 g, 6.7 mmol) was added dropwise. After the addition, the mixture was stirred at rt for 2 hours. After the reaction was complete, ammonium hydroxide (2 mL) was added. The resulting mixture was stirred for 1 hour, then partitioned. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 1) to give the title compound as a gray solid (0.8 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.52 (m, 2H), 7.32 (m, 2H), 5.18 (t, 1H), 4.18 (t, 1H), 3.37 (t, 3H), 2.85 (m, 2H), 2.59 (m, 2H), 2.45 (m, 2H), 1.25 (m, 3H), 1.01 (m, 6H) ppm; MS-ESI, *m/z*: 557.3$[M+H]^+$.

Step 3) synthesis of compound **4-12**

[00240] A mixture of compound **1-11** (0.731 g, 1.5 mmol), compound **4-9** (0.853 g, 1.5 mmol), $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol) and K_2CO_3 (0.61 mg, 4.4 mmol) in EtOH/H_2O (V : V = 3 : 1, 30 mL) was stirred at 90 °C under N_2 for 3 hours. After the reaction was complete, most of the solvent was removed. The resulting mixture was extracted with DCM (20 mL × 2). The combined organic layers were dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 2 : 1) to give the title compound as a gray solid (0.7 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.62 (d, 2H), 7.36 (m, 2H), 7.21 (m, 2H), 5.43 (s, 1H), 5.10 (s, 2H), 3.56 (m, 4H), 3.16 (m,4H), 3.10 (m, 4H), 2.66 (m, 4H), 2.56 (m, 2H), 2.36 (m, 4H), 2.09 (m, 6H), 1.35 (m, 3H), 1.05 (m, 9H) ppm; MS-ESI, *m/z*: 792.3$[M+H]^+$.

Step 4) synthesis of compound **4-13**

[00241] To a solution of compound **4-12** (0.8 g, 1.0 mmol) in DCM (15 mL) was added HCl/EtOAc (4 N, 4 mL) dropwise at 0 °C. After the addition, the mixture was stirred at rt. After the reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was recrystallized from EtOAc to give a brown solid (0.6 g, 90%).

MS-ESI, *m/z*: 661.5$[M+H]^+$.

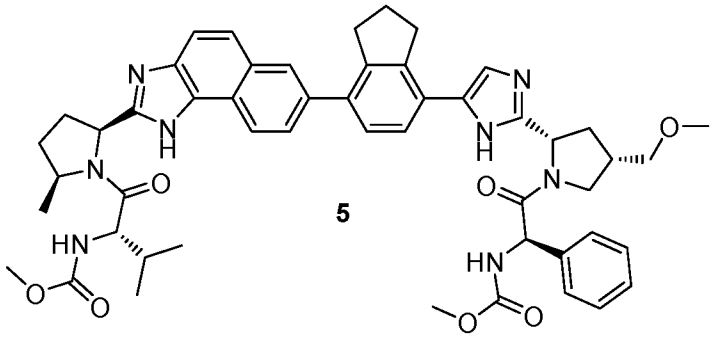
Step 5) synthesis of compound **4**

[00242] A mixture of compound **4-13** (0.60 g, 0.92 mmol), compound **3-14** (0.23 g, 1.1 mmol), EDCI (0.21 g, 1.1 mmol) and ethyl cyanoglyoxylate-2-oxime (0.06 g, 0.37 mmol) in DCM (10 mL) was stirred at 0 °C, and DIPEA (0.360 g, 2.8 mmol) was added dropwise. After the addition,

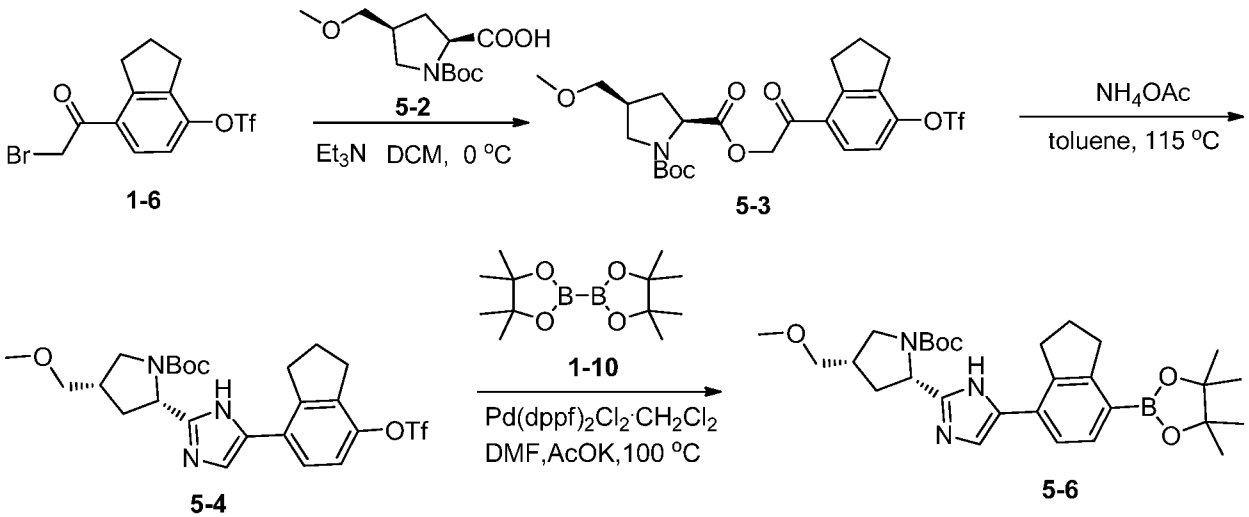
the mixture was stirred at rt for 2 hours. After the reaction was complete, ammonium hydroxide (2 mL) was added. The resulting mixture was stirred for 1 hour, then partitioned. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 1) to give the title compound as a gray solid (0.40 g, 50%).

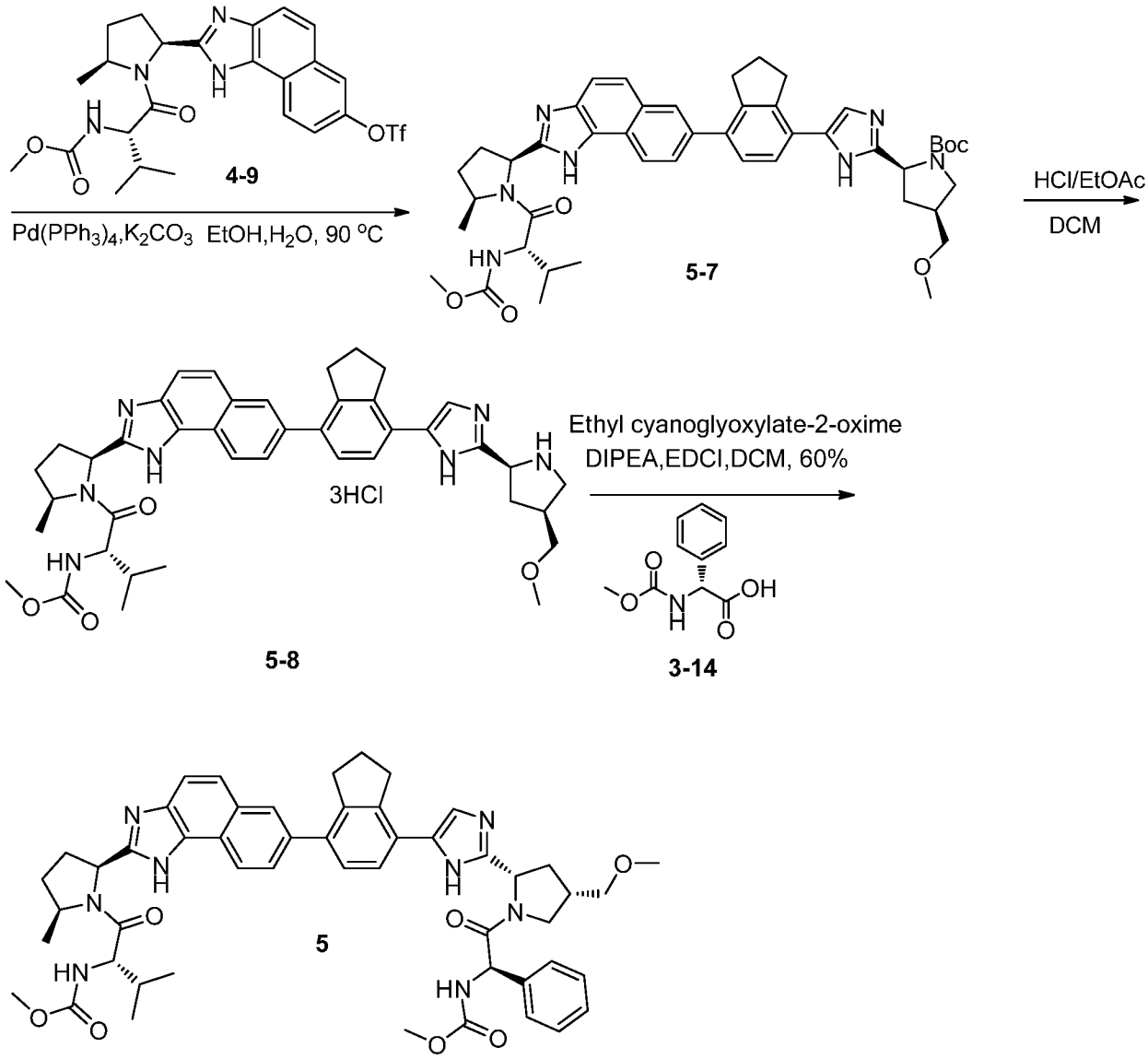
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.62 (d, 4H), 7.36 (m, 4H), 7.21 (m, 3H), 5.43 (s, 2H),5.10 (s, 2H), 3.56 (m, 4H), 3.16 (m, 4H), 3.10 (m, 4H), 2.66 (m, 4H), 2.36 (m, 3H), 2.09 (m, 6H), 1.59 (m, 3H), 1.05 (m, 6H) ppm; MS-ESI, *m/z*: 852.5$[M+H]^+$.

Example 5



Synthesis route:





Synthesis steps:

Step 1) synthesis of compound **5-3**

[00243] To a solution of compound **1-6** (2.5 g, 5.81 mmol) and compound **5-2** (1.5 g, 5.81 mmol) in DCM (20 mL) was added triethylamine (0.98 g, 9.68 mmol) dropwise at 0 °C. After the addition, the mixture was stirred at rt and monitored by TLC. After the reaction was complete, the mixture was washed with water (10 mL) and saturated aqueous NaCl. The organic layer was dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 6 : 1)) to give the title compound (2.0 g, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.6 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 5.28 (ddd, J = 60.3, 53.6, 16.3 Hz, 2H), 4.43 (dt, J = 15.2, 8.0 Hz, 1H), 3.82–3.66 (m, 1H), 3.46–3.34 (m, 5H), 3.32 (t, J = 7.5 Hz, 2H), 3.23 (dd, J = 10.7, 7.7 Hz, 1H), 3.05 (t, J = 7.4 Hz, 2H), 2.61–2.46 (m,

2H), 2.25–2.12 (m, 2H), 1.77 (s, 1H), 1.45 (d, J = 10.3 Hz, 9H) ppm; MS-ESI, *m/z*: 566.2[M+H]$^+$.

Step 2) synthesis of compound **5-4**

[00244] A mixture of compound **5-3** (2.1 g, 3.71 mmol) and ammonium acetate (1.72 g, 22.3 mmol) in toluene (20 mL) was stirred at 115 °C for 12 hours. After the reaction was completed, the mixture was diluted with water, and the resulting mixture was extracted with EtOAc (30 mL × 2). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 4 : 1) to give the title compound as a gray solid (1.5 g, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (s, 1H), 7.10 (d, J = 8.6 Hz, 1H), 5.00 (t, J = 7.1 Hz, 1H), 3.81 (s, 1H), 3.52 (d, J = 4.9 Hz, 1H), 3.41–3.32 (m, 4H), 3.11 (dt, J = 15.1, 6.8 Hz, 5H), 2.78 (d, J = 47.9 Hz, 1H), 2.63–2.39 (m, 2H), 2.25–2.15 (m, 2H), 1.51 (s, 9H) ppm; MS-ESI, *m/z*: 546.3[M+H]$^+$.

Step 3) synthesis of compound **5-6**

[00245] A mixture of compound **5-4** (1.55 g, 2.84 mmol), 4,4,4',4',5,5,5',5'-octamethyl -2,2'-bi-1,3,2-dioxaborolane **1-10** (0.866 g, 3.41 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (0.232 g, 0.284 mmol) and KOAc (0.835 g, 8.52 mmol) in DMF (20 mL) was stirred at 100 °C under N_2 for 4 hours. The mixture was cooled to rt and diluted with water (10 mL). The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with water twice and dried, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 3 : 1） to give the title compound (1.3 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (s, 1H), 7.10 (d, J = 8.6 Hz, 1H), 5.00 (t, J = 7.1 Hz, 1H), 3.81 (s, 1H), 3.52 (d, J = 4.9 Hz, 1H), 3.41–3.32 (m, 4H), 3.11 (m, 5H), 2.78 (d, 1H), 2.63–2.39 (m, 2H), 2.25–2.15 (m, 2H), 1.51 (s, 9H), 1.25 (m, 12H) ppm; MS-ESI, *m/z*: 524.3[M+H]$^+$.

Step 4) synthesis of compound **5-7**

[00246] A mixture of compound **5-6** (0.500 g, 0.955 mmol), compound **4-9** (0.53 g, 0.955 mmol), $Pd(PPh_3)_4$ (0.110 g, 0.095 mmol) and K_2CO_3 (0.391 mg, 2.87 mmol) in EtOH/H_2O (V : V = 3 : 1, 30 mL) was stirred at 90 °C under N_2 for 3 hours. After the reaction was complete, most of the solvent was removed. The resulting mixture was extracted with DCM (20 mL × 2). The combined organic layers were dried and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM : EtOAc (V : V) = 1 : 2) to give the title compound as a

gray solid (0.5 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.62 (d, 2H), 7.36 (m, 2H), 7.21 (m, 2H), 5.43 (s, 1H), 5.10 (s, 2H), 3.56 (m, 4H), 3.16 (m, 4H), 3.11 (m, 5H), 3.00 (m, 4H), 2.66 (m, 4H), 2.56 (m, 2H), 2.36 (m, 3H), 2.09 (m, 6H), 1.35 (m, 3H), 1.05 (m, 9H) ppm; MS-ESI, *m/z*: 804.8$[M+H]^+$.

Step 5) synthesis of compound **5-8**

[00247] To a solution of compound **5-7** (0.6 g, 0.7 mmol) in DCM (15 mL) was added HCl/EtOAc (4 N, 4 mL) dropwise at 0 °C. After the addition, the mixture was stirred at rt. After the reaction was complete, the reaction mixture was concentrated *in vacuo*. The residue was washed with EtOAc to give a brown solid (0.45 g, 84%).

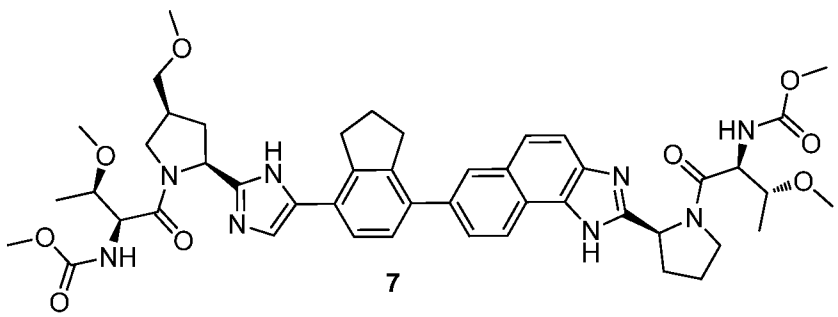
MS-ESI, *m/z*: 705.4$[M+H]^+$.

Step 6) synthesis of compound **5**

[00248] A mixture of compound **5-8** (0.55 g, 0.72 mmol), compound **3-14** (0.178 g, 0.852 mmol), EDCI (0.163 g, 0.852 mmol) and ethyl cyanoglyoxylate-2-oxime (0.04 g, 0.284 mmol) in DCM (10 mL) was stirred at 0 °C, and DIPEA (0.275 g, 2.13 mmol) was added dropwise. After the addition, the mixture was stirred at rt for 2 hours. After the reaction was complete, ammonium hydroxide (2 mL) was added. The resulting mixture was stirred for 1 hour, then partitoned. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 3) to give the title compound as a gray solid (0.35 g, 55%).

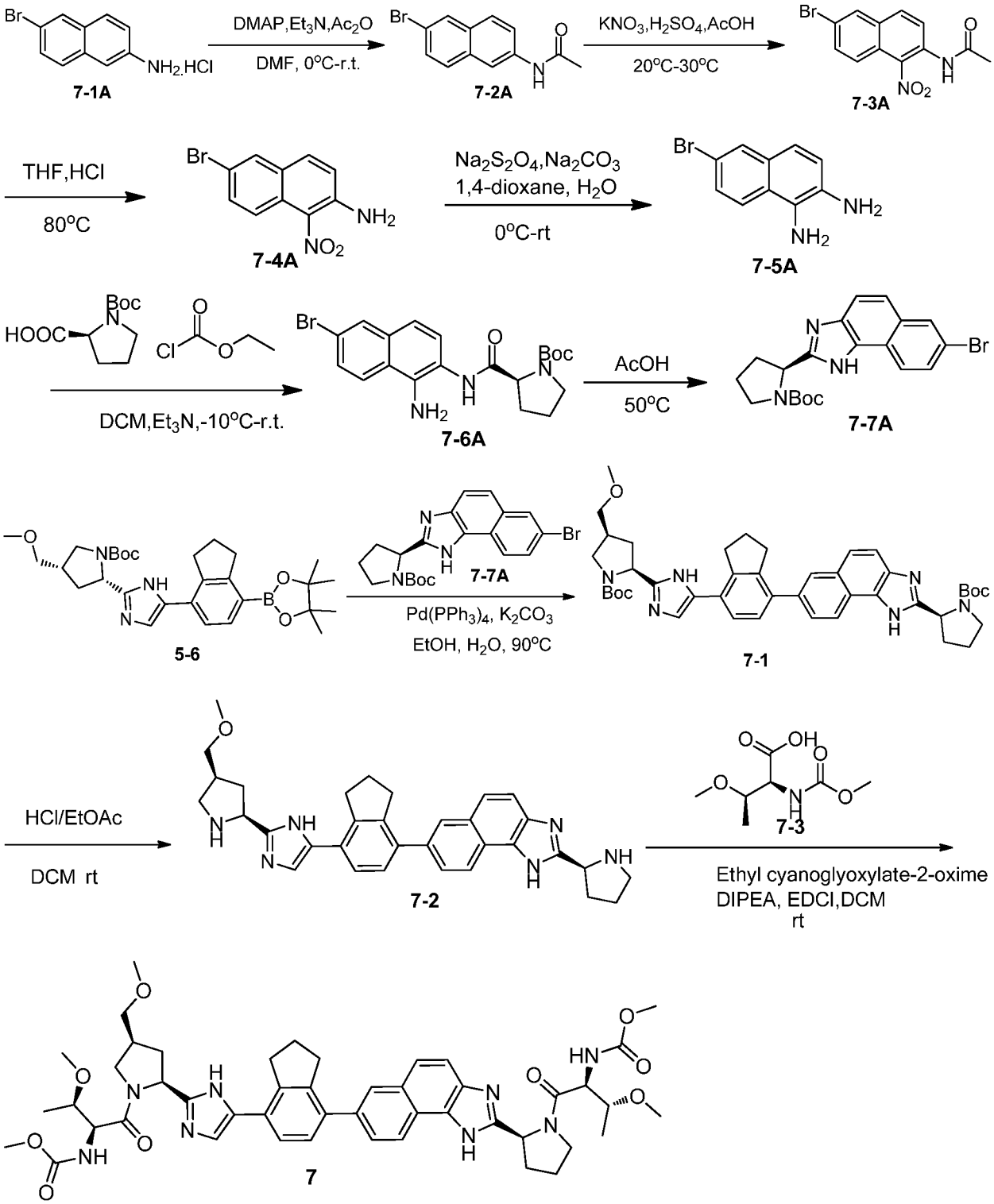
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.52 (d, 4H), 7.36 (m, 4H), 7.31 (m, 3H), 5.43 (s, 2H), 5.10 (s, 2H), 3.56 (m, 4H), 3.21 (m, 5H), 3.09 (m, 4H), 3.01 (m, 4H), 2.66 (m, 4H), 2.26 (m, 2H), 2.09 (m, 6H), 1.59 (m, 3H), 1.05 (m, 6H) ppm; MS-ESI, *m/z*:896.0$[M+H]^+$.

Example 6



7

Synthesis route:



Synthesis steps:

Step 1) synthesis of compound **7-2A**

[00249] To a mixture of 6-bromonaphthalen-2-amine hydrochloride **7-1A** (2.00 g, 7.73 mmol, 1.00 eq) in DMF (15 mL) were added DMAP (0.02 g, 0.16 mmol, 0.02 eq) and Et_3N (3.70 mL, 2.70 mmol, 3.50 eq). The resulting mixture was cooled to 0 °C, then acetic anhydride (1.09 mL, 11.60 mmol, 1.50 eq) was added. The mixture was stirred for 3 h at rt. After the reaction was

completed, the reaction mixture was poured into 30 mL of water, then there was a white solid precipitated out. The resulting mixture was stirred for 0.5 h, then filtered. The filter cake was washed with water three times and dried to give the product as a white solid (1.78 g, 87.46%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 8.31 (s, 1H), 8.10 (s, 1H), 7.84 (d, J = 8.9 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.56 (dd, J = 8.7, 1.5 Hz, 1H), 2.11 (s, 3H) ppm.

Step 2) synthesis of compound **7-3A**

[00250] To a solution of compound **7-2A** (5.0 g, 18.93 mmol, 1.00 eq), KNO_3 (2.30 g, 22.71 mmol, 1.20 eq) in AcOH (35 mL) was added dropwise H_2SO_4 (5.14 mL, 94.65 mmol, 5.00 eq) at 20 °C. After the addition, the mixture was stirred at 30 °C for 7 h. After the reaction was completed, the reaction mixture was poured into 50 mL of water, then there was a brown solid precipitated out. The resulting mixture was filtered. The filter cake was washed with water (20 mL × 3) and dried to give the product as a brown solid (5.34 g, 91.31%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (s, 1H), 8.49 (d, J = 9.2 Hz, 1H), 8.03 (s, 1H), 7.92 (t, J = 8.0 Hz, 2H), 7.72 (dd, J = 9.2, 1.4 Hz, 1H), 2.31 (s, 3H) ppm.

Step 3) synthesis of compound **7-4A**

[00251] To a solution of compound **7-3A** (3.78 g, 12.23 mmol, 1.00 eq) in THF (20 mL) was added HCl (6 N, 10.5 mL, 61.10 mmol, 5.00 eq), then the mixture was stirred at 80 °C for 7 h. After the reaction was completed, the reaction mixture was cooled to rt and poured into 50 mL of ice water, then there was a yellow solid precipitated. The resulting mixture was filtered. The filter cake was washed with water (15 mL × 3) and dried to give the product as a brown solid (3.00 g, 91.90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, J = 9.3 Hz, 1H), 7.84 (s, 1H), 7.68 (t, J = 8.6 Hz, 2H), 6.94 (d, J = 9.0 Hz, 1H), 6.46 (s, 2H) ppm; MS-ESI, *m/z*: 267.1$[M+H]^+$.

Step 4) synthesis of compound **7-5A**

[00252] To a solution of compound **7-4A** (4.00 g, 14.97 mmol, 1.00 eq) in 1,4-dioxane (30 mL) were added dropwise $Na_2S_2O_4$ (8.68 g, 44.93mmol, 3.00 eq) and Na_2CO_3 (1.58g, 14.97 mmol, 1.00 eq) under ice-bath condition. After the addition, the mixture was stirred at rt for 5 h. After the reaction was completed, the reaction mixture was poured into 30 mL of water, then there was a cinerous solid precipitated. The resulting mixture was filterd. The filter cake was washed with water (15 mL × 3) and dried to give the product as a cinerous solid (3.2 g, 91.01%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 1.4 Hz, 1H), 7.60 (d, J = 9.0 Hz, 1H), 7.49 (dd, J = 9.0, 1.7 Hz, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.05 (d, J = 8.5 Hz, 1H), 3.70 (d, J = 18.9 Hz, 4H) ppm; MS-ESI, *m/z*: 237.2$[M+H]^+$.

Step 5) synthesis of compound **7-6A**

[00253] To a solution of (*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (9.06 g , 42.17 mmol, 1.00 eq), ethyl carbonochloridate (4.58 g, 42.17 g, 1.00 eq) in DCM (100 mL) was added dropwise Et_3N (8.8 mL, 63.26 mmol, 1.50 eq) at -10 °C. After the addition, the mixture was maintained at -10 °C for 10 min, then filtered. The filter cake was washed with DCM (10 mL × 2), and the filtrate was collected and reserved for the later use. To a solution of compound **7-5A** (10 g, 42.17 mmol, 1.00 eq) in DCM (80 mL) was added dropwise the filtrate at -5 °C. After the addition, the resulting mixture was stirrd at rt for 2 h. After the reaction was completed, 100 mL of water was added, then the mixture was partitioned. The aqueous layer was extracted with DCM (50 mL × 2). The combined organic layers were dried and concentrated to give the crude product as a brown black solid (18.00 g, 95.18%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.16 (d, J = 8.6 Hz, 1H), 4.61 – 4.34 (m, 3H), 4.00 (d, J = 5.1 Hz, 1H), 2.43 (s, 2H), 2.13 (dd, J = 12.8, 7.1 Hz, 2H), 1.90 – 1.63 (m, 2H), 1.54 (s, 9H) ppm; MS-ESI, *m/z*: 434.2$[M+H]^+$.

Step 6) synthesis of compound **7-7A**

[00254] The solution of compound **7-6A** (18.00 g, 43.27 mmol, 1.00 eq) in acetic acid (80 mL) was stirred at 50 °C for 5 h. After the reaction was completed, the solution was concentrated to remove most of the acetic acid. To the residue were added EtOAc (100 mL) and water (50 mL), and the mixture was stirred. The residue of acetic acid was removed by adding sodium carbonate to adjust the pH of the mixture to 8. The resulting mixture waspartitioned and the aqueous layer was extracted with EtOAc (20 mL × 2). The combined organic layers were washed with water (50 mL), dried and concentrated to give the product as a brown solid (16.03 g, 93.06%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.52 (m, 2H), 7.32 (m, 2H), 5.18 (t, 1H), 3.37-3.21 (t, 2H), 2.59-2.30 (t, 2H), 2.35-2.11 (m, 2H), 1.26 (t, 9H) ppm; MS-ESI, *m/z*: 416.2$[M+H]^+$.

Step 7) synthesis of compound **7-1**

[00255] To the mixture of ethanol (10 mL) and water (3 mL) were added compound **5-6** (600 mg,

1.15 mmol, 1.0 eq), compound **7-7A** (477 mg, 1.15 mmol, 1.0 eq), potassium carbonate (316 mg, 2.29 mmol, 2.0 eq), $Pd(PPh_3)_4$ (29 mg, 0.034 mmol, 0.03 eq). The mixture was stirred at 90 °C for 18 h. The reaction mixture was poured into 50 mL of water, then the mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 1) to give the crude product as a white solid (0.68 g, 80.9%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.61-10.64 (m, 2H), 8.67 (s, 1H), 7.79 (dd, J = 98.4, 31.8 Hz, 5H), 7.39 (d, J = 7.2 Hz, 1H), 7.21 (s, 1H), 5.26 (d, J = 4.3 Hz, 1H), 5.06 (t, J = 7.3 Hz, 1H), 3.93 – 3.78 (m, 1H), 3.62 – 3.47 (m, 2H), 3.43 – 3.29 (m, 4H), 3.27 – 3.04 (m, 5H), 2.90 – 2.70 (m, 1H), 2.51 (ddd, J = 19.3, 13.9, 6.6 Hz, 2H), 2.29 (d, J = 4.2 Hz, 2H), 2.17 – 2.03 (m, 4H), 1.54 (d, J = 11.0 Hz, 18H) ppm; MS-ESI, *m/z*: 733.20 $[M+H]^+$.

Step 8) synthesis of compound **7-2**

[00256] To the mixture of compound **7-1** (0.68 g, 0.93 mmol, 1.0 eq) in DCM (15 mL) was added dropwise HCl/EtOAc (4 N, 3 mL) at 0 °C. After the addition, the mixture was stirred at rt for 12 h. The mixture was concentrated to remove the solvent, and to the residue was added EtOAc (20 mL). The resulting mixture was triturated for 1 h and filtered by suction to give the filter cake as a light yellow solid. The filter cake was dissolved in water (10 mL), then to the solution was added aqueous sodium carbonate to precipitate out a solid. The mixure was filtered and the filter cake was dried to give the yellow solid (320 mg, 63.1%).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.48 (d, J = 8.3 Hz, 1H), 8.04 (s, 1H), 7.78 (d, J = 50.0 Hz, 1H), 7.73 – 7.51 (m, 3H), 7.34 (d, J = 7.6 Hz, 1H), 7.24 (s, 1H), 4.46 (t, J = 7.0 Hz, 1H), 4.20 (t, J = 7.7 Hz, 1H), 3.32 (d, J = 7.2 Hz, 4H), 3.25 (s, 3H), 3.08 (dt, J = 24.6, 6.9 Hz, 4H), 3.01 – 2.91 (m, 2H), 2.74 (dd, J = 10.1, 5.5 Hz, 1H), 2.40 (dd, J = 13.6, 7.1 Hz, 1H), 2.29 – 2.15 (m, 2H), 2.05 (dd, J = 13.7, 6.8 Hz, 2H), 1.82 (td, J = 13.5, 6.3 Hz, 2H), 1.69 – 1.52 (m, 1H) ppm; MS-ESI, *m/z*: 533.3 $[M+H]^+$.

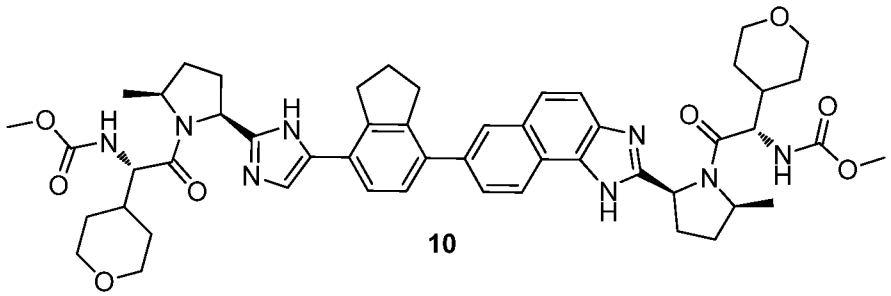
Step 9) synthesis of compound **7**

[00257] To DCM (15 mL) were added compound **7-2** (250 mg, 0.469 mmol, 1.0 eq), compound **7-3** (209 mg, 1.03 mmol, 2.2 eq), ethyl cyanoglyoxylate-2-oxime (61 mg, 0.43 mmol, 0.8 eq) and DIPEA (35 mg, 0.27 mmol, 0.5 eq), then EDCI (227 mg, 1.19 mmol, 2.2 eq) was added. The resulting mixture was stirrd at rt for 5 h. The reaction mixture was poured into 30 mL of water,

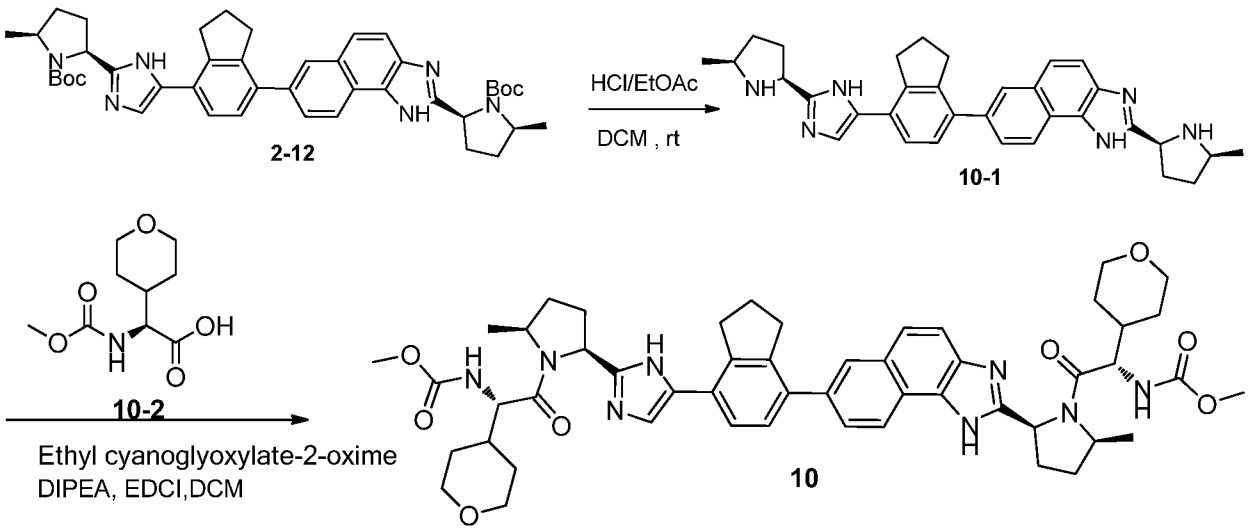
then the mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (DCM : EtOAc : MeOH (V : V : V) = 5 : 10 : 1) to give the product as a white solid (300 mg, 72.7%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.35 – 10.31 (m, 2H), 8.65 (s, 1H), 7.91 (d, J = 45.9 Hz, 2H), 7.69 (d, J = 23.4 Hz, 2H), 7.48 (s, 1H), 7.36 (d, J = 6.2 Hz, 1H), 7.15 (d, J = 19.1 Hz, 1H), 5.93 – 5.71 (m, 2H), 5.70 – 5.54 (m, 1H), 5.38 (t, J = 7.7 Hz, 1H), 4.83 – 4.31 (m, 2H), 4.14 – 3.98 (m, 1H), 3.88 (d, J = 20.9 Hz, 2H), 3.73 (d, J = 5.9 Hz, 6H), 3.66 – 3.54 (m, 2H), 3.45 (d, J = 8.8 Hz, 1H), 3.39 (t, J = 22.3 Hz, 6H), 3.24 – 2.88 (m, 7H), 2.79 (dd, J = 10.1, 9.2 Hz, 1H), 2.72 – 2.58 (m, 1H), 2.51 (dd, J = 12.3, 7.7 Hz, 1H), 2.36 (dd, J = 23.8, 11.5 Hz, 1H), 2.22 – 2.11 (m, 2H), 1.99 (s, 2H), 1.17 (dd, J = 18.8, 5.7 Hz, 4H), 0.89 (dd, J = 6.9, 4.0 Hz, 2H) ppm; MS-ESI, *m/z*: 879.3 $[M+H]^+$.

Example 7



Synthesis route:



Synthesis steps:

Step 1) synthesis of compound **10-1**

[00258] To the mixture of compound **2-12** (1.25 g, 1.74 mmol, 1.0 eq) in DCM (15 mL) was added dropwise HCl/EtOAc (3 mL) at 0 °C. After the addition, the mixture was stirred at rt for 6 h. The mixture was concentrated to remove the solvent, and to the residue was added EtOAc (20 mL). The resulting mixture was triturated at rt for 1 h and filtered by suction to give the filter cake as a light yellow solid. The filter cake was dissolved in water (10 mL), then to the solution was added aqueous sodium carbonate to precipitate out the solid. The mixure was filtered and the filter cake was dried to give a yellow solid (800 mg, 89%).

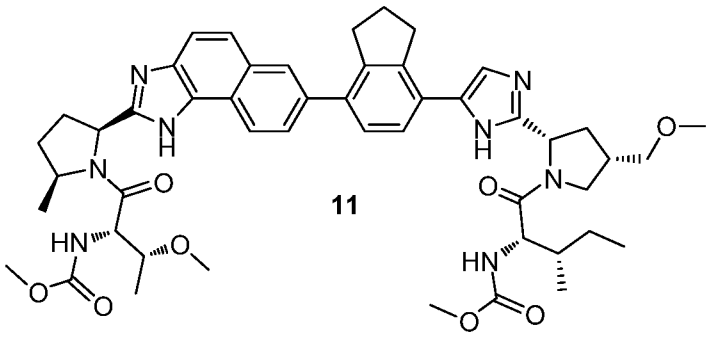
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 8.00 (s, 1H), 7.71 (d, J = 12.3 Hz, 4H), 7.40 (d, J = 7.9 Hz, 1H), 7.21 (s, 1H), 4.71 (dd, J = 8.5, 5.9 Hz, 1H), 4.58 – 4.43 (m, 1H), 3.43 (ddd, J = 30.0, 14.4, 6.3 Hz, 2H), 3.25 – 3.00 (m, 4H), 2.42 (dd, J = 12.8, 8.4 Hz, 1H), 2.30 (dt, J = 20.9, 8.3 Hz, 1H), 2.24 – 2.08 (m, 4H), 1.99 (dd, J = 12.6, 5.9 Hz, 2H), 1.52 – 1.37 (m, 2H), 1.34 – 1.25 (m, 6H) ppm; MS-ESI, *m/z*: 517.3 $[M+H]^+$.

Step 2) synthesis of compound **10**

[00259] To DCM (15 mL) were added compound **10-1** (280 mg, 0.54 mmol, 1.0 eq), compound **10-2** (294 mg, 1.36 mmol, 2.5 eq), ethyl cyanoglyoxylate-2-oxime (61 mg, 0.43 mmol, 0.8 eq) and DIPEA (35 mg, 0.27 mmol, 0.5 eq), then EDCI (227 mg, 1.19 mmol, 2.2 eq) was added. The resulting mixture was stirrd at rt for 6 h. The reaction mixture was poured into 30 mL of water, then the mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (DCM : EtOAc (V : V) = 1 : 2) to give the product as a light yellow solid (368 mg, 74.2%).

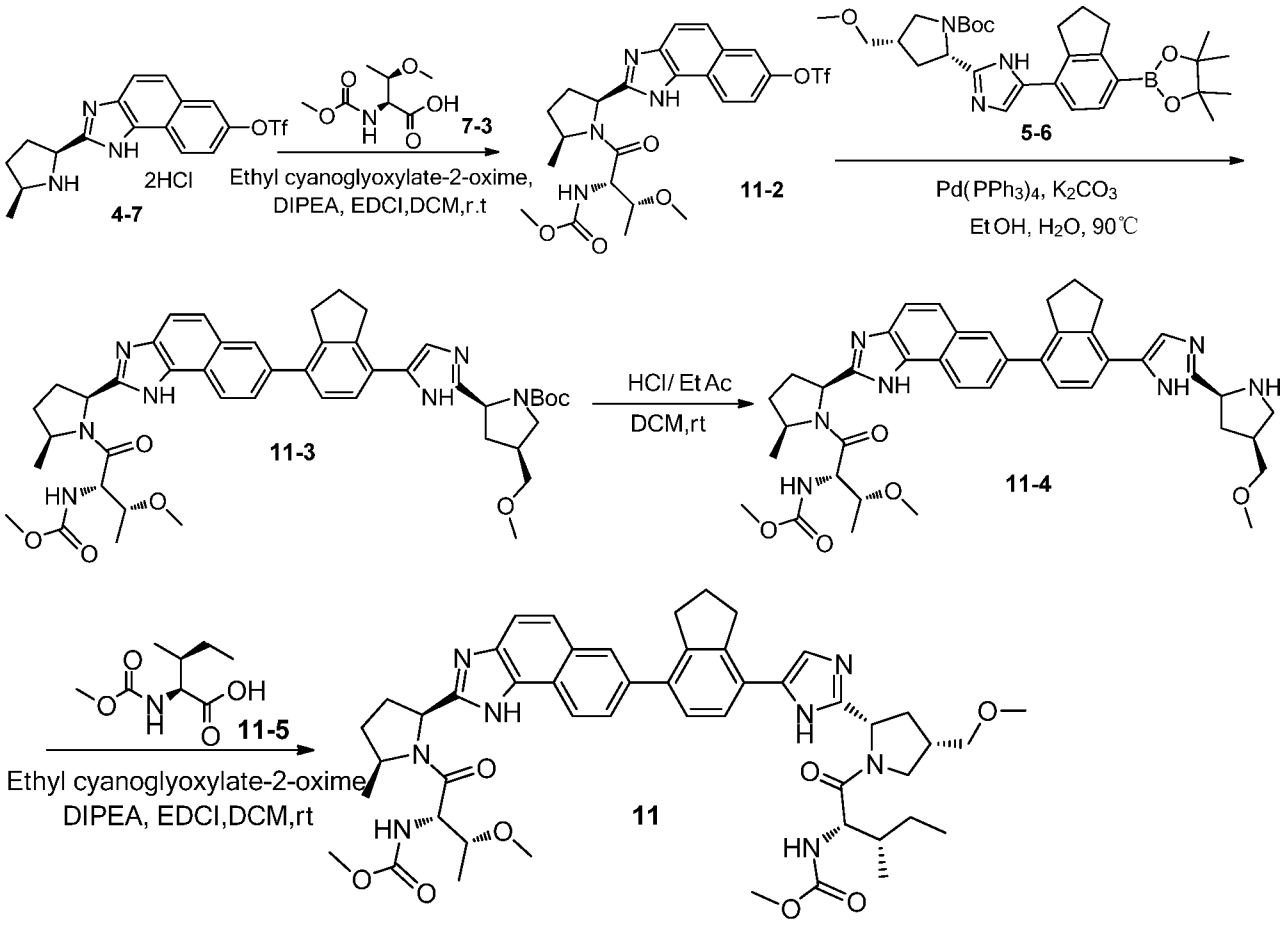
^{1}H NMR (400 MHz, $CDCl_3$): δ 12.21 – 10.33 (m, 2H), 8.80 – 8.46 (m, 1H), 8.07 – 7.85 (m, 2H), 7.82 – 7.62 (m, 2H), 7.51 (dd, J = 42.1, 33.3 Hz, 1H), 7.33 (s, 1H), 7.26 – 7.04 (m, 1H), 5.49 (dt, J = 14.2, 7.7 Hz, 2H), 5.28 – 5.16 (m, 1H), 4.75 – 4.62 (m, 1H), 4.41 – 4.29 (m, 2H), 4.03 (dd, J = 16.4, 9.9 Hz, 2H), 3.90 – 3.68 (m, 6H), 3.54 – 2.94 (m, 10H), 2.42 (ddd, J = 33.7, 17.1, 9.5 Hz, 2H), 2.20 – 2.08 (m, 3H), 1.90 (ddd, J = 52.2, 26.1, 7.8 Hz, 10H), 1.68 – 1.49 (m, 3H), 1.40 – 1.27 (m, 6H), 1.17 (d, J = 5.8 Hz, 2H) ppm; MS-ESI, *m/z*: 915.5 $[M+H]^+$.

Example 8



11

Synthesis route:



Synthesis steps:

Step 1) synthesis of compound **11-2**

[00260] To DCM (20 mL) were added compound **4-7** (1.27 g, 2.7 mmol), compound **7-3** (0.62 g, 3 mmol), EDCI (0.62 g, 3.3 mmol) and ethyl cyanoglyoxylate-2-oxime (0.15 g, 1.1 mmol). Then to the mixture was added dropwise DIPEA (1.1 g, 8.2 mmol) at 0 °C. The resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with EtOAc (100 mL). The organic layer was washed with saturated aqueous sodium chloride (50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 3 :1) to give a brown

solid (0.93 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.71 – 10.69 (m, 1H), 8.57 – 8.34 (m, 1H), 7.94 (dd, J = 70.9, 22.8 Hz, 2H), 7.59 (dd, *J* = 24.5, 15.0 Hz, 1H), 7.43 (s, 1H), 5.96 (dd, *J* = 87.7, 33.4 Hz, 1H), 5.46 (dd, J = 38.5, 30.6 Hz, 1H), 4.73 – 4.23 (m, 2H), 3.70 (s, 3H), 3.36 (s, 3H), 2.55 – 2.12 (m, 2H), 2.04 (s, 3H), 1.44 – 1.35 (m, 3H), 1.13 (d, *J* = 5.9 Hz, 3H) ppm; MS (ESI, pos.ion) *m/z*: 572.2 $[M+H]^+$.

Step 2) synthesis of compound **11-3**

[00261] To the mixture of ethanol (20 mL) and water (4 mL) were added compound **5-6** (0.65 g, 1.2 mmol), compound **11-2** (0.69 g, 1.2 mmol), $Pd(PPh_3)_4$ (0.2 g, 0.12 mmol) and K_2CO_3 (0.6 g, 3.6 mmol). The mixture was stirred at 90 °C under nitrogen atmosphere. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated to remove the solvent. The residue was extracted with EtOAc (200 mL), and the organic layer was washed with saturated aqueous sodium chloride (50 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 3) to give a brown solid (0.45 g, 44%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.55 – 10.67 (m, 1H), 8.05 – 7.82 (m, 2H), 7.75 – 7.59 (m, 3H), 7.41 – 7.29 (m, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 6.21 – 5.87 (m, 1H), 5.67 – 5.36 (m, 1H), 5.05 (t, *J* = 7.3 Hz, 1H), 4.46 (ddd, *J* = 76.6, 33.7, 27.1 Hz, 2H), 3.92 – 3.80 (m, 3H), 3.75 – 3.66 (m, 2H), 3.54 (s, 1H), 3.37 (s, 6H), 3.30 (s, 2H), 3.20 – 3.04 (m, 6H), 2.64 – 2.42 (m, 3H), 2.30 – 1.95 (m, 6H), 1.51 (s, 9H), 1.26 (m, 6H) ppm; MS (ESI, pos.ion) *m/z*: 820.4$[M+H]^+$.

Step 3) synthesis of compound **11-4**

[00262] To the mixture of compound **11-3** (0.45 g, 0.54 mmol) in DCM (10 mL) was added dropwise HCl/EtOAc (4 M/L, 3 mL) at 0 °C. After the addition, the mixture was stirred at rt for 3 h. The mixture was concentrated and the residue was triturated with ethyl acetate, then the resulting mixture was filtered. The filter cake was dissolved in water (10 mL), and the pH of the solution was adjusted with potassium carbonate to 8-9. The resulting mixture was filtered by suction to give the product (0.35 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.55 – 10.67 (m, 1H), 8.05 – 7.82 (m, 2H), 7.75 – 7.59 (m, 3H), 7.41 – 7.29 (m, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 6.21 – 5.87 (m, 1H), 5.67 – 5.36 (m, 1H), 5.05 (t, *J* = 7.3 Hz, 1H), 4.46 (ddd, *J* = 76.6, 33.7, 27.1 Hz, 2H), 3.92 – 3.80 (m, 3H), 3.75 – 3.66 (m, 2H),

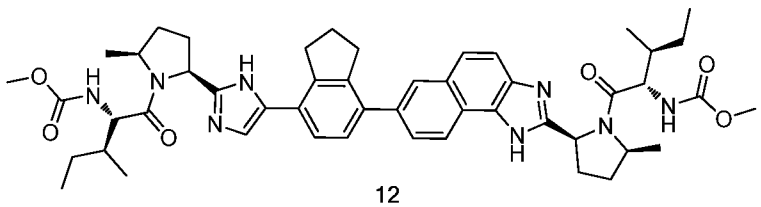
3.54 (s, 1H), 3.37 (s, 6H), 3.30 (s, 1H), 3.20 – 3.04 (m, 6H), 2.64 – 2.42 (m, 3H), 2.30 – 1.95 (m, 7H), 1.26 (m, 6H) ppm; MS (ESI, pos.ion) *m/z*: 720.2 $[M+H]^+$.

Step 4) synthesis of compound **11**

[00263] To DCM (20 mL) were added compound **11-4** (0.35 g, 0.49 mmol), compound **11-5** (0.1 g, 0.53 mmol), EDCI (0.11 g, 0.58 mmol) and ethyl cyanoglyoxylate-2-oxime (0.028 g, 0.19 mmol). Then to the mixture was added dropwise DIPEA (0.19 g, 1.5 mmol) at 0 °C. The resulting mixture was stirrd at rt for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc (100 mL). The resulting mixture was washed with saturated aqueous sodium chloride (50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM : EtOAc (V : V) =2 : 1) to give a white solid (0.3 g, 70%).

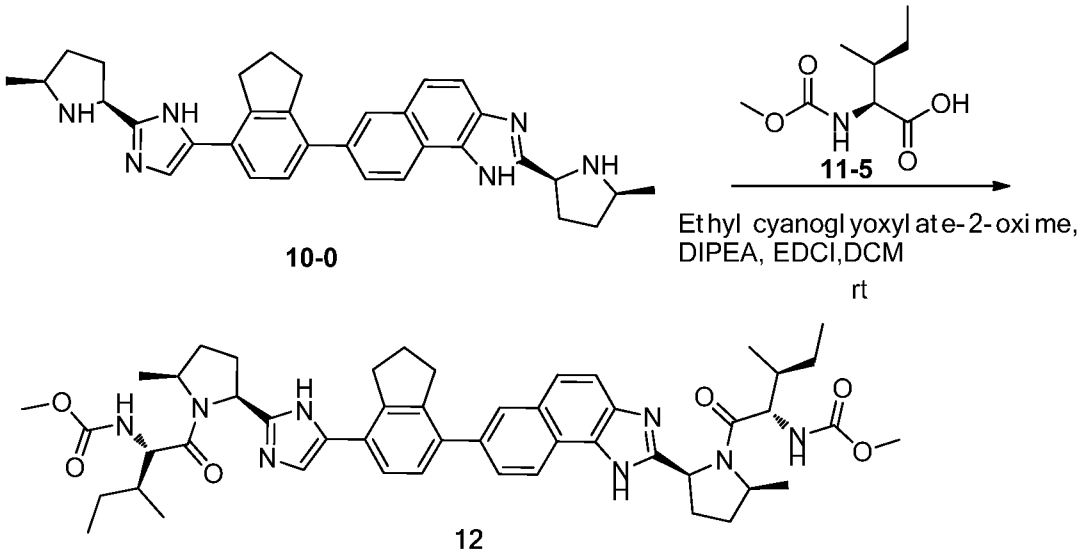
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 7.98 (d, J = 13.6 Hz, 1H), 7.68 (dd, J = 20.5, 8.0 Hz, 3H), 7.35 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 6.7 Hz, 1H), 5.98 – 5.68 (m, 1H), 5.56 (dd, J = 20.1, 6.7 Hz, 2H), 5.36 – 5.24 (m, 2H), 4.70 – 4.28 (m, 3H), 4.19 – 3.82 (m, 3H), 3.79 – 3.56 (m, 6H), 3.40 (s, 6H), 3.29 (d, J = 11.8 Hz, 2H), 3.14 – 3.04 (m, 6H), 2.34 – 1.97 (m, 5H), 1.83 – 1.40 (m, 4H), 1.39 – 1.22 (m, 7H), 1.13 (d, J = 6.0 Hz, 2H), 0.91 – 0.71 (m, 6H) ppm; MS (ESI, pos.ion) *m/z*: 891.5 $[M+H]^+$.

Example 9



12

Synthesis route:



10-0

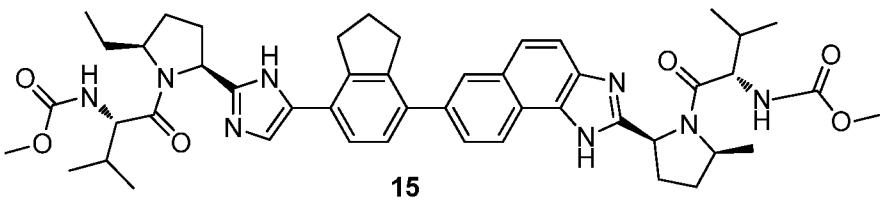
12

Synthesis steps:

[00264] To DCM (15 mL) were added compound **10-0** (280 mg, 0.54 mmol, 1.0 eq), compound **11-5** (256 mg, 1.36 mmol, 2.5 eq), ethyl cyanoglyoxylate-2-oxime (61 mg, 0.43 mmol, 0.8 eq) and DIPEA (35 mg, 0.27 mmol, 0.5 eq), then EDCI (227 mg, 1.19 mmol, 2.2 eq) was added. The resulting mixture was stirred at rt for 18 h. The reaction mixture was poured into 30 mL of water, then the mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (DCM : EtOAc (V : V) =1 : 2) to give the product as a light yellow solid (150 mg, 32.2%).

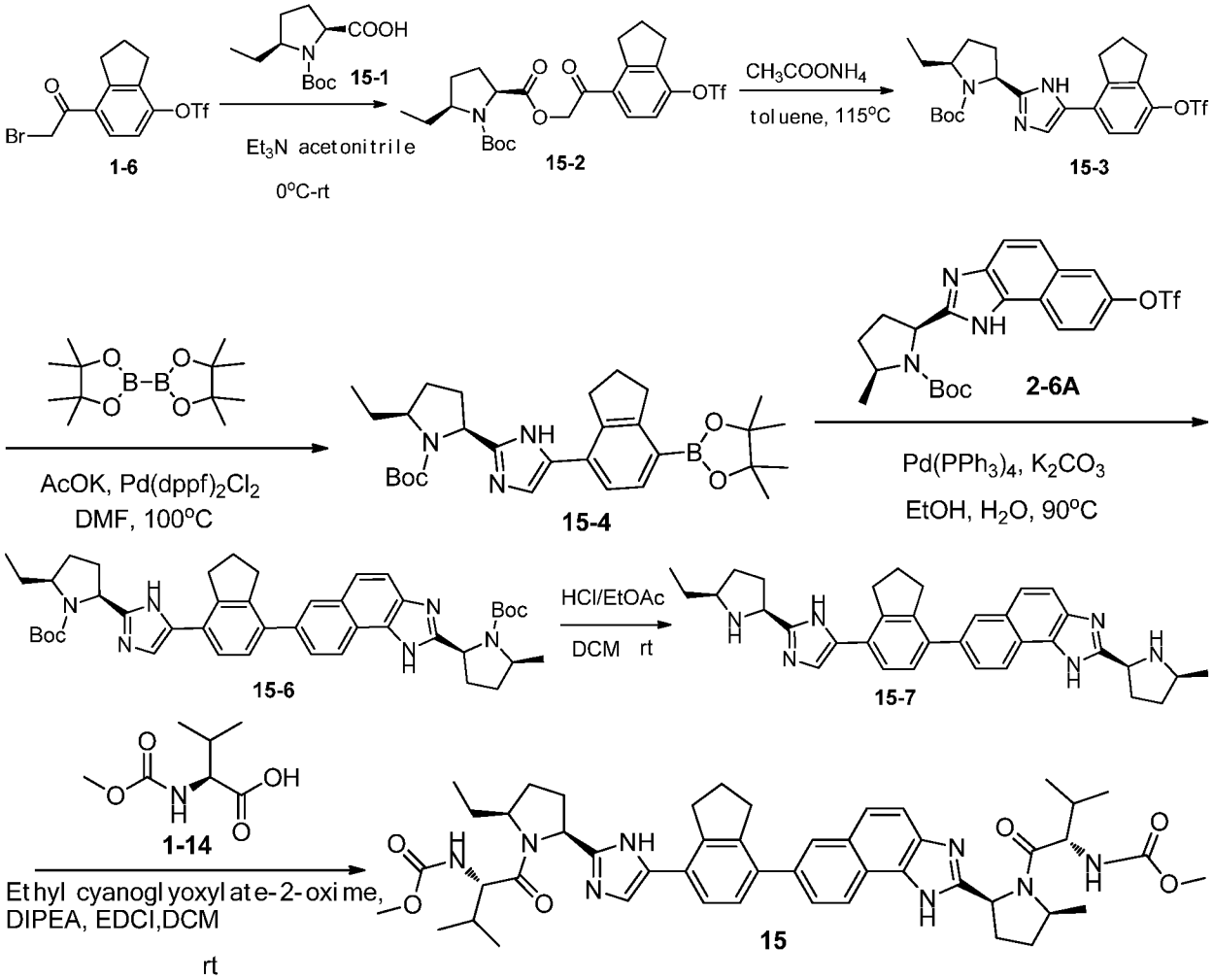
^{1}H NMR (400 MHz, $CDCl_3$): δ 11.96 – 10.36 (m, 2H), 8.83 – 8.50 (m, 1H), 7.94 (dd, J = 39.4, 12.5 Hz, 2H), 7.83 – 7.62 (m, 2H), 7.46 (dd, J = 92.2, 12.5 Hz, 2H), 7.21 (d, J = 17.5 Hz, 1H), 5.60 – 5.40 (m, 2H), 5.26 (dd, J = 20.5, 11.7 Hz, 1H), 4.82 – 4.63 (m, 1H), 4.39 – 4.23 (m, 2H), 3.72 (d, J = 6.9 Hz, 6H), 3.25 – 3.01 (m, 4H), 2.57 – 2.25 (m, 2H), 2.14 (dd, J = 20.5, 14.8 Hz, 3H), 2.05 – 1.95 (m, 1H), 1.94 – 1.77 (m, 3H), 1.66 (dd, J = 7.2, 4.4 Hz, 3H), 1.30 (d, J = 5.2 Hz, 6H), 1.20 (t, J = 13.7 Hz, 4H), 1.05 (dd, J = 15.6, 6.7 Hz, 2H), 0.99 – 0.94 (m, 2H), 0.89 (dd, J = 13.8, 6.3 Hz, 6H), 0.77 (dd, J = 12.2, 6.6 Hz, 2H) ppm; MS-ESI, m/z: 859.5 $[M+H]^+$.

Example 10



15

Synthesis route:



Synthesis steps:

Step 1) synthesis of compound **15-2**

[00265] To the solution of compound **15-1** (0.664 g, 2.73 mmol, 1.05 eq) and compound **1-6** (1.0 g, 2.6 mmol, 1.0 eq) in acetonitrile (10 mL) was added dropwise triethylamine (0.39 g, 3.9 mmol, 1.5 eq) at 0 °C. After the addition, the mixture was stirred at rt for 2 h. The reaction mixture was concentrated to remove the solvent and to the residue was added 20 mL of water. Then the mixture was extracted with DCM (20 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to give the product as brown oil (1.42 g, 100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 5.54 – 5.35 (m, 1H), 5.20 (dd, J = 25.2, 13.6 Hz, 1H), 4.62 (dt, J = 21.6, 8.3 Hz, 1H), 4.06 – 3.52 (m, 3H), 3.40-3.22 (m, 1H), 3.06 (t, J = 7.5 Hz, 2H), 2.83 – 2.64 (m, 1H), 2.58 – 2.33 (m, 1H), 2.20 (dt, J = 14.2, 7.3 Hz, 2H), 1.48 (m, 13H), 0.9 (t, J = 5.6 Hz, 3H) ppm.

Step 2) synthesis of compound **15-3**

[00266] The solution of compound **15-2** (1.42 g, 2.6 mmol, 1.0 eq) and ammonium acetate (1.2 g,

15.6 mmol, 6.0 eq) in toluene (15 mL) was stirred at 115 °C for 20 h. The reaction mixture was concentrated to remove toluene, and 50 mL of water was added to the residue. Then the mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (PE : EtOAc (V : V) =5 : 1) to give the product as a light yellow solid (1.31 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.97 (d, J = 188.0 Hz, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.19 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 5.33 (d, J = 52.9 Hz, 1H), 5.19 (t, J = 7.0 Hz, 1H), 3.98 (dd, J = 21.0, 13.0 Hz, 1H), 3.61 – 3.22 (m, 1H), 3.12 (dt, J = 15.0, 7.1 Hz, 4H), 2.85 – 2.59 (m, 1H), 2.29 – 2.14 (m, 2H), 1.52 (m, 12H), 0.9 (t, J = 5.6 Hz, 3H) ppm; MS-ESI, *m/z*: 530.2 $[M+H]^+$.

Step 3) synthesis of compound **15-4**

[00267] To DMF (15 mL) were added compound **15-3** (1.26 g, 2.37 mmol, 1.0 eq), bis(pinacolato)diboron (0.63 g, 2.49 mmol, 1.05 eq), potassium acetate (0.70 g, 7.1 mmol, 3.0 eq) and $Pd(dppf)_2Cl_2$ (69 mg, 0.094 mmol, 0.04 eq). The mixture was stirred at 100 °C for 10 h under nitrogen atomosphere. The reaction mixture was poured into 60 mL of water, then the mixture was filtered by suction to give a gray solid. The gray solid was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give a light yellow solid (0.85 g, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.89 (d, J = 186.4 Hz, 1H), 7.78 (s, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.20 (s, 1H), 5.27 (dd, J = 42.7, 30.3 Hz, 2H), 3.97 (dd, J = 20.7, 13.3 Hz, 1H), 3.48-3.40 (m, 1H), 3.38 – 2.88 (m, 4H), 2.80 – 2.59 (m, 1H), 2.19 – 2.07 (m, 2H), 1.52 -1.34 (m, 12H), 1.36 (s, 12H), 0.9 (t, J = 5.6 Hz, 3H) ppm; MS-ESI, *m/z*: 508.3 $[M+H]^+$.

Step 4) synthesis of compound **15-6**

[00268] To the mixture of ethanol (10 mL) and water (3 mL) were added compound **15-4** (558 mg, 1.10 mmol, 1.0 eq), compound **2-6A** (473 g, 1.10 mmol, 1.0 eq), potassium carbonate (0.30 g, 2.21 mmol, 2.0 eq) and $Pd(PPh_3)_4$ (38 mg, 0.033 mmol, 0.03 eq). The mixture was stirred at 90 °C for 6 h under nitrogen atomosphere. The reaction mixture was poured into 50 mL of water, then the mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous sodim sulfate and concentrated to give the crude product as a white solid (0.70 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.88 – 10.35 (m, 2H), 8.67 (d, J = 8.1 Hz, 1H), 8.22 – 7.30 (m, 6H), 7.18 (d, J = 23.9 Hz, 1H), 5.51 – 5.11 (m, 3H), 4.00 (dd, J = 21.1, 13.2 Hz, 1H), 3.57 (dd, J

= 32.1, 9.6 Hz, 3H), 3.30-3.11 (m, 4H), 2.44 – 2.21 (m, 2H), 2.20 – 2.08 (m, 2H), 2.00 – 1.86 (m, 2H), 1.55-1.34 (m, 21H), 1.32-1.18 (m, 3H), 0.9 (t, J = 5.6 Hz, 3H) ppm; MS-ESI, *m/z*: 731.3 $[M+H]^+$.

Step 5) synthesis of compound 1**5-7**

[00269] To the mixture of compound **15-6** (0.70 g, 0.95 mmol, 1.0 eq) in DCM (10 mL) was added dropwise HCl/EtOAc (4 N, 3 mL) at 0 °C. After the addition, the mixture was stirred at rt for 10 h. The mixture was concentrated to remove the solvent, and to the residue was added EtOAc (20 mL). The resulting mixture was triturated for 1 h and filtered by suction to give the filter cake as a light yellow solid. The filter cake was dissolved in water (10 mL), then to the solution was added sodium carbonate to precipitate out the solid. The mixure was filtered and the filter cake was dried to give a yellow solid (428 mg, 85%).

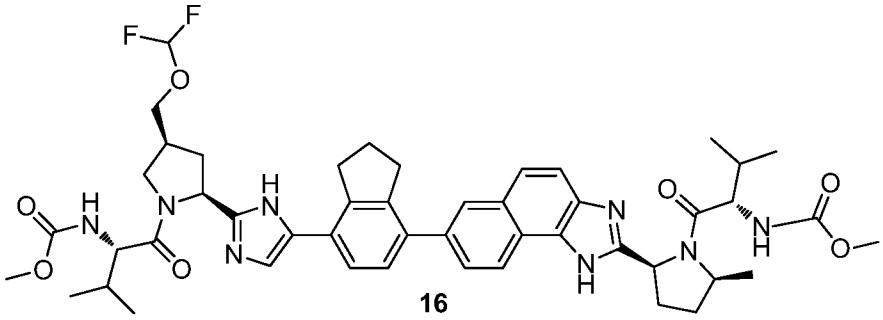
^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (s, 2H), 8.48 (d, J = 7.8 Hz, 1H), 8.03 (s, 1H), 7.96 – 7.49 (m, 4H), 7.45 – 7.08 (m, 2H), 5.37 (d, J = 55.4 Hz, 1H), 4.70 – 4.18 (m, 2H), 3.30 – 3.15 (m, 1H), 3.15 – 2.85 (m, 6H), 2.28 (ddd, J = 39.8, 14.5, 9.4 Hz, 3H), 2.04 (d, J = 5.5 Hz, 2H), 1.94 – 1.65 (m, 5H), 1.32-1.18 (m, 3H), 0.9 (t, J = 5.6 Hz, 3H) ppm; MS-ESI, *m/z*: 531.4 $[M+H]^+$.

Step 6) synthesis of compound 1**5**

[00270] To DCM (15 mL) were added compound **15-6** (265 mg, 0.5 mmol, 1.0 eq), compound **1-14** (193 mg, 1.1 mmol, 2.2 eq), ethyl cyanoglyoxylate-2-oxime (57 mg, 0.4 mmol, 0.8 eq) and DIPEA (32 mg, 0.25 mmol, 0.5 eq), then EDCI (211 mg, 1.1 mmol, 2.2 eq) was added. The resulting mixture was stirrd at rt for 3 h. The reaction mixture was poured into 30 mL of water, then the mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhdrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (DCM : MeOH (V : V) = 10 : 1) to give the product as a white solid (232 mg, 55%).

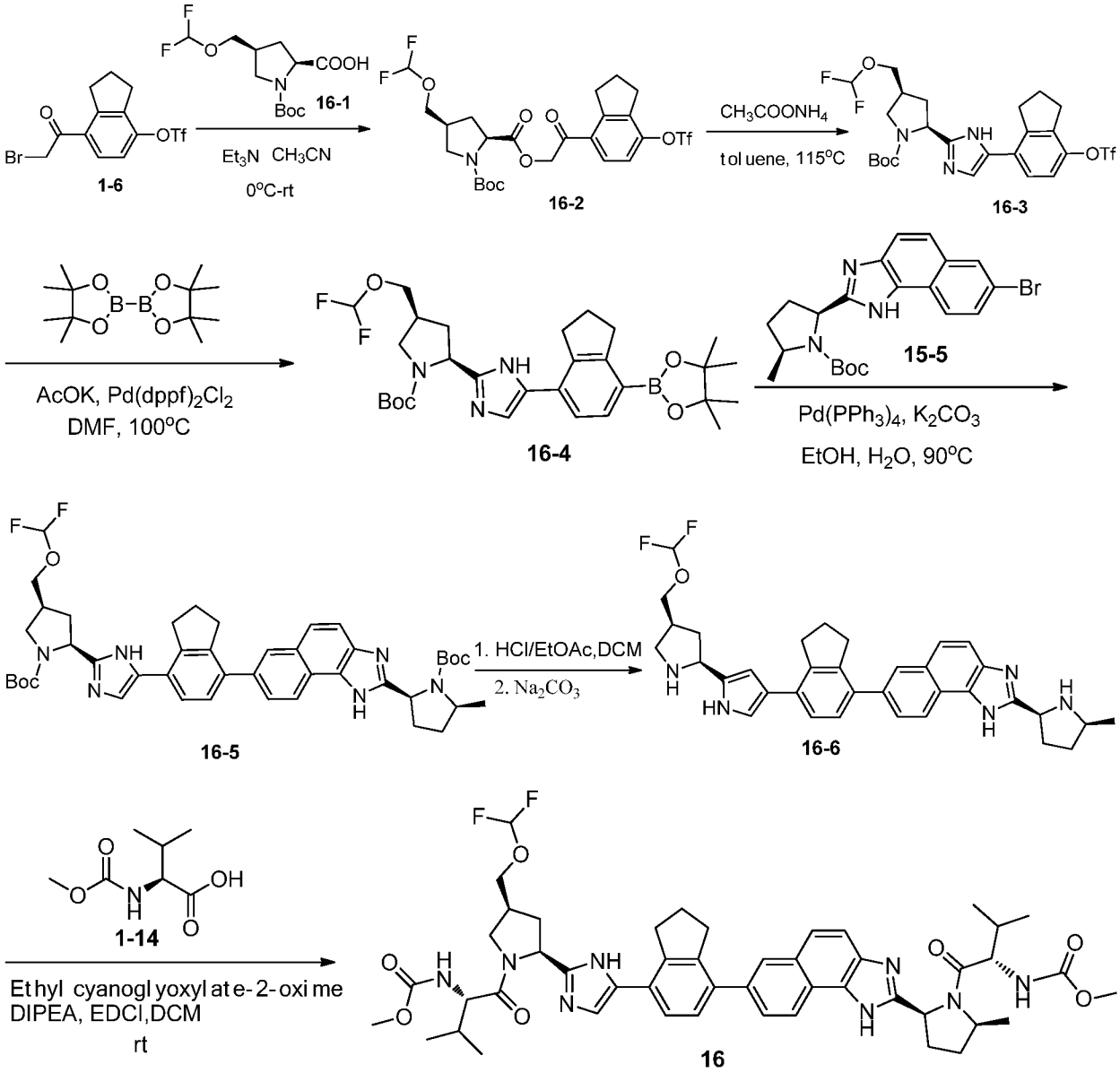
^{1}H NMR (400 MHz, $CDCl_3$): δ 12.09 – 10.24 (m, 2H), 8.63 (s, 1H), 8.19 – 7.54 (m, 4H), 7.42 (d, J = 39.2 Hz, 1H), 7.13 (dd, J = 75.7, 30.2 Hz, 2H), 6.47 – 5.62 (m, 2H), 5.62 – 5.26 (m, 3H), 4.38 (dd, J = 23.1, 15.4 Hz, 3H), 4.14 (q, J = 7.1 Hz, 2H), 3.97 (s, 1H), 3.76 (d, J = 27.7 Hz, 6H), 3.46 – 3.19 (m, 1H), 3.06 (s, 3H), 2.72 (dd, J = 26.7, 14.6 Hz, 1H), 2.59 – 2.07 (m, 4H), 1.94 (d, J = 1.3 Hz, 2H), 1.80 – 1.58 (m, 3H), 1.32-1.18 (m, 4H) 0.89 (m, 15H) ppm; MS-ESI, *m/z*: 845.4 $[M+H]^+$.

Example 11



16

Synthesis route:



Synthesis steps:

Step 1) synthesis of compound **16-2**

[00271] To the solution of compound **16-1** (0.81 g, 2.73 mmol, 1.05 eq) and compound **1-6** (1.0 g, 2.6 mmol, 1.0 eq) in acetonitrile (10 mL) was added dropwise triethylamine (0.39 g, 3.9 mmol,

1.5 eq) at 0 °C. After the addition, the mixture was stirred at rt for 2 h. The reaction mixture was concentrated to remove the solvent and 20 mL of water was added to the residue. Then the mixture was extracted with DCM (20 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to give the product as brown oil (1.56 g, 100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 6.50 (t, 1H), 5.54 – 5.35 (m, 1H), 5.20 (dd, J = 25.2, 13.6 Hz, 1H), 4.62 (dt, J = 21.6, 8.3 Hz, 1H), 4.06 – 3.52 (m, 3H), 3.40-3.22 (m, 4H), 3.06 (t, J = 7.5 Hz, 2H), 2.83 – 2.64 (m, 1H), 2.58 – 2.33 (m, 1H), 2.20 (dt, J = 14.2, 7.3 Hz, 2H), 1.48 (m, 10H) ppm.

Step 2) synthesis of compound **16-3**

[00272] The solution of compound **16-2** (1.56 g, 2.6 mmol, 1.0 eq) and ammonium acetate (1.2 g, 15.6 mmol, 6.0 eq) in toluene (15 mL) was stirred at 115 °C for 20 h. The mixture was concentrated to remove the toluene, and to the residue was added 50 mL of water. Then the mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhdrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give the product as a light yellow solid (1.38 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.97 (d, J = 188.0 Hz, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.19 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.50 (t, 1H), 5.33 (d, J = 52.9 Hz, 1H), 5.19 (t, J = 7.0 Hz, 1H), 3.98 (dd, J = 21.0, 13.0 Hz, 1H), 3.61 – 3.22 (m, 4H), 3.12 (dt, J = 15.0, 7.1 Hz, 4H), 2.85 – 2.59 (m, 1H), 2.29 – 2.14 (m, 2H), 1.52 (s, 9H) ppm; MS-ESI, m/z: 582.2 $[M+H]^+$.

Step 3) synthesis of compound **16-4**

[00273] To DMF (15 mL) were added compound **16-3** (1.38 g, 2.37 mmol, 1.0 eq), bis(pinacolato)diboron (0.63 g, 2.49 mmol, 1.05 eq), potassium acetate (0.70 g, 7.1 mmol, 3.0 eq) and $Pd(dppf)_2Cl_2$ (69 mg, 0.094 mmol, 0.04 eq). The mixture was stirred at 100 °C for 10 h under nitrogen atomosphere. The reaction mixture was poured into 60 mL of water, then the mixture was filtered by suction to give a gray solid. The gray solid was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give a light yellow solid (0.95 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.89 (d, J = 186.4 Hz, 1H), 7.78 (s, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.20 (s, 1H), 6.5 (t, 1H), 5.27 (dd, J = 42.7, 30.3 Hz, 2H), 3.97 (dd, J = 20.7, 13.3 Hz, 1H), 3.48 (dd, J = 35.4, 12.0 Hz, 1H), 3.38 – 2.88 (m, 7H), 2.80 – 2.59 (m, 1H), 2.19 – 2.07 (m, 2H),

1.52 (s, 9H), 1.36 (s, 12H) ppm; MS-ESI, *m/z*: 560.3 $[M+H]^+$.

Step 4) synthesis of compound **16-5**

[00274] To the mixture of ethanol (10 mL) and water (3 mL) were added compound **16-4** (615 mg, 1.10 mmol, 1.0 eq), compound **2-6A** (473 g, 1.10 mmol, 1.0 eq), potassium carbonate (0.30 g, 2.21 mmol, 2.0 eq) and $Pd(PPh_3)_4$ (38 mg, 0.033 mmol, 0.03 eq). The mixture was stirred at 90 °C for 6 h. The reaction mixture was poured into 50 mL of water, then the mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried and concentrated. The residue was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 1) to give a white solid (0.82 g, 95%).

^1H NMR (400 MHz, $CDCl_3$): δ 11.88 – 10.35 (m, 2H), 8.67 (d, J = 8.1 Hz, 1H), 8.22 – 7.30 (m, 6H), 7.18 (d, J = 23.9 Hz, 1H), 6.50 (t, 1H), 5.51 – 5.11 (m, 3H), 4.00 (dd, J = 21.1, 13.2 Hz, 1H), 3.57 (dd, J = 32.1, 9.6 Hz, 3H), 3.30-3.11 (m, 7H), 2.44 – 2.21 (m, 2H), 2.20 – 2.08 (m, 2H), 2.00 – 1.86 (m, 2H), 1.55 (d, J = 6.7 Hz, 18H), 1.32-1.18 (m, 3H) ppm; MS-ESI, *m/z*: 783.3 $[M+H]^+$.

Step 5) synthesis of compound **16-6**

[00275] To the mixture of compound **16-5** (0.82 g, 1.05 mmol, 1.0 eq) in DCM (10 mL) was added dropwise HCl/EtOAc (3 mL) at 0 °C. After the addition, the mixture was stirred at rt for 10 h. The mixture was concentrated to remove the solvent, and to the residue was added EtOAc (20 mL). The resulting mixture was triturated for 1 h and filtered by suction to give the filter cake as a light yellow solid. The filter cake was dissolved in water (10 mL), then to the solution was added sodium carbonate to precipitate out the solid. The mixure was filtered and the filter cake was dried to give a yellow solid (543 mg, 89%).

^1H NMR (400 MHz, DMSO-d_6): δ 12.10 (s, 2H), 8.48 (d, J = 7.8 Hz, 1H), 8.03 (s, 1H), 7.96 – 7.49 (m, 4H), 7.45 – 7.08 (m, 2H), 6.50 (t, 1H), 5.37 (d, J = 55.4 Hz, 1H), 4.70 – 4.18 (m, 2H), 3.30 – 3.15 (m, 4H), 3.15 – 2.85 (m, 6H), 2.28 (ddd, J = 39.8, 14.5, 9.4 Hz, 3H), 2.04 (d, J = 5.5 Hz, 2H), 1.94 – 1.65 (m, 2H), 1.32-1.18 (m, 3H) ppm; MS-ESI, *m/z*: 583.4 $[M+H]^+$.

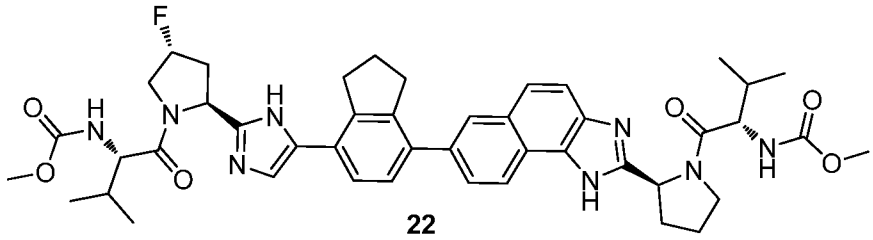
Step 6) synthesis of compound **16**

[00276] To DCM (15 mL) were added compound **16-6** (291 mg, 0.5 mmol, 1.0 eq), compound **1-14** (193 mg, 1.1 mmol, 2.2 eq) and ethyl cyanoglyoxylate-2-oxime (57 mg, 0.4 mmol, 0.8 eq), then EDCI (211 mg, 1.1 mmol, 2.2 eq) was added. The resulting mixture was stirrd at rt for 3 h.

The reaction mixture was poured into 30 mL of water, then the mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhdrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (DCM : MeOH (V : V) = 10 : 1) to give the product as a white solid (256 mg, 57%).

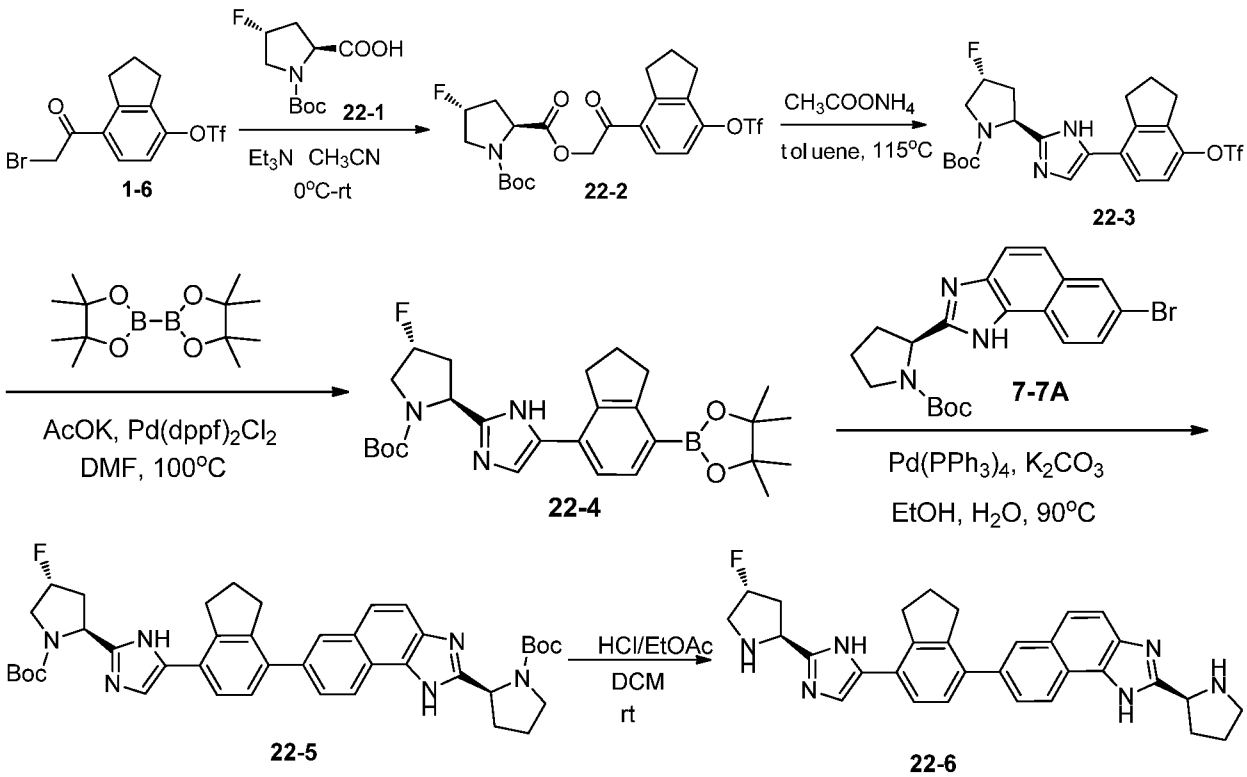
^{1}H NMR (400 MHz, $CDCl_3$): δ 12.09 – 10.24 (m, 2H), 8.63 (s, 1H), 8.19 – 7.54 (m, 4H), 7.42 (d, J = 39.2 Hz, 1H), 7.13 (dd, J = 75.7, 30.2 Hz, 2H), 6.47 – 5.62 (m, 3H), 5.62 – 5.26 (m, 3H), 4.38 (dd, J = 23.1, 15.4 Hz, 3H), 4.14 (q, J = 7.1 Hz, 2H), 3.97 (s, 1H), 3.76 (d, J = 27.7 Hz, 6H), 3.46 – 3.19 (m, 3H), 3.06 (s, 4H), 2.72 (dd, J = 26.7, 14.6 Hz, 1H), 2.59 – 2.07 (m, 4H), 1.94 (d, J = 1.3 Hz, 2H), 1.80 – 1.58 (m, 1H), 1.32-1.18 (m, 3H) 0.89 (dd, J = 16.3, 5.8 Hz, 12H) ppm; MS-ESI, *m/z*: 897.4 $[M+H]^+$.

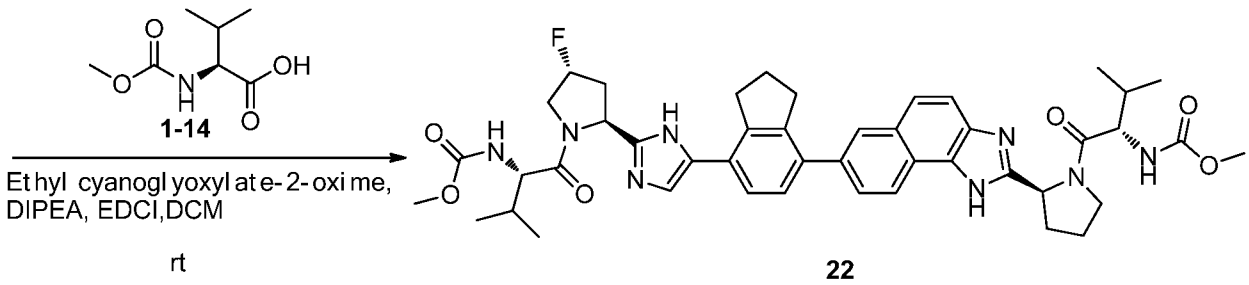
Example 12



22

Synthesis route:





Synthesis steps:

Step 1) synthesis of compound **22-2**

[00277] To the solution of compound **22-1** (0.63 g, 2.7 mmol, 1.05 eq) and compound **1-6** (1.0 g, 2.6 mmol, 1.0 eq) in acetonitrile (10 mL) was added dropwise triethylamine (0.39 g, 3.9 mmol, 1.5 eq) at 0 °C. After the addition, the mixture was stirred at rt for 2 h. The reaction mixture was concentrated to remove the solvent and to the residue was added 20 mL of water. Then the mixture was extracted with DCM (20 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to give the product as brown oil (1.43 g, 100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 5.54 – 5.35 (m, 1H), 5.20 (dd, J = 25.2, 13.6 Hz, 1H), 4.62 (dt, J = 21.6, 8.3 Hz, 1H), 4.06 – 3.52 (m, 3H), 3.31 (t, J = 7.4 Hz, 2H), 3.06 (t, J = 7.5 Hz, 2H), 2.83 – 2.64 (m, 1H), 2.58 – 2.33 (m, 1H), 2.20 (dt, J = 14.2, 7.3 Hz, 2H), 1.48 (d, J = 10.1 Hz, 10H) ppm.

Step 2) synthesis of compound **22-3**

[00278] The solution of compound **22-2** (1.40 g, 2.59 mmol, 1.0 eq) and ammonium acetate (1.2 g, 15.6 mmol, 6.0 eq) in toluene (15 mL) was stirred at 115 °C for 20 h. The reaction mixture concentrated to remove the solvent and to the residue was added 50 mL of water, then the mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhdrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give the product as a light yellow solid (1.23 g, 91.2%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.97 (d, J = 188.0 Hz, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.19 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 5.33 (d, J = 52.9 Hz, 1H), 5.19 (t, J = 7.0 Hz, 1H), 3.98 (dd, J = 21.0, 13.0 Hz, 1H), 3.61 – 3.22 (m, 2H), 3.12 (dt, J = 15.0, 7.1 Hz, 4H), 2.85 – 2.59 (m, 1H), 2.29 – 2.14 (m, 2H), 1.52 (s, 9H) ppm; MS-ESI, m/z: 520.2 $[M+H]^+$.

Step 3) synthesis of compound **22-4**

[00279] To DMF (15 mL) were added compound **22-3** (1.23 g, 2.37 mmol, 1.0 eq),

bis(pinacolato)diboron (0.63 g, 2.49 mmol, 1.05 eq), potassium acetate (0.70 g, 7.1 mmol, 3.0 eq), $Pd(dppf)_2Cl_2$ (69 mg, 0.094 mmol, 0.04 eq). The mixture was stirred at 100 °C for 10 h under nitrogen atomosphere. The reaction mixture was poured into water, then the mixture was filtered by suction to give a gray solid. The gray solid was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give a light yellow solid (0.74 g, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.89 (d, J = 186.4 Hz, 1H), 7.78 (s, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.20 (s, 1H), 5.27 (dd, J = 42.7, 30.3 Hz, 2H), 3.97 (dd, J = 20.7, 13.3 Hz, 1H), 3.48 (dd, J = 35.4, 12.0 Hz, 1H), 3.38 – 2.88 (m, 5H), 2.80 – 2.59 (m, 1H), 2.19 – 2.07 (m, 2H), 1.52 (s, 9H), 1.36 (s, 12H) ppm; MS-ESI, *m/z*: 498.4 $[M+H]^+$.

Step 4) synthesis of compound **22-5**

[00280] To the mixture of ethanol (10 mL) and water (3 mL) were added compound **22-4** (550 mg, 1.10 mmol, 1.0 eq), compound **7-7A** (460 g, 1.10 mmol, 1.0 eq), potassium carbonate (0.30 g, 2.21 mmol, 2.0 eq), $Pd(PPh_3)_4$ (38 mg, 0.033 mmol, 0.03 eq). The mixture was stirred at 90 °C for 6 h under nitrogen atomosphere. The reaction mixture was poured into 50 mL of water, then the mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over ahydrous sodium sulfate and concentrated to give the crude product as a white solid (0.765 g, 97.8%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.88 – 10.35 (m, 2H), 8.67 (d, J = 8.1 Hz, 1H), 8.22 – 7.30 (m, 6H), 7.18 (d, J = 23.9 Hz, 1H), 5.51 – 5.11 (m, 3H), 4.00 (dd, J = 21.1, 13.2 Hz, 1H), 3.57 (dd, J = 32.1, 9.6 Hz, 3H), 3.14 (dd, J = 20.9, 13.7 Hz, 5H), 2.81 – 2.62 (m, 1H), 2.44 – 2.21 (m, 2H), 2.20 – 2.08 (m, 2H), 2.00 – 1.86 (m, 2H), 1.55 (d, J = 6.7 Hz, 18H) ppm; MS-ESI, *m/z*: 707.4 $[M+H]^+$.

Step 5) synthesis of compound **22-6**

[00281] To the mixture of compound **22-5** (0.76 g, 1.1 mmol, 1.0 eq) in DCM (10 mL) was added dropwise HCl/EtOAc (4 N, 3 mL) at 0 °C. After the addition, the mixture was stirred at rt for 10 h. The mixture was concentrated to remove the solvent, and to the residue was added EtOAc (20 mL). The resulting mixture was triturated for 1 h and filtered by suction to give the filter cake as a light yellow solid. The filter cake was dissolved in water (10 mL), then to the solution was added sodium carbonate to precipitate out the solid. The mixure was filtered and the filter cake was dried to give a yellow solid (500 mg, 92%).

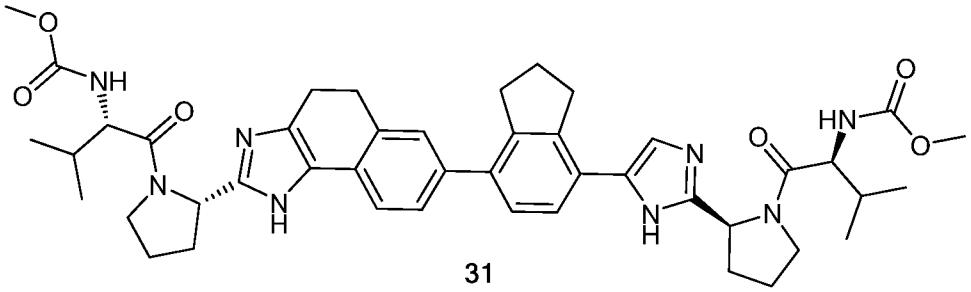
^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (s, 2H), 8.48 (d, J = 7.8 Hz, 1H), 8.03 (s, 1H), 7.96 – 7.49 (m, 4H), 7.45 – 7.08 (m, 2H), 5.37 (d, J = 55.4 Hz, 1H), 4.70 – 4.18 (m, 2H), 3.30 – 3.21 (m, 2H), 3.15 – 2.85 (m, 7H), 2.28 (ddd, J = 39.8, 14.5, 9.4 Hz, 3H), 2.04 (d, J = 5.5 Hz, 2H), 1.94 – 1.65 (m, 2H) ppm; MS-ESI, *m/z*: 507.4 $[M+H]^+$.

Step 6) synthesis of compound **22**

[00282] To DCM (15 mL) were added compound **22-6** (280 mg, 0.552 mmol, 1.0 eq), compound **1-14** (213 mg, 1.22 mmol, 2.2 eq), ethyl cyanoglyoxylate-2-oxime (62 mg, 0.44 mmol, 0.8 eq) and DIPEA (35 mg, 0.27 mmol, 0.5 eq), then EDCI (232 mg, 1.22 mmol, 2.2 eq) was added. The resulting mixture was stirrd at rt for 3 h. The reaction mixture was poured into 30 mL of water, then the mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (DCM : EtOAc : MeOH (V : V : V) = 5 : 10 : 1) to give the product as a white solid (270 mg, 59.50%).

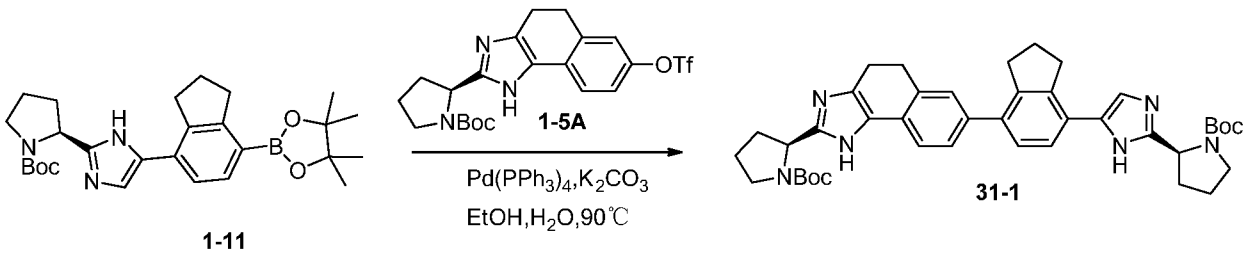
^{1}H NMR (400 MHz, $CDCl_3$): δ 12.09 – 10.24 (m, 2H), 8.63 (s, 1H), 8.19 – 7.54 (m, 4H), 7.42 (d, J = 39.2 Hz, 1H), 7.13 (dd, J = 75.7, 30.2 Hz, 2H), 6.47 – 5.62 (m, 2H), 5.62 – 5.26 (m, 3H), 4.38 (dd, J = 23.1, 15.4 Hz, 3H), 4.14 (q, J = 7.1 Hz, 2H), 3.97 (s, 1H), 3.76 (d, J = 27.7 Hz, 6H), 3.46 – 3.19 (m, 1H), 3.06 (s, 4H), 2.72 (dd, J = 26.7, 14.6 Hz, 1H), 2.59 – 2.07 (m, 5H), 1.94 (d, J = 1.3 Hz, 2H), 1.80 – 1.58 (m, 1H), 0.89 (dd, J = 16.3, 5.8 Hz, 12H) ppm; MS-ESI, *m/z*: 821.2 $[M+H]^+$.

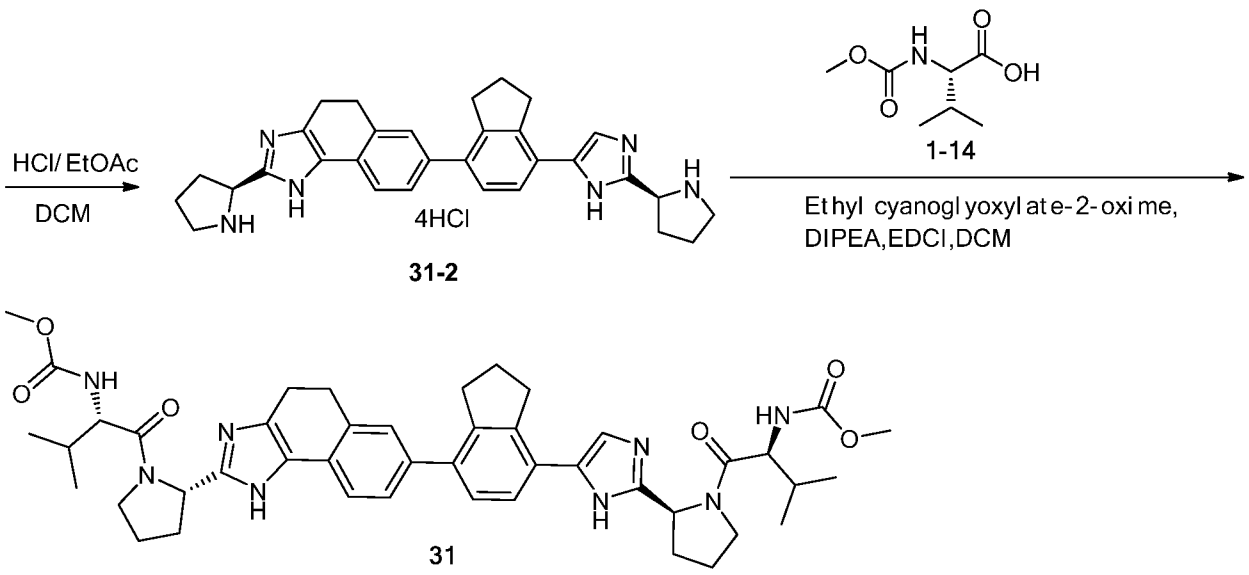
Example 13



31

Synthesis route:





Synthesis steps:

Step 1) synthesis of compound **31-1**

[00283] To EtOH/H_2O (30 mL, V : V = 3 : 1) were added compound **1-11** (0.8 g, 1.7 mmol), compound **1-5A** (0.73 g, 1.5 mmol, 0.9 eq), $Pd(PPh_3)_4$ (0.20 g, 0.17 mmol, 0.1 eq) and K_2CO_3 (0.69 mg, 5.0 mmol, 3 eq). The mixture was stirred at 90 °C under nitrogen atmosphere for 3 h. After the reaction was complete, the reaction mixture was concentrated to remove most of the solvent. Then the residue was extracted with DCM (20 mL × 2). The combined organic layers were dried and concentrated. The residue was purfied by silica gel column chromatography (PE : EA (V : V) = 2 : 1) to give the product as a gray solid (0.5 g, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.52 (d, 2H),7.22 (m, 2H), 5.33 (s, 1H),4.93 (s, 2H), 3.26 (m, 4H), 3.20 (m,2H),3.10 (m,4H),2.76-2.62 (m, 4H), 2.19-1.95 (m, 6H), 1.25 (m, 9H), 1.29 (m, 9H) ppm; MS-ESI, *m/z*: 691.5$[M+H]^+$.

Step 2) synthesis of compound **31-2**

[00284] To a solution of compound **31-1** (0.5 g, 0.7 mmol, 1eq) in DCM (15 mL) was added dropwise HCl/EtOAc (4 N, 4 mL) at 0 °C. The mixture was stirred at rt for 6 h. After the reaction was complete, the reaction mixture was concentrated to remove the solvent, and the residue was triturated with EtOAc (20 mL) to give a yellow solid (0.4 g, 87%).

MS-ESI, *m/z*: 491.6$[M+H]^+$.

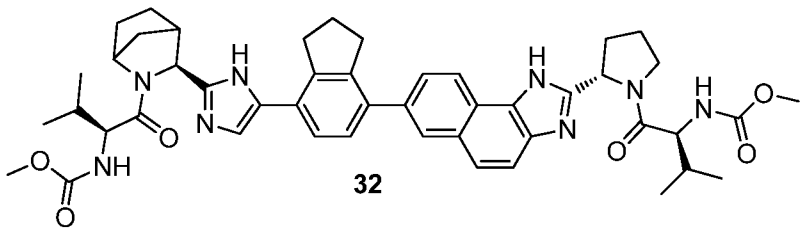
Step 3) synthesis of compound **31**

[00285] To DCM (10 mL) were added compound **31-2** (0.40 g, 0.82 mmol, 1eq), compound **1-14** (0.316 g, 1.8 mmol, 2.2 eq), EDCI (0.377 g, 1.97 mmol, 2.4 eq) and ethyl

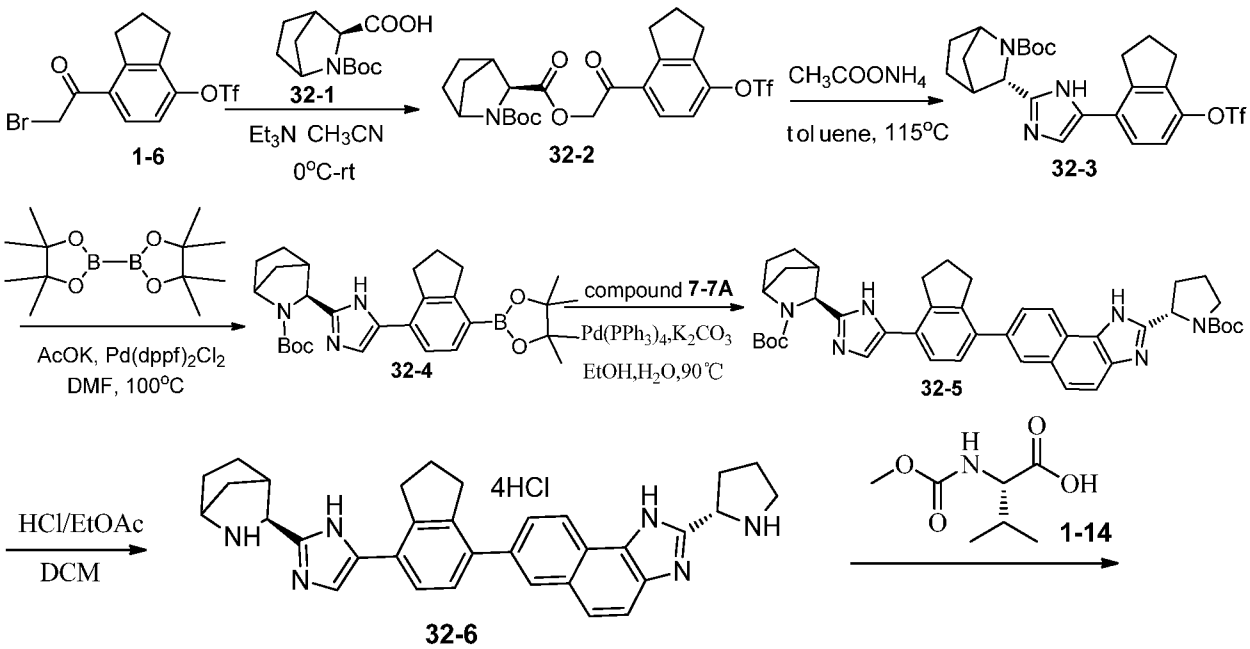
cyanoglyoxylate-2-oxime (0.07 g, 0.49 mmol, 0.6 eq). Then to the mixture was added dropwise DIPEA (0.530 g, 4.1 mmol, 5 eq) at 0 °C. The resulting mixture was stirrd at rt for 2 h. After the reaction was completed, to the reaction mixture was added ammonium hydroxide (2 mL). The resulting mixture was stirred for 1 h, then partitioned. The organic layer was washed with saturated aqueous ammonium chloride, dried over anhydrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 1) to give the product as a gray solid (0.35 g, 53%).

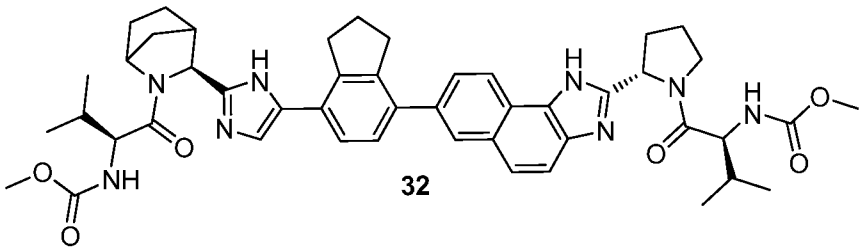
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.62 (d, 2H), 7.21 (m, 2H), 5.43 (s, 1H),5.10 (s, 2H), 3.56-3.42 (m, 4H) 3.31 (m, 2H), 3.16-2.83 (m,4H), 2.72-2.63 (m,4H),2.56-2.41 (m, 4H), 2.38 (m, 2H),2.36-2.21 (m, 4H), 2.09-1.82 (m, 6H), 1.05 (m, 12H) ppm; MS-ESI, *m/z*: 806.3[M+H]$^+$.

Example 14



Synthesis route:





32

Synthesis steps:

Step 1) synthesis of compound **32-2**

[00286] To the solution of compound **1-6** (1.45 g, 2.65 mmol, 1.0 eq) and (3*S*)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid **32-1** (0.82 g, 0.34 mmol, 1.1 eq) in acetonitrile (10 mL) was added dropwise triethylamine (0.39 g, 3.9 mmol, 1.5 eq) at 0 °C. After the addition, the mixture was stirred at rt for 2 h. The reaction mixture was concentrated to remove the solvent and to the residue was added 20 mL of water. Then the mixture was extracted with DCM (10 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to give the product as brown oil (1.45 g, 100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.61 (m, 1H), 7.20 (d, J = 8.5 Hz, 1H), 5.28 (ddd, J = 62.1, 49.1, 16.3 Hz, 2H), 4.32 (d, J = 51.5 Hz, 1H), 3.95 (d, J = 29.9 Hz, 1H), 3.32 (t, J = 6.0 Hz, 2H), 3.06 (t, J = 7.2 Hz, 2H), 2.97 – 2.82 (m, 1H), 2.27 – 2.11 (m, 2H), 2.06 – 1.94 (m, 1H), 1.85 – 1.76 (m, 1H), 1.69 – 1.62 (m, 2H), 1.56 (dd, J = 11.3, 6.9 Hz, 1H), 1.46 (d, J = 18.4 Hz, 9H), 1.36 – 1.30 (m, 1H) ppm.

Step 2) synthesis of compound **32-3**

[00287] The solution of compound **32-2** (1.45 g, 2.65 mmol, 1.0 eq) and ammonium acetate (1.22 g, 15.9 mmol, 6.0 eq) in toluene (10 mL) was stirred at 115 °C for 15 h. The reaction mixture was concentrated to remove the toluene and to the residue was added 50 mL of water, then the mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhdrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give the product as a light yellow solid (1.1 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.73 (d, J = 211.3 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.12 (t, J = 13.6 Hz, 2H), 4.43 (d, J = 8.5 Hz, 1H), 4.16 (s, 1H), 3.41 (d, J = 18.3 Hz, 1H), 3.11 (dt, J = 23.2, 7.3 Hz, 4H), 2.19 (dt, J = 15.0, 7.6 Hz, 2H), 2.00 (d, J = 10.0 Hz, 1H), 1.87 (td, J = 11.1, 5.1 Hz, 1H), 1.77 – 1.67 (m, 4H), 1.53 (s, 9H) ppm; MS-ESI, *m/z*: 528.10[M+H]$^+$.

Step 3) synthesis of compound **32-4**

[00288] To DMF (10 mL) were added compound **32-3** (1.03 g, 1.95 mmol, 1.0 eq), bis(pinacolato)diboron (0.52 g, 2.05 mmol, 1.05 eq), potassium acetate (0.57 g, 5.86 mmol, 3.0 eq) and $Pd(dppf)_2Cl_2$ (57 mg, 0.078 mmol, 0.04 eq). The mixture was stirred at 100 °C for 11 h under nitrogen atomosphere. The reaction mixture was poured into water, then the mixture was filtered by suction to give a gray solid. The gray solid was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give a light yellow solid (0.96 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.67 (d, J = 221.7 Hz, 1H), 7.79 (s, 0.5H), 7.66 (d, J = 7.7 Hz, 1H), 7.25 (s, 0.5H), 7.19 (s, 1H), 4.45 (s, 1H), 4.17 (s, 1H), 3.42 (d, J = 20.6 Hz, 1H), 3.19 (t, J = 7.5 Hz, 2H), 3.10 – 3.02 (m, 2H), 2.11 (dd, J = 14.6, 7.3 Hz, 2H), 2.02 (d, J = 9.9 Hz, 1H), 1.93 – 1.84 (m, 1H), 1.74 (dd, J = 15.4, 10.4 Hz, 4H), 1.53 (s, 9H), 1.36 (s, 12H) ppm; MS-ESI, *m/z*: 506.25 $[M+H]^+$.

Step 4) synthesis of compound **32-5**

[00289] To EtOH/H_2O (30 mL, 3:1) were added compound **32-4** (0.6 g, 1.2 mmol, 1eq), compound **7-7A** (0.49 g, 1.2 mmol, 1 eq), $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol, 0.1 eq) and K_2CO_3 (0.49 mg, 3.6 mmol, 1 eq). The mixture was stirred at 90 °C under nitrogen atmosphere for 3 h. After the reaction was completed, the reaction mixture was concentrated to remove most of the solvent and the residue was extracted with DCM (20 mL × 2). The combined organic layers were dried and concentrated. The residue was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 2 : 1) to give the product as a gray solid (0.6 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.72 (d, 2H), 7.32 (m, 2H),7.22 (m, 2H), 5.53 (s, 1H),4.63 (s, 2H), 3.26 (m, 4H), 3.10-2.85 (m, 4H), 2.76-2.51 (m, 4H), 2.23- 2.09 (m, 6H), 1.82-1.69 (m, 2H), 1.25 (m, 9H), 1.29 (m, 9H) ppm.

Step 5) synthesis of compound **32-6**

[00290] To a solution of compound **32-5** (0.5 g, 0.7 mmol, 1eq) in DCM (15 mL) was added dropwise HCl/EtOAc (4 N, 4 mL) at 0 °C. The mixture was stirred at rt for 6 h. After the reaction was completed, the reaction mixture was concentrated to remove the solvent, and the residue was triturated with EtOAc (20 mL) to give a brown solid (0.36 g, 79%).

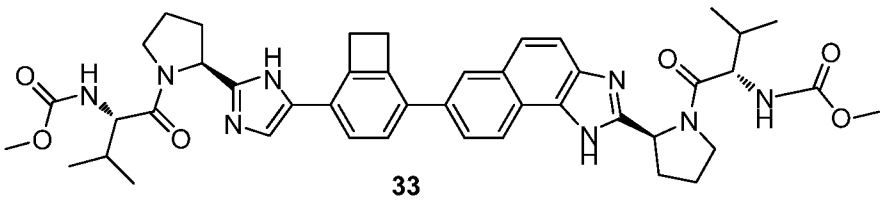
Step 6) synthesis of compound **32**

[00291] To DCM (10 mL) were added compound **32-6** (0.67 g, 1.02 mmol, 1.0 eq), compound

1-14 (0.429 g, 2.45 mmol, 2.4 eq), EDCI (0.472 g, 2.45 mmol, 2.4 eq) and ethyl cyanoglyoxylate-2-oxime (0.116 g, 0.817 mmol, 0.8 eq). Then to the mixture was added dropwise DIPEA (0.792 g, 6.13 mmol, 6.0 eq) at 0 °C. The resulting mixture was stirrd at rt for 2 h. After the reaction was completed, to the reaction mixture was added ammonium hydroxide (2 mL). The resulting mixture was stirred for 1 h, then partitioned. The organic layer was washed with saturated aqueous ammonium chloride, dried over anhydrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 1) to give the product as a gray solid (0.4 g, 51%).

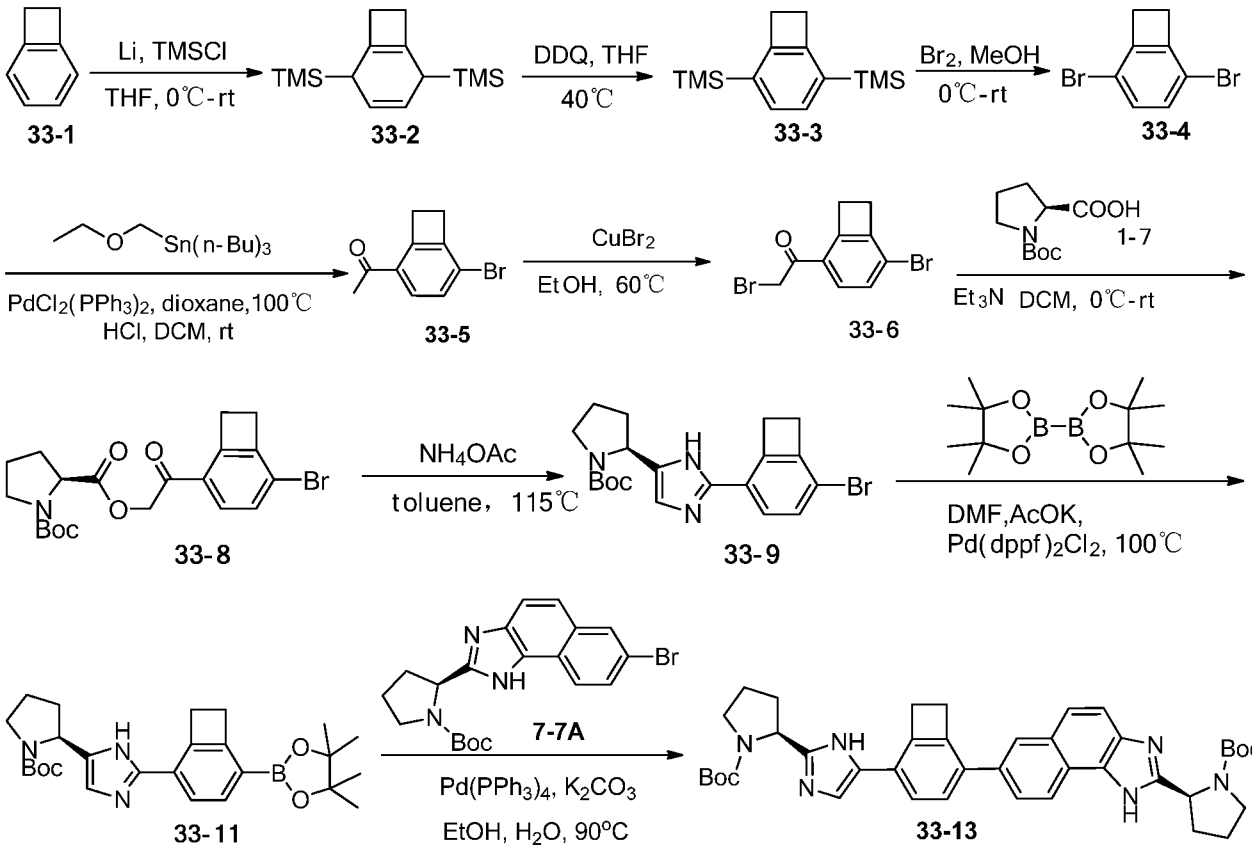
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.72 (d, 2H), 7.46 (m, 2H),7.21 (m, 2H), 5.43 (s, 1H), 5.10 (s, 2H), 3.56-3.45 (m, 4H) 3.16-3.01 (m,4H), 3.10-2.87 (m, 4H), 2.66-2.51 (m, 4H), 2.56-2.39 (m, 2H),2.36 (m, 4H), 2.09-1.93 (m, 6H), 1.81-1.72 (m, 2H) 1.23-1.05 (m, 12H) ppm.

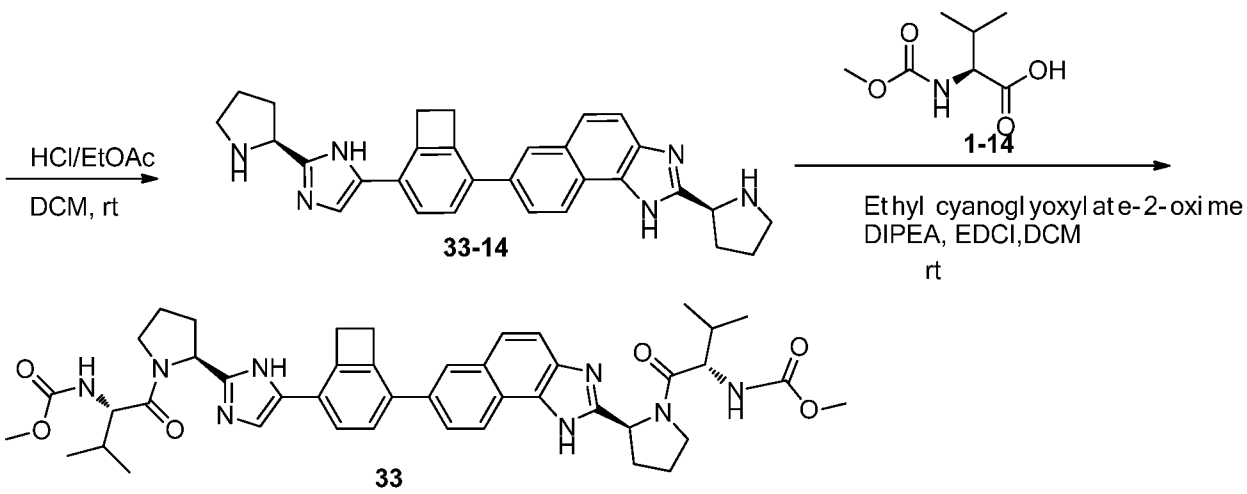
Example 15



33

Synthesis route:





Synthesis steps:

Step 1) synthesis of compound **33-2**

[00292] To tetrahydrofuran (20 mL) was added lithium (0.56 g, 80 mmol, 4 eq), then to the suspension were added TMSCl (7.67 mL, 60 mmol, 3 eq) at 0 °C. Then to the mixture was added dropwise compound **33-1** (2.08 g, 20 mmol, 1 eq). After the addtion, the mixture was stirred at rt for 6 days. The reaction was quenched with methanol (10 mL) at 0 °C, then water (25 mL) was added. The mixture was extrated with PE (40 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated at 25 °C to give yellow oil (4.9 g, 98%).

GC/MS: $[M^+]$ = 250.2.

Step 2) synthesis of compound **33-3**

[00293] To a solution of compound **33-2** (4.9 g, 19.6 mmol, 1 eq) in THF (50 mL) was added dropwise a solution of DDQ (2.22 g, 9.8 mmol, 0.5 eq) in THF (15 mL) at 40 °C. The mixture was sirred at 40 °C for 1 h, then water (100 mL) was added to quench the reaction. The resulting mixture was extracted with ethyl acetate (40 mL × 4). The combined organic layers were washed with water (50 mL), saturated aqueous sodium carbonate (80 mL), saturated brine (50 mL) in turn, dried over anhydrous sodium sulfate, and concentrated at 25 °C to give the crude product (5.0 g, 103%).

GC/MS: $[M^+]$ = 248.1.

Step 3) synthesis of compound **33-4**

[00294] To a solution of compound **33-3** (4.96 g, 20 mmol, 1 eq) in methanol (50 mL) was added dropwise a solution of bromine (3.1 mL, 60 mmol, 3 eq) in methanol (10 mL) at 0 °C. After the addition, the mixture was stirred at rt overnight. The reaction was quenched with water

(100 mL), then the mixture was extrated with PE (100 mL × 3). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (PE) to give the product (2.5 g, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (s, 2H), 3.09 (s, 4H) ppm.

Step 4) synthesis of compound **33-5**

[00295] To dioxane (25 mL) were added compound **33-4** (2.5 g, 9.54 mmol, 1 eq), tributyl(1-ethoxyvinyl)tin (2.93 mL, 8.60 mmol, 0.9 eq) and $Pd(PPh_3)_2Cl_2$ (0.35 g, 0.48 mmol, 0.05 eq). The mixture was reacted in a microwave oven for 1 h at 100 °C under nitrogen atomosphere. The reaction mixture was filtered through a celite pad, and to the filtrate were added dichloromethane (20 mL) and hydrochloric acid (1.5 N, 20 mL). The mixture was stirred at rt for 2 h, then extracted with DCM (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated at 25 °C. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 30:1 - 20:1) to give a white solid (1.2 g, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J=8.4, 1H), 7.40 (d, J=8.4, 1H), 3.41 (t, J = 7.6 Hz, 2H), 3.21 (t, J = 7.6 Hz, 2H), 2.49 (s, 3H) ppm.

Step 5) synthesis of compound **33-6**

[00296] To EtOH (20 mL) were added compound **33-5** (1.2 g, 5.33 mmol, 1 eq) and cupric bromide (2.38 g, 10.7 mmol, 2 eq). The mixture was stirred at 60 °C for 2 h. After the reaction, the mixture was filtered through a celite pad. The filtrate was concentrated, and to the residue was added dichloromethane (40 mL). The mixture was washed with water (20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 6 : 1) to give brownish red oil (1.38 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.6 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.43 (s, 2H), 3.36 (t, J = 7.6 Hz, 2H), 3.07 (t, J = 7.6 Hz, 2H) ppm.

Step 6) synthesis of compound **33-8**

[00297] To a solution of compound **33-6** (1.1 g, 3.6 mmol, 1eq), compound **1-7** (1.0 g, 4.6 mmol, 1.3eq) in dichloromethane (20 mL) was added triethylamine (0.6 g, 6 mmol, 1.5 eq) at 0 °C. After the addition, the mixture was sirred at rt, and the reaction was monitored by TLC. After the reaction was completed, the mixture was washed with water (10 mL) and saturated aqueous

sodium chloride. The organic layer was dried and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 6:1) to give the product (1.29 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.6 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 5.13 (m, 1H), 4.43 (s, 2H), 3.36 (m, 2H), 3.16 (m, 2H), 3.07 (m, 4H), 2.29 (m, 2H), 1.36 (t, 9H) ppm; MS-ESI, *m/z*: 438.1$[M+H]^+$.

Step 7) synthesis of compound **33-9**

[00298] The solution of compound **33-8** (1.13 g, 2.6 mmol, 1.0 eq) and ammonium acetate (1.2 g, 15.6 mmol, 6.0 eq) in toluene (15 mL) was stirred at 115 °C for 20 h. The reaction mixture was concentrated to remove the toluene, and to the residue was added 50 mL of water. The mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give the crude product as a light yellow solid (1.01 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.97 (s, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.19 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 5.33 (d, J = 52.9 Hz, 1H), 5.19 (t, J = 7.0 Hz, 1H), 3.98 (dd, J = 21.0, 13.0 Hz, 1H), 3.61 – 3.22 (m, 2H), 3.12 (dt, J = 15.0, 7.1 Hz, 4H), 2.85 – 2.59 (m, 2H), 1.52 (s, 9H) ppm; MS-ESI, *m/z*: 418.2 $[M+H]^+$.

Step 8) synthesis of compound **33-11**

[00299] To DMF (15 mL) were added compound **33-9** (1.0 g, 2.4 mmol, 1.0 eq), bis(pinacolato)diboron (0.63 g, 2.5 mmol, 1.05 eq), potassium acetate (0.71 g, 7.2 mmol, 3.0 eq), $Pd(dppf)_2Cl_2$ (69 mg, 0.094 mmol, 0.04 eq). The mixture was stirred at 100 °C for 10 h under nitrogen atomosphere. The reaction mixture was poured into water, then the mixture was filtered by suction to give a gray solid. The gray solid was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give a light yellow solid (0.78 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.89 (s, 1H), 7.78 (s, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.20 (s, 1H), 5.27 (dd, J = 42.7, 30.3 Hz, 2H), 3.97 (dd, J = 20.7, 13.3 Hz, 1H), 3.48 (dd, J = 35.4, 12.0 Hz, 1H), 3.38 – 2.88 (m, 5H), 2.80 – 2.59 (m, 2H), 1.52 (s, 9H), 1.36 (s, 12H) ppm; MS-ESI, *m/z*: 466.4 $[M+H]^+$.

Step 9) synthesis of compound **33-13**

[00300] To the mixture of ethanol (10 mL) and water (3 mL) were added compound **33-11** (512 mg, 1.1 mmol, 1.0 eq), compound **7-7A** (460 mg, 1.1 mmol, 1.0 eq), potassium carbonate (0.30 g,

2.2 mmol, 2.0 eq) and $Pd(PPh_3)_4$ (38 mg, 0.033 mmol, 0.03 eq). The mixture was stirred at 90 °C for 6 h under nitrogen atomosphere. The reaction mixture was poured into 50 mL of water, then the mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 1) to give the crude product as a white solid (0.727 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.88 – 10.35 (m, 2H), 8.67 (d, J = 8.1 Hz, 1H), 8.22 – 7.30 (m, 6H), 7.18 (d, J = 23.9 Hz, 1H), 5.51 – 5.11 (m, 3H), 4.00 (dd, J = 21.1, 13.2 Hz, 1H), 3.57 (dd, J = 32.1, 9.6 Hz, 3H), 3.14 (dd, J = 20.9, 13.7 Hz, 5H), 2.81 – 2.62 (m, 2H), 2.44 – 2.21 (m, 2H), 2.00 – 1.86 (m, 2H), 1.55 (d, J = 6.7 Hz, 18H) ppm; MS-ESI, *m/z*: 675.4 $[M+H]^+$.

Step 10) synthesis of compound **33-14**

[00301] To the mixture of compound **33-13** (0.72 g, 1.07 mmol, 1.0 eq) in DCM (10 mL) was added dropwise HCl/EtOAc (3 mL) at 0 °C. After the addition, the mixture was stirred at rt for 10 h. The mixture was concentrated to remove the solvent, and to the residue was added EtOAc (20 mL). The resulting mixture was triturated for 1 h and filtered by suction to give the filter cake as a light yellow solid. The filter cake was dissolved in water (10 mL), then to the solution was added aqueous sodium carbonate to precipitate out the solid. The mixure was filtered and the filter cake was dried to give a yellow solid (471 mg, 93%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (s, 2H), 8.48 (d, J = 7.8 Hz, 1H), 8.03 (s, 1H), 7.96 – 7.49 (m, 4H), 7.45 – 7.08 (m, 2H), 5.37 (d, J = 55.4 Hz, 1H), 4.70 – 4.18 (m, 2H), 3.30 – 3.21 (m, 2H), 3.15 – 2.85 (m, 8H), 2.28 (m, 1H), 2.04 (d, J = 5.5 Hz, 2H), 1.94 – 1.65 (m, 2H) ppm; MS-ESI, *m/z*: 475.4 $[M+H]^+$.

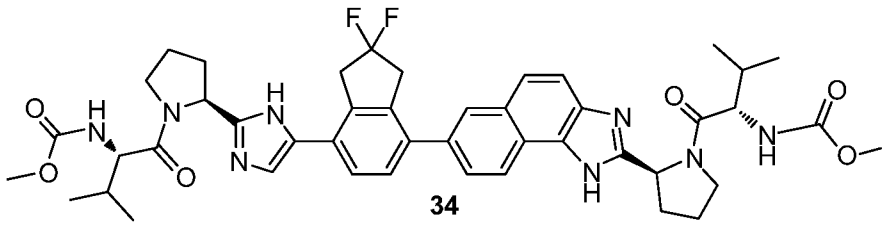
Step 11) synthesis of compound **33**

[00302] To DCM (15 mL) were added compound **33-14** (238 mg, 0.5 mmol, 1.0 eq), compound **1-14** (193 mg, 1.1 mmol, 2.2 eq), ethyl cyanoglyoxylate-2-oxime (57 mg, 0.4 mmol, 0.8 eq) and DIPEA (32 mg, 0.25 mmol, 0.5 eq), then EDCI (211 mg, 1.1 mmol, 2.2 eq) was added. The resulting mixture was stirrd at rt for 3 h. The reaction mixture was poured into 30 mL of water, then the mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhdrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (DCM : MeOH (V : V) = 10 : 1) to give the product as a white solid (241 mg,

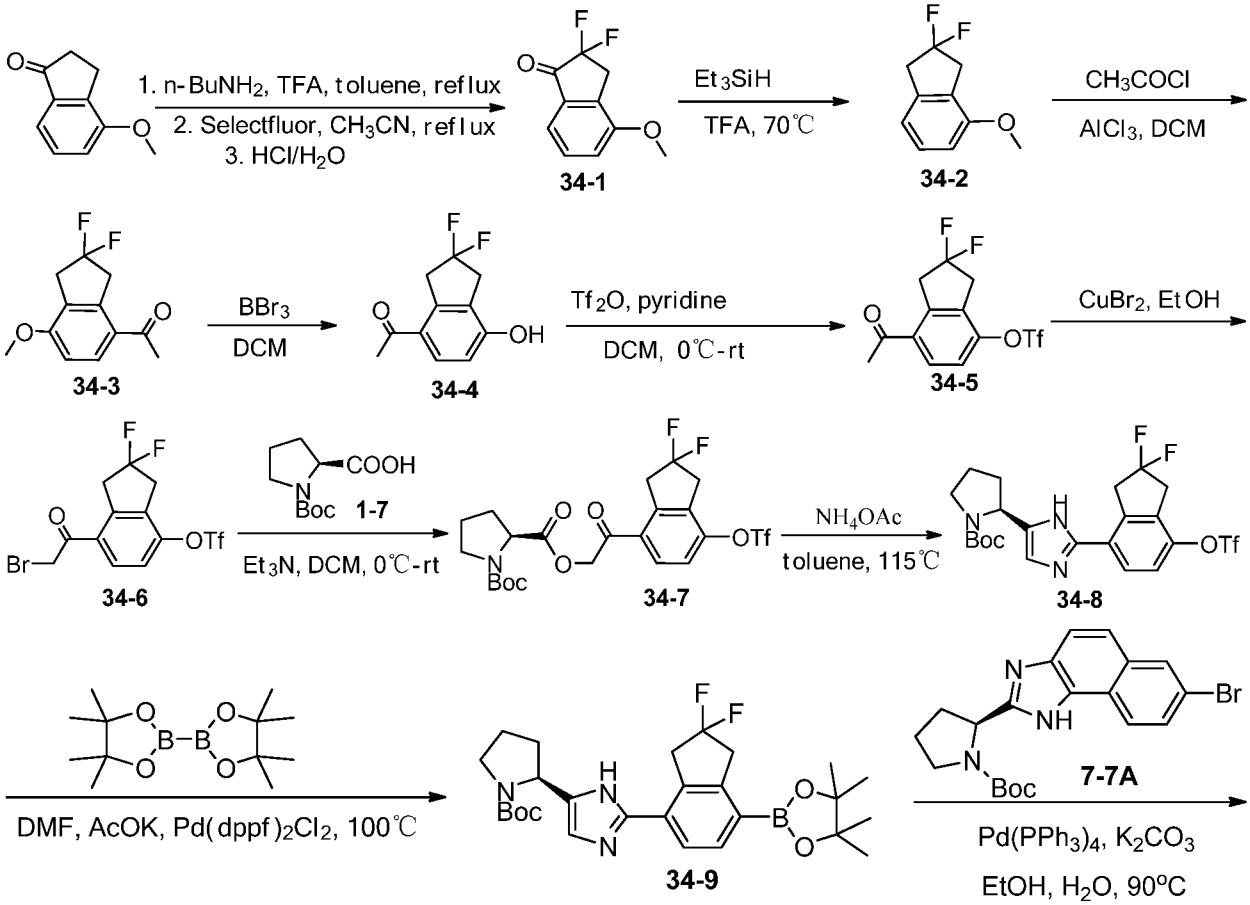
61%).

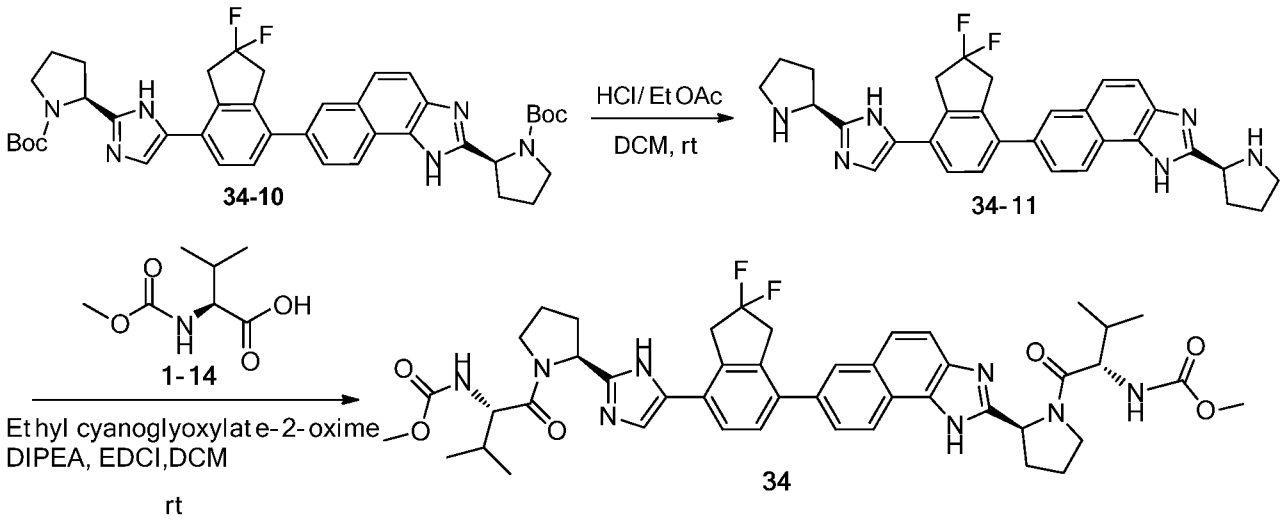
^{1}H NMR (400 MHz, $CDCl_3$): δ 12.09 – 10.24 (m, 2H), 8.63 (s, 1H), 8.19 – 7.54 (m, 4H), 7.42 (d, J = 39.2 Hz, 1H), 7.13 (dd, J = 75.7, 30.2 Hz, 2H), 6.47 – 5.62 (m, 2H), 5.62 – 5.26 (m, 3H), 4.38 (dd, J = 23.1, 15.4 Hz, 3H), 4.14 (q, J = 7.1 Hz, 2H), 3.97 (s, 1H), 3.76 (d, J = 27.7 Hz, 6H), 3.46 – 3.19 (m, 1H), 3.06 (s, 4H), 2.72 (dd, J = 26.7, 14.6 Hz, 2H), 2.59 – 2.07 (m, 3H), 1.94 (d, J = 1.3 Hz, 2H), 1.80 – 1.58 (m, 1H), 0.89 (dd, J = 16.3, 5.8 Hz, 12H) ppm; MS-ESI, *m/z*: 789.3 $[M+H]^+$.

Example 16



Synthesis route:





Synthesis steps:

Step 1) synthesis of compound **34-1**

[00303] The solution of compound **1-1** (8.1 g, 50 mmol, 1 eq), *n*-butylamine (4.38 g, 60 mmol, 1.2 eq) and TFA (1.14 g, 10 mmol, 0.2 eq) in toluene (100 mL) was refluxed at 120 °C overnight. The reaction mixture was concentrated to remove the solvent, and to the residue was added ethyl acetate (100 mL). The resulting mixture was washed with saturated aqueous sodium bicarbonate (30 mL). The organic layer was dried and concentrated. The residue was dissolved in acetonitrile (100 mL), then to the solution was added Selectfluor (35.4 g, 100 mmol, 2 eq). The solution was refluxed at 85 °C for 3 h. The reaction solution was cooled to rt, and concentrated hydrochloric acid (30 mL) wad added dropwise slowly. The resulting mixture was stirred for 10 min, then ethyl acetate (200 mL) was added. The mixture was washed with water (50 mL × 2). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) =10 : 1) to give yellow oil (4.0 g, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (t, J = 7.6 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 3.90 (s, 3H), 3.06 (t, J = 12.3Hz, 2H) ppm.

Step 2) synthesis of compound **34-2**

[00304] The mixture of compound **34-1** (4.0 g, 20 mmol, 1 eq), triethyl silicane (11.6 g, 100 mmol, 5 eq) and TFA (40 mL) in two-neck flask was refluxed, and the reaction was monitored by TLC. The reaction was completed after 6 h and the mixture was poured into ice water. The resulting mixture was extrated with EtOAc (40 mL × 2). The combined organic layers were neutralized with sodium bicarbonate, and the mixture was washed with water. The organic layer was dried and concentrated. The residue was purified by silica gel column chromatography (PE)

to give the product (3.35 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 3.90 (s, 3H), 3.23 (t, J = 12.3, 4H) ppm.

Step 3) synthesis of compound **34-3**

[00305] To compound **34-2** (3.32 g, 18 mmol, 1 eq), aluminum chloride (3.11 g, 23.4 mmol, 1.3 eq) in DCM (20 mL) was added dropwise acetyl chloride (1.7 g, 21.6 mmol, 1.2 eq) at 0 °C. After the addition, the mixture was stirred at rt. After the reaction was completed, the mixture was pourd into ice water, and the resulting mixture was extrated with DCM (20 mL ×2). The combined organic layers were dried and concentrated. The residue was purified by silica gel column chromatography (PE : DCM (V : V) = 5 : 1) to give the product (3.38 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 3.90 (s, 3H), 3.23 (t, J = 12.3, 4H), 2.55 (s, 3H) ppm.

Step 4) synthesis of compound **34-4**

[00306] To a solution of compound **34-3** (3.38 g, 15 mmol, 1eq) in dichloromethane (50 mL) was added dropwise boron tribromide (4.51 g, 18 mmol, 1.2 eq) at 0 °C. After the addition, the mixture was stirred at 0 °C. After the reaction was completed, the mixture was poured into ice water. The resulting mixture was extrated with EtOAc (40 mL × 3). The combined organic layers were dried and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 6 : 1) to give the product (2.23 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 3.23 (t, J = 12.3, 4H), 2.55 (s, 3H) ppm.

Step 5) synthesis of compound **34-5**

[00307] To a solution of compound **34-4** (2.12 g, 10 mmol, 1eq), pyridine (1.96 g, 20 mmol, 2 eq) in dichloromethane (40 mL) was added trifluoromethanesulfonic anhydride (3.4 g, 12 mmol, 1.2 eq) at 0 °C. After the addition, the mixture was stirred at rt, and the reaction was monitored by TLC. After the reaction was completed, the mixture was washed with water (10 mL) and saturated aqueous sodium chloride. The organic layer was dried and concentrated. The residue was purified by silica gel column chromatography (PE) to give the product (3.27 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.2 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 3.23 (t, J = 12.3, 2H), 3.03 (t, J = 12.3, 2H), 2.55 (s, 3H) ppm.

Step 6) synthesis of compound **34-6**

[00308] To EtOH (20 mL) were added compound **34-5** (1.84 g, 5.33 mmol, 1 eq) and cupric bromide (2.38 g, 10.7 mmol, 2 eq). The mixture was stirred at 60 °C for 2 h. After the reaction, the mixture was filtered through a celite pad. The filtrate was concentrated, and to the residue was added dichloromethane (40 mL). The mixture was washed with water (20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 6 : 1) to give brownish red oil (1.38 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.6 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 4.43 (s, 2H), 3.36 (t, J = 12.3 Hz, 2H), 3.07 (t, J = 12.3 Hz, 2H) ppm.

Step 7) synthesis of compound **34-7**

[00309] To a solution of compound **34-6** (1.52 g, 3.6 mmol, 1eq) and BOC-*L*-proline (1.0 g, 4.6 mmol, 1.3 eq) in dichloromethane (20 mL) was added triethylamine (0.6 g, 6 mmol, 1.5 eq) at 0 °C. After the addition, the mixture was stirred at rt, and the reaction was monitored by TLC. After the reaction was completed, the mixture was washed with water (10 mL) and saturated aqueuous sodium chloride. The organic layer was dried and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 6 : 1) to give the product (1.63 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.6 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 5.13 (m, 1H), 4.43 (s, 2H), 3.36 (m, 2H), 3.16 (m, 2H), 3.07 (m, 4H), 2.29 (m, 2H), 1.36 (t, 9H) ppm; MS-ESI, *m/z*: 558.1$[M+H]^+$.

Step 8) synthesis of compound **34-8**

[00310] The solution of compound **34-7** (1.45 g, 2.6 mmol, 1.0 eq) and ammonium acetate (1.2 g, 15.6 mmol, 6.0 eq) in toluene (15 mL) was stirred at 115 °C for 20 h. The reaction mixture was concentrated to remove the toluene, and to the residue was added 50 mL of water. The mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give the crude product as a light yellow solid (1.33 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.97 (s, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.19 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 5.33 (d, J = 52.9 Hz, 1H), 5.19 (t, J = 7.0 Hz, 1H), 3.98 (dd, J = 21.0, 13.0 Hz, 1H), 3.61 – 3.22 (m, 2H), 3.12 (dt, J = 15.0, 7.1 Hz, 4H), 2.85 – 2.59 (m, 2H), 1.52 (s, 9H) ppm;

MS-ESI, *m/z*: 538.2 $[M+H]^+$.

Step 9) synthesis of compound **34-9**

[00311] To DMF (15 mL) were added compound **34-8** (1.29 g, 2.4 mmol, 1.0 eq), bis(pinacolato)diboron (0.63 g, 2.5 mmol, 1.05 eq), potassium acetate (0.71 g, 7.2 mmol, 3.0 eq) and $Pd(dppf)_2Cl_2$ (69 mg, 0.094 mmol, 0.04 eq). The mixture was stirred at 100 °C for 10 h under nitrogen atomosphere. The reaction mixture was poured into water, then the mixture was filtered by suction to give a gray solid. The gray solid was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give a light yellow solid (0.89 g, 72%).

^1H NMR (400 MHz, $CDCl_3$): δ 10.89 (s, 1H), 7.78 (s, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.20 (s, 1H), 5.27 (dd, J = 42.7, 30.3 Hz, 2H), 3.97 (dd, J = 20.7, 13.3 Hz, 1H), 3.48 (dd, J = 35.4, 12.0 Hz, 1H), 3.38 – 2.88 (m, 5H), 2.80 – 2.59 (m, 2H), 1.52 (s, 9H), 1.36 (s, 12H) ppm; MS-ESI, *m/z*: 516.4 $[M+H]^+$.

Step 10) synthesis of compound **34-10**

[00312] To the mixture of ethanol (10 mL) and water (3 mL) were added compound **34-9** (567 mg, 1.1 mmol, 1.0 eq), compound **7-7A** (460 mg, 1.1 mmol, 1.0 eq), potassium carbonate (0.30 g, 2.2 mmol, 2.0 eq), $Pd(PPh_3)_4$ (38 mg, 0.033 mmol, 0.03 eq). The mixture was stirred at 90 °C for 6 h under nitrogen atomosphere. The reaction mixture was poured into 50 mL of water, then the mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 1) to give the crude product as a white solid (0.757 g, 95%).

^1H NMR (400 MHz, $CDCl_3$): δ 11.88 – 10.35 (m, 2H), 8.67 (d, J = 8.1 Hz, 1H), 8.22 – 7.30 (m, 6H), 7.18 (d, J = 23.9 Hz, 1H), 5.51 – 5.11 (m, 3H), 4.00 (dd, J = 21.1, 13.2 Hz, 1H), 3.57 (dd, J = 32.1, 9.6 Hz, 3H), 3.14 (dd, J = 20.9, 13.7 Hz, 5H), 2.81 – 2.62 (m, 2H), 2.44 – 2.21 (m, 2H), 2.00 – 1.86 (m, 2H), 1.55 (d, J = 6.7 Hz, 18H) ppm; MS-ESI, *m/z*: 725.4 $[M+H]^+$.

Step 11) synthesis of compound **34-11**

[00313] To the mixture of compound **34-10** (0.725 g, 1.0 mmol, 1.0 eq) in DCM (10 mL) was added dropwise HCl/EtOAc (4 N, 3 mL) at 0 °C. After the addition, the mixture was stirred at rt for 10 h. The mixture was concentrated to remove the solvent, and to the residue was added EtOAc (20 mL). The resulting mixture was triturated for 1 h at rt and filtered by suction to give

the filter cake as a light yellow solid. The filter cake was dissolved in water (10 mL), then to the solution was added aqueous sodium carbonate to precipitate out the solid. The mixture was filtered and the filter cake was dried to give a yellow solid (483 mg, 92%).

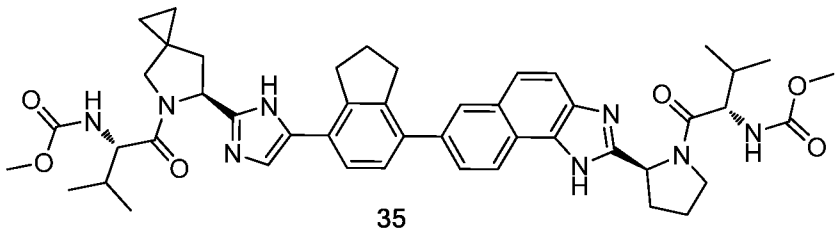
^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (s, 2H), 8.48 (d, J = 7.8 Hz, 1H), 8.03 (s, 1H), 7.96 – 7.49 (m, 4H), 7.45 – 7.08 (m, 2H), 5.37 (d, J = 55.4 Hz, 1H), 4.70 – 4.18 (m, 2H), 3.30 – 3.21 (m, 2H), 3.15 – 2.85 (m, 8H), 2.28 (m, 1H), 2.04 (d, J = 5.5 Hz, 2H), 1.94 – 1.65 (m, 2H) pm; MS-ESI, m/z: 525.4 $[M+H]^+$.

Step 12) synthesis of compound **34**

[00314] To DCM (15 mL) were added compound **34-11** (263 mg, 0.5 mmol, 1.0 eq), compound **1-14** (193 mg, 1.1 mmol, 2.2 eq), ethyl cyanoglyoxylate-2-oxime (57 mg, 0.4 mmol, 0.8 eq) and DIPEA (32 mg, 0.25 mmol, 0.5 eq), then EDCI (211 mg, 1.1 mmol, 2.2 eq) was added. The resulting mixture was stirred at rt for 3 h. The reaction mixture was poured into 30 mL of water, then the mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhdrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (DCM : MeOH (V : V) = 10 : 1) to give the product as a white solid (239 mg, 57%).

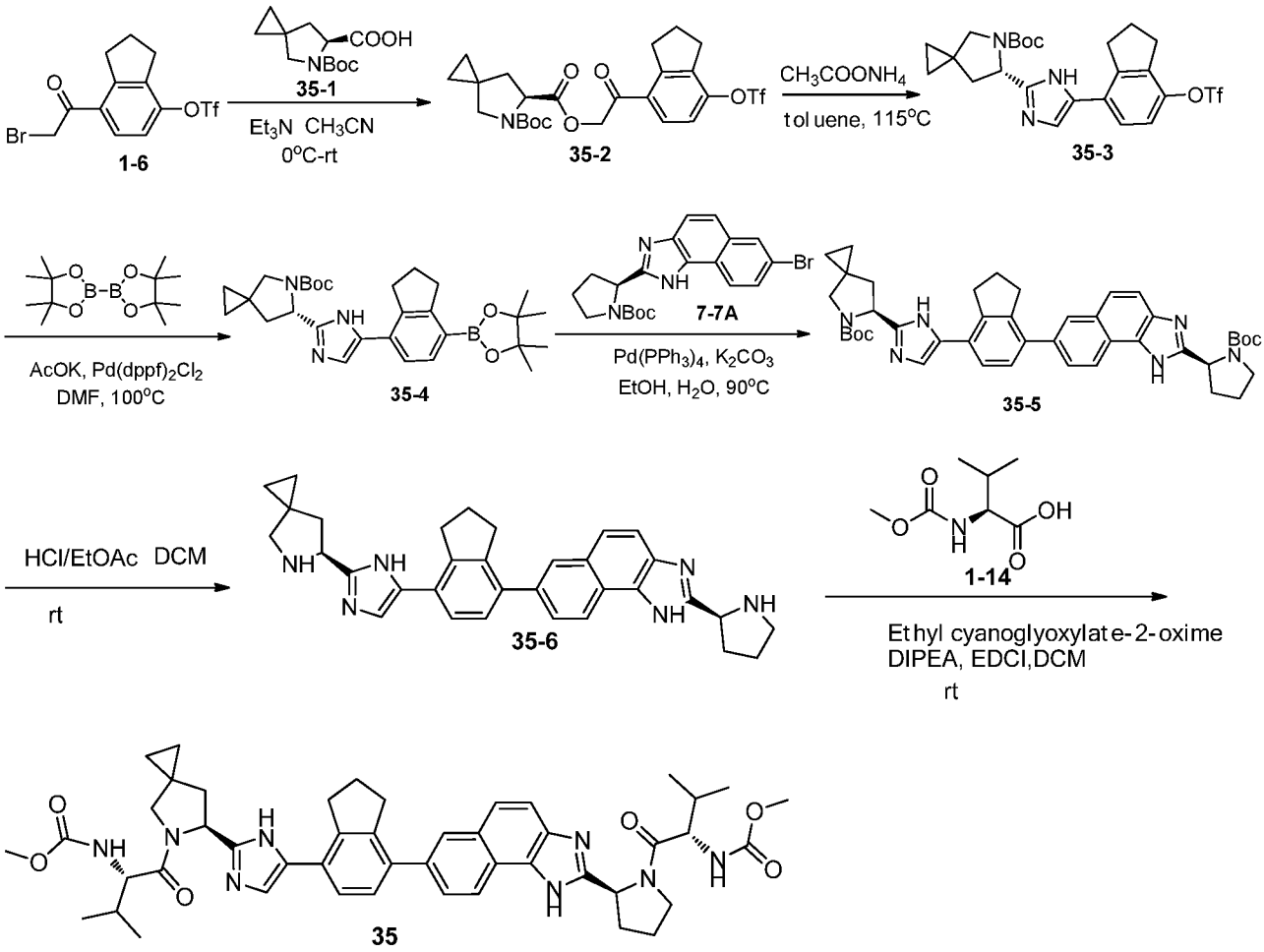
^{1}H NMR (400 MHz, $CDCl_3$): δ 12.09 – 10.24 (m, 2H), 8.63 (s, 1H), 8.19 – 7.54 (m, 4H), 7.42 (d, J = 39.2 Hz, 1H), 7.13 (dd, J = 75.7, 30.2 Hz, 2H), 6.47 – 5.62 (m, 2H), 5.62 – 5.26 (m, 3H), 4.38 (dd, J = 23.1, 15.4 Hz, 3H), 4.14 (q, J = 7.1 Hz, 2H), 3.97 (s, 1H), 3.76 (d, J = 27.7 Hz, 6H), 3.46 – 3.19 (m, 1H), 3.06 (s, 4H), 2.72 (dd, J = 26.7, 14.6 Hz, 2H), 2.59 – 2.07 (m, 3H), 1.94 (d, J = 1.3 Hz, 2H), 1.80 – 1.58 (m, 1H), 0.89 (dd, J = 16.3, 5.8 Hz, 12H) ppm; MS-ESI, m/z: 839.3 $[M+H]^+$.

Example 17



35

Synthesis route:



Synthesis steps:

Step 1) synthesis of compound **35-2**

[00315] To the solution of compound **1-6** (1.2 g, 3.1 mmol, 1.0 eq) and compound **35-1** (0.82 g, 0.34 mmol, 1.1 eq) in acetonitrile (10 mL) was added dropwise triethylamine (0.47 g, 4.6 mmol, 1.5 eq) at 0 °C. After the addition, the mixture was stirred at rt for 2 h. The reaction mixture was concentrated to remove the solvent and the residue was poured into 20 mL of water. Then the mixture was extracted with DCM (20 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to give the product as brown oil (1.72 g, 100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 5.45 (dd, J = 63.1, 16.2 Hz, 1H), 5.12 (dd, J = 55.0, 16.2 Hz, 1H), 4.58 (ddd, J = 26.2, 8.5, 3.4 Hz, 1H), 3.51 – 3.34 (m, 2H), 3.32 (d, J = 7.0 Hz, 2H), 3.05 (t, J = 7.1 Hz, 2H), 2.39 (dd, J = 12.6, 8.8 Hz, 1H), 2.26 – 2.12 (m, 2H), 2.09 (d, J = 12.7 Hz, 1H), 1.46 (d, J = 3.4 Hz, 9H), 0.63 (dd, J = 13.4, 8.3 Hz, 4H) ppm.

Step 2) synthesis of compound **35-3**

[00316] The solution of compound **35-2** (1.70 g, 3.1 mmol, 1.0 eq) and ammonium acetate (1.4 g, 19 mmol, 6.0 eq) in toluene (10 mL) was stirred at 115 °C for 15 h. The reaction mixture was concentrated to remove the toluene, and to the residue was added 50 mL of water. The mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give the crude product as a light yellow solid (1.33 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.88 (d, J = 214.7 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.18 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 5.13 (s, 1H), 3.53 (d, J = 10.0 Hz, 1H), 3.20 – 3.07 (m, 5H), 2.80 (d, J = 10.6 Hz, 1H), 2.37 (s, 1H), 2.21 (d, J = 6.8 Hz, 2H), 1.52 (s, 9H), 0.89 (dd, J = 9.6, 5.4 Hz, 1H), 0.63 (ddd, J = 18.6, 11.0, 4.9 Hz, 3H) ppm; MS-ESI, *m/z*: 528.20 $[M+H]^+$.

Step 3) synthesis of compound **35-4**

[00317] To DMF (10 mL) were added compound **35-3** (1.25 g, 2.37 mmol, 1.0 eq), bis(pinacolato)diboron (0.63 g, 2.49 mmol, 1.05 eq), potassium acetate (0.69 g, 7.11 mmol, 3.0 eq), $Pd(dppf)_2Cl_2$ (52 mg, 0.071 mmol, 0.03 eq). The mixture was stirred at 100 °C for 16 h under nitrogen atomosphere. The reaction mixture was poured into water, then the mixture was filtered by suction to give a gray solid. The gray solid was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give a light yellow solid (1.0 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.83 (d, J = 222.3 Hz, 1H), 7.81 (s, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.22 (s, 1H), 5.14 (d, J = 6.2 Hz, 1H), 3.52 (d, J = 10.3 Hz, 1H), 3.38 – 2.97 (m, 5H), 2.79 (s, 1H), 2.56 – 2.28 (m, 1H), 2.21 – 2.08 (m, 2H), 1.52 (s, 9H), 1.36 (s, 12H), 0.90 (s, 1H), 0.73 – 0.52 (m, 3H) ppm; MS-ESI, *m/z*: 506.4 $[M+H]^+$.

Step 4) synthesis of compound **35-5**

[00318] To the mixture of ethanol (10 mL) and water (3 mL) were added compound **35-4** (600 mg, 1.19 mmol, 1.0 eq), compound **7-7A** (494 g, 1.19 mmol, 1.0 eq), potassium carbonate (0.33 g, 2.37 mmol, 2.0 eq) and $Pd(PPh_3)_4$ (41 mg, 0.035 mmol, 0.03 eq). The mixture was stirred at 90 °C for 10 h under nitrogen atomosphere. The reaction mixture was poured into 50 mL of water, then the mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 1) to give a white solid (0.80 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.56-10.55 (m, 2H), 8.68 (d, J = 13.5 Hz, 1H), 8.00 (s, 1H),

7.87 (d, J = 7.1 Hz, 1H), 7.72 (d, J = 25.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 1H), 7.41 (s, 1H), 7.23 (s, 1H), 5.32 – 5.09 (m, 2H), 3.56 (dd, J = 37.5, 26.4 Hz, 3H), 3.15 (dd, J = 26.7, 3.2 Hz, 4H), 2.84 (dd, J = 13.4, 10.1 Hz, 1H), 2.46 – 2.25 (m, 2H), 2.20 – 2.08 (m, 2H), 1.79-170 (m, 4H), 1.61 – 1.44 (m, 18H), 0.86 (d, J = 2.9 Hz, 1H), 0.79 – 0.43 (m, 3H) ppm; MS-ESI, *m/z*: 715.4 $[M+H]^+$.

Step 5) synthesis of compound **35-6**

[00319] To the mixture of compound **35-5** (0.80 g, 1.1 mmol, 1.0 eq) in DCM (15 mL) was added dropwise HCl/EtOAc (4 N, 3 mL) at 0 °C. After the addition, the mixture was stirred at rt for 15 h. The mixture was concentrated to remove the solvent, and to the residue was added EtOAc (20 mL). The resulting mixture was triturated for 1 h and filtered by suction to give the filter cake as a light yellow solid. The filter cake was dissolved in water (10 mL), then to the solution was added aqueous sodium carbonate to precipitate out the solid. The mixture was filtered and the filter cake was dried to give a yellow solid (590 mg, 100%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.48 (d, J = 8.4 Hz, 1H), 8.04 (s, 1H), 7.81 (s, 1H), 7.69 (d, J = 11.0 Hz, 3H), 7.34 (d, J = 7.9 Hz, 1H), 7.24 (s, 1H), 4.43 (dt, J = 14.8, 7.2 Hz, 2H), 3.45 (d, J = 7.0 Hz, 2H), 3.09 (dd, J = 16.1, 7.5 Hz, 4H), 3.01 – 2.90 (m, 2H), 2.82 (d, J = 9.9 Hz, 1H), 2.21 (dt, J = 14.2, 7.8 Hz, 1H), 2.12 – 1.98 (m, 4H), 1.81 (dd, J = 14.0, 7.0 Hz, 2H), 1.06 (t, J = 7.0 Hz, 1H), 0.56 (t, J = 13.3 Hz, 3H) ppm; MS-ESI, *m/z*: 515.2 $[M+H]^+$.

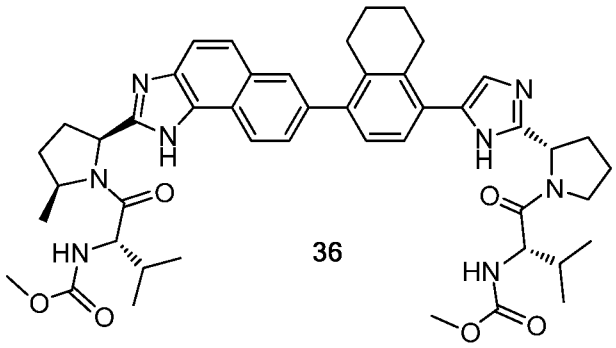
Step 6) synthesis of compound **35**

[00320] To DCM (15 mL) were added compound **35-6** (280 mg, 0.54 mmol, 1.0 eq), compound **1-14** (209 mg, 1.20 mmol, 2.2 eq), ethyl cyanoglyoxylate-2-oxime (61 mg, 0.43 mmol, 0.8 eq) and DIPEA (35 mg, 0.27 mmol, 0.5 eq), then EDCI (227 mg, 1.19 mmol, 2.2 eq) was added. The resulting mixture was stirrd at rt for 18 h. The reaction mixture was poured into 30 mL of water, then the mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhdrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (DCM : EtOAc : MeOH (V : V : V) = 5 : 10 : 1) to give the product as a white solid (243 mg, 53.88%).

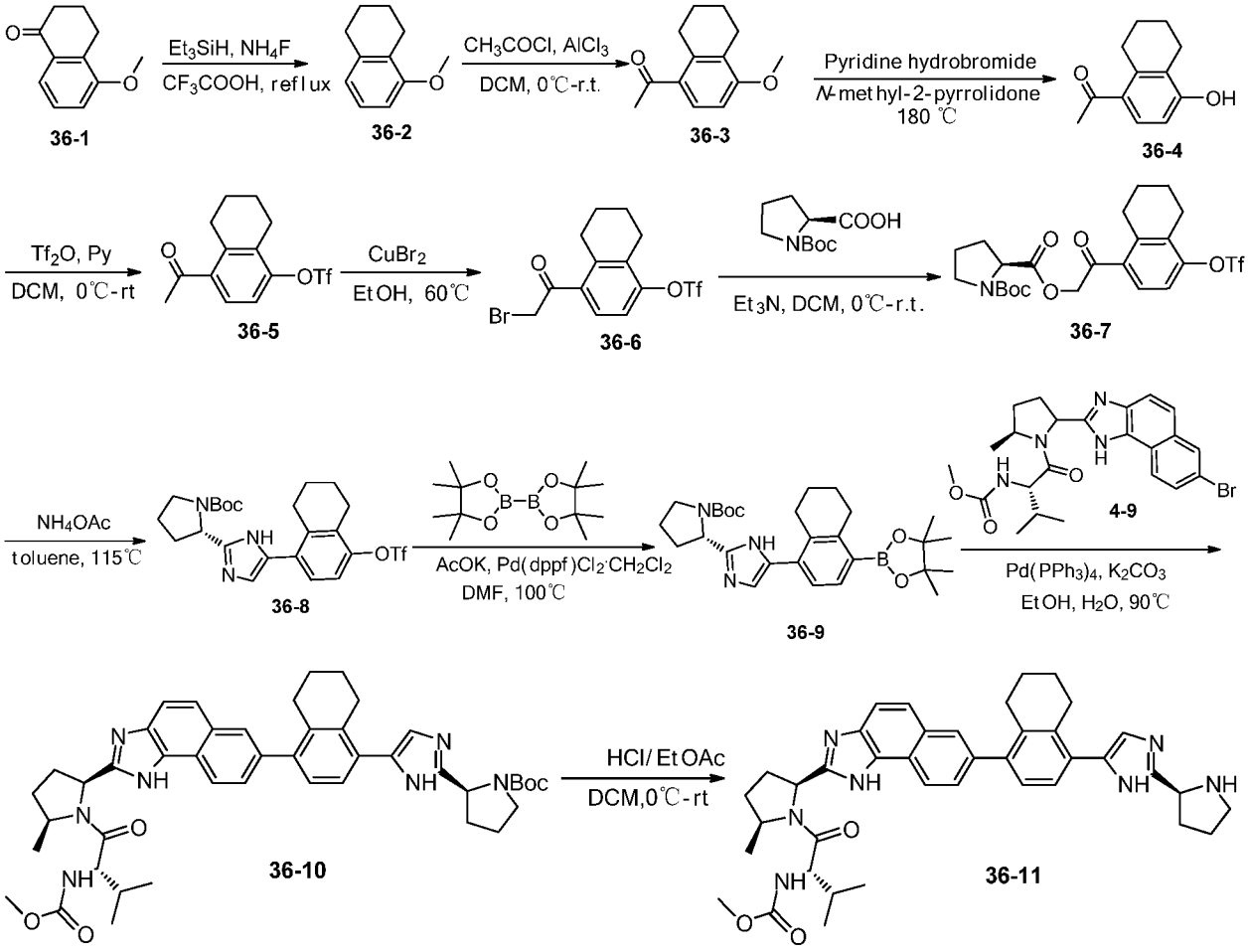
^{1}H NMR (400 MHz, $CDCl_3$): δ 12.97 – 10.31 (m, 2H), 8.63 (d, J = 7.6 Hz, 1H), 7.90 (dd, J = 45.6, 19.8 Hz, 2H), 7.68 (dd, J = 21.5, 8.3 Hz, 2H), 7.39 (d, J = 32.9 Hz, 2H), 7.19 (s, 1H), 5.64 (dd, J = 83.6, 38.2 Hz, 4H), 4.48 – 4.26 (m, 1H), 4.15 (dd, J = 6.0, 4.1 Hz, 1H), 4.00 – 3.87 (m, 1H), 3.83 (s, 1H), 3.73 (s, 3H), 3.62 (s, 3H), 3.13 (dd, J = 18.7, 11.1 Hz, 4H), 2.51 (dd, J = 27.9,

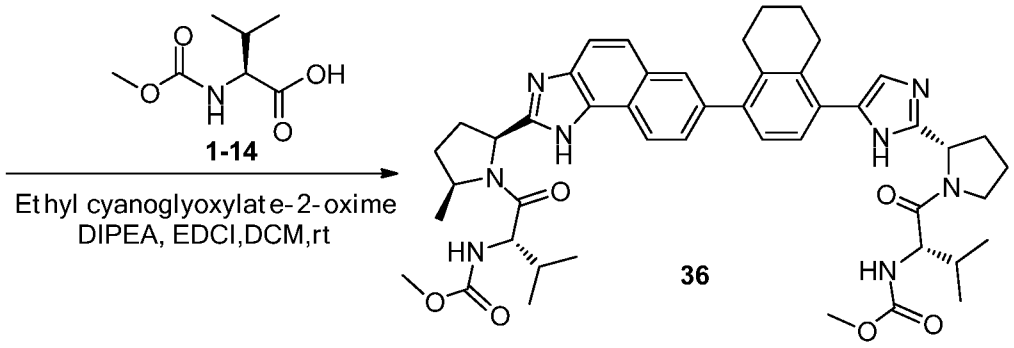
23.1 Hz, 2H), 2.40 – 2.26 (m, 1H), 2.26 –1.96 (m, 5H), 1.79 – 1.69 (m, 1H), 1.69 – 1.58 (m, 1H), 1.05 – 0.83 (m, 12H), 0.84–0.56 (m, 4H) ppm; MS-ESI, *m/z*: 829.4 $[M+H]^+$.

Example 18



Synthesis route:





Synthesis steps:

Step 1) synthesis of compound **36-2**

[00321] To trifluoroacetic acid (100 mL) were added 5-methoxy-3,4-dihydronaphthalen -1(2*H*)-one **36-1** (12 g, 68 mmol), triethyl silicane (26.3 g, 272 mmol) and ammonium fluoride (8.3 g, 272 mmol). The mixture was stirrd at 72 °C for 6 h. The mixture was concentrated to remove the solvent, and the residue was dissloved in EtOAc (300 mL × 2). The organic layer was neutralized with aqueous sodium bicarbonate. The resulting mixture was washed with water. The oragnic layer was dried and concentrated. The residue was purfied by silica gel column chromatography (PE) to give the product as colourless oil (10 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (t, J = 7.9 Hz, 1H), 6.75 (dd, J = 21.5, 7.9 Hz, 2H), 3.88 (s, 3H), 2.84 (t, J = 5.6 Hz, 2H), 2.74 (t, J = 5.9 Hz, 2H), 1.91 – 1.80 (m, 4H) ppm; MS (ESI, pos.ion) *m/z*: 163.2 $[M+H]^+$.

Step 2) synthesis of compound **36-3**

[00322] To compound **36-2** (11 g, 67.8 mmol), aluminum chloride (13.7 g, 100 mmol) in DCM (100 mL) was added dropwise acetyl chloride (7 g, 88 mmol) at 0 °C. After the addition, the mixture was stirred at rt for 24 h. The mixture was poured into ice water, and the resulting mixture was extrated with ethyl acetate (200 mL × 2). The combined organic layers were washed with water, dried and concentrated. The residue was purified by silica gel column chromatography (PE) to give light yellow oil (4 g, 28%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.6 Hz, 1H), 6.69 (d, J = 8.6 Hz, 1H), 3.87 (s, 3H), 3.04 (t, J = 5.8 Hz, 2H), 2.75 – 2.57 (m, 2H), 2.55 (s, 3H), 1.75 (td, J = 7.3, 3.6 Hz, 4H) ppm; MS (ESI, pos.ion) *m/z*: 205.1 $[M+H]^+$.

Step 3) synthesis of compound **36-4**

[00323] To a solution of compound **36-3** (9 g, 44 mmol) in *N*-methyl-2-pyrrolidone (90 mL) was

added pyridine hydrobromide (28 g, 176 mmol). The mixture was stirred at 180 °C for 4 h. To the reaction mixture was added water (400 mL), and the mixture was extrated with ethyl acetate (300 mL × 2). The combined organic layers were washed with saturated brine (150 mL), dried and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 10 : 1) to give a white solid (4 g, 47.7%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 3.10 (t, J = 6.1 Hz, 2H), 2.82 – 2.60 (m, 2H), 2.57 (s, 3H), 1.98 – 1.70 (m, 4H) ppm; MS (ESI, pos.ion) *m/z*: 191.2 $[M+H]^+$.

Step 4) synthesis of compound **36-5**

[00324] To a solution of compound **36-4** (4 g, 21 mmol), pyridine (2.2 g, 27 mmol) in DCM (120 mL) was added trifluoromethanesulfonic anhydride (6.5 g, 23 mmol) at 0 °C. The mixture was stirred at rt for 3 h. The reaction mixture was washed with water (30 mL), and the organic layer was dried and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) =10 : 1) to give colourless oil (2.8 g, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 3.10 (t, J = 6.1 Hz, 2H), 2.82 – 2.60 (m, 2H), 2.57 (s, 3H), 1.98 – 1.70 (m, 4H) ppm; MS (ESI, pos.ion) *m/z*: 323.2 $[M+H]^+$.

Step 5) synthesis of compound **36-6**

[00325] The mixture of compound **36-5** (2.6 g, 8 mmol) and cupric bromide (3.6 g, 16 mmol) in ethanol (50 mL) was stirred at 60 °C for 2 h. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated. The residue was dissolved in DCM (50 mL × 2). The resulting mixture was washed with saturated aqueous sodium chloride (30 mL), dried over anhydrous sodium sulfate and concentrated to give a yellow solid (2.8 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 4.66 (s, 2H), 3.10 (t, J = 6.1 Hz, 2H), 2.82 – 2.60 (m, 2H), 1.98 – 1.70 (m, 4H) ppm; MS (ESI, pos.ion) *m/z*: 401.3 $[M+H]^+$.

Step 6) synthesis of compound **36-7**

[00326] To a solution of compound **36-6** (2.8 g, 7 mmol), *N*-(*tert*-Butoxycarbonyl)-*L*-proline (2.0 g, 9 mmol) in DCM (60 mL) was added triethylamine (1.1 g, 10 mmol) at 0 °C. The mixture was stirred at rt for 8 h. The reaction mixture was washed with water (20 mL), dried over

anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 6 :1) to give colourless oil (3 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.5 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 5.05 (ddd, J = 63.0, 51.9, 16.7 Hz, 2H), 4.48 – 4.26 (m, 1H), 3.64 – 3.22 (m, 2H), 2.98 – 2.65 (m, 4H), 2.13 – 1.67 (m, 8H), 1.43 (d, J = 13.2 Hz, 9H) ppm; MS (ESI, pos.ion) *m/z*: 536.0 $[M+H]^+$.

Step 7) synthesis of compound **36-8**

[00327] The solution of compound **36-7** (3 g, 5.6 mmol) and ammonium acetate (2.6 g, 33 mmol) in toluene (60 mL) was stirred at 110 °C for 12 h. After the addition, to the reaction mixture was added water (20 mL). The resulting mixture was extracted with EtOAc (50 mL × 2). The combined organic layers were washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 4 :1) to give brown oil (0.8 g, 30%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s, 1H), 7.21 – 7.07 (m, 1H), 7.04 (s, 1H), 4.99 (d, J = 5.2 Hz, 1H), 3.43 (s, 2H), 3.00 – 2.75 (m, 4H), 2.24 – 1.95 (m, 5H), 1.78 (dt, J = 48.8, 24.0 Hz, 4H), 1.58 – 1.41 (m, 9H) ppm; MS (ESI, pos.ion) *m/z*: 516.1 $[M+H]^+$.

Step 8) synthesis of compound **36-9**

[00328] To DMF (20 mL) were added compound **36-8** (0.8 g, 1.6 mmol), bis(pinacolato)diboron (0.5 g, 1.9 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.25 g, 0.3 mmol), AcOK (0.5 g, 4.7 mmol). The mixture was stirred at 100 °C for 4 h under nitrogen atomosphere. The reaction mixture was cooled to rt, and water (60 mL) was added. The mixture was filtered, and the filter cake was dissolved in dichloromethane. Then the solution was concentrated and the residue was purified by silica gel column chromatography (PE : EtOAc (V : V) =4 : 1) to give brown oil (0.65 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.76 (s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.03 (s, 2H), 5.00 (d, J = 5.4 Hz, 1H), 3.43 (d, J = 5.3 Hz, 2H), 2.84 (s, 3H), 2.10 (dd, J = 60.9, 20.7 Hz, 3H), 1.86 – 1.69 (m, 6H), 1.51 (s, 9H), 1.36 (s, 12H) ppm; MS (ESI, pos.ion) *m/z*: 494.3 $[M+H]^+$.

Step 9) synthesis of compound **36-10**

[00329] To the mixture of ethanol (16 mL) and water (4 mL) were added compound **36-9** (0.65 g, 1.3 mmol), compound **4-9** (0.64 g, 1.03 mmol), $Pd(PPh_3)_4$ (0.23 g, 0.2 mmol) and K_2CO_3 (0.54 g, 4 mmol). The mixture was stirred at 90 °C for 3 h under nitrogen atmosphere. The reaction

mixture was concentrated *in vacuo* and the residue was extracted with DCM (80 mL) two times. The organic layer was washed with saturated aqueous sodium chloride (20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM : EtOAc (V : V) =2 : 1) to give a yellow solid (0.7 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.87 – 9.99 (m, 2H), 8.62 (d, J = 8.5 Hz, 1H), 8.05 – 7.77 (m, 2H), 7.68 (t, J = 8.6 Hz, 1H), 7.63 – 7.48 (m, 1H), 7.20 (s, 1H), 7.06 (s, 1H), 5.49 (dd, J = 45.6, 22.5 Hz, 1H), 5.03 (d, J = 5.4 Hz, 1H), 4.29 (s, 1H), 3.98 – 3.68 (m, 3H), 3.57 – 3.38 (m, 3H), 2.94 (t, J = 30.7 Hz, 3H), 2.70 (s, 2H), 2.19 (s, 3H), 2.05 (s, 2H), 1.90 – 1.66 (m, 9H), 1.52 (s, 9H), 1.34 – 1.22 (m, 4H), 1.19 – 1.09 (m, 5H) ppm; MS (ESI, pos.ion) *m/z*: 774.6 $[M+H]^+$.

Step 10) synthesis of compound **36-11**

[00330] To a solution of compound **36-10** (0.7 g, 0.9 mmol) in DCM (16 mL) was added dropwise HCl/EtOAc (4 N, 4 mL) at 0 °C. The mixture was stirred at rt for 3 h. The mixture was concentrated and the residue was triturated with ethyl acetate, then the resulting mixture was filtered. The filter cake was dissolved in water (10 mL), and the pH of the solution was adjusted with potassium carbonate to 8-9. The resulting mixture was filtered by suction to give a yellow solid (0.58 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.87 – 9.99 (m, 2H), 8.62 (d, J = 8.5 Hz, 1H), 8.05 – 7.77 (m, 2H), 7.68 (t, J = 8.6 Hz, 1H), 7.63 – 7.48 (m, 1H), 7.20 (s, 1H), 7.06 (s, 1H), 5.49 (dd, J = 45.6, 22.5 Hz, 1H), 5.03 (d, J = 5.4 Hz, 1H), 4.29 (s, 1H), 3.98 – 3.68 (m, 3H), 3.57 – 3.38 (m, 4H), 2.94 (t, J = 30.7 Hz, 3H), 2.70 (s, 2H), 2.19 (s, 3H), 2.05 (s, 2H), 1.90 – 1.66 (m, 9H), 1.34 – 1.22 (m, 4H), 1.19 – 1.09 (m, 5H) ppm; MS (ESI, pos.ion) *m/z*: 674.3 $[M+H]^+$.

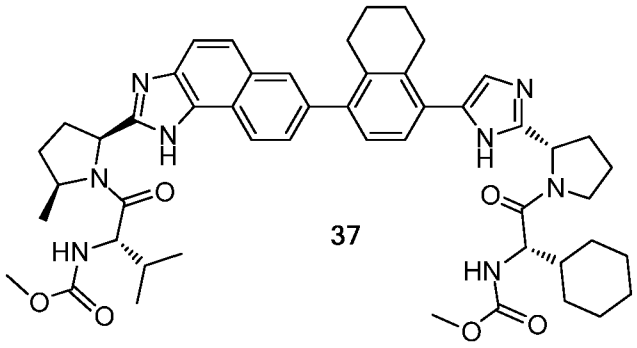
Step 11) synthesis of compound **36**

[00331] To DCM (10 mL) were added compound **36-11** (0.28 g, 0.41 mmol), (*S*)-2-((methoxycarbonyl)amino)-3-methylbutanoic acid **1-14** (0.09 g, 0.5 mmol) and ethyl cyanoglyoxylate-2-oxime (0.024 g, 0.165 mmol), then EDCI (0.1 g, 0.5 mmol) was added. The resulting mixture was stirred at rt for 2 h. The reaction was quenched with water, and the mixture was extracted with DCM (50 mL). The organic layer was concentrated, and the residue was dissolved in methanol (20 mL). To the mixture was added ammonium hydroxide (1 mL), and the resulting mixture was stirred for 5 min, then concentrated. The residue was extracted with DCM (50 mL), and the organic layer was washed with saturated aqueous sodium chloride (10 mL),

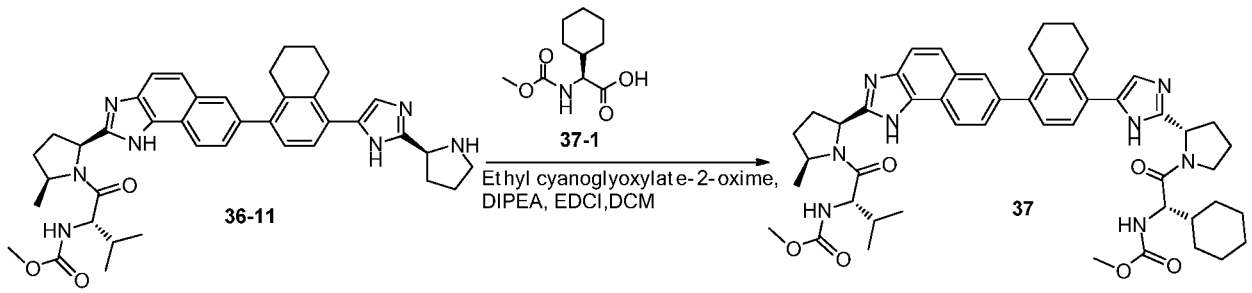
dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM : EtOAc : MeOH (V : V : V) = 20 : 10 : 1) to give a white solid (0.2 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.80 (m, 2H), 8.78 – 8.40 (m, 1H), 8.02 – 7.80 (m, 2H), 7.73 – 7.48 (m, 3H), 7.19 (m, 2H), 7.05 (s, 1H), 5.63 – 5.38 (m, 3H), 5.32 (s, 1H), 4.48 – 4.24 (m, 3H), 3.94 (s, 1H), 3.85 (s, 1H), 3.77 – 3.63 (m, 4H), 3.50 – 3.22 (m, 2H), 3.09 – 2.78 (m, 4H), 2.69 (s, 1H), 2.52 – 2.25 (m, 1H), 2.20 (s, 1H),2.04 (s, 3H), 1.45 (s, 1H), 1.28 (t, J = 7.1 Hz, 4H), 1.18 (d, J = 6.0 Hz, 2H), 1.12 (m, 4H), 1.02 – 0.76 (m, 11H) ppm; MS (ESI, pos.ion) *m/z*: 831.6 $[M+H]^+$.

Example 19



Synthesis route:



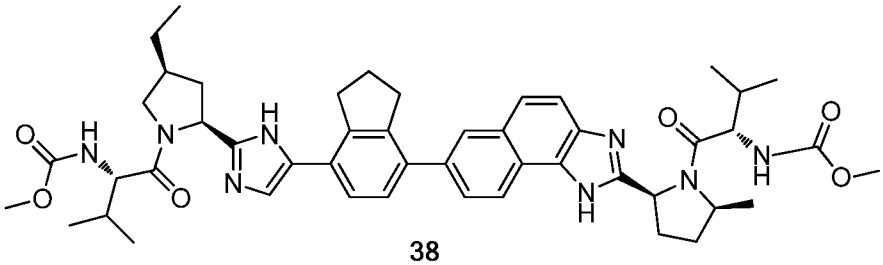
Synthesis steps:

[00332] To DCM (10 mL) were added compound **36-11** (0.28 g, 0.41 mmol), (*S*)-2-cyclohexyl-2-((methoxycarbonyl)amino)acetic acid **37-1** (0.102 g, 0.46 mmol) and ethyl cyanoglyoxylate-2-oxime (0.024 g, 0.16 mmol), then EDCI (0.098 g, 0.5 mmol) was added at rt. The resulting mixture was stirred at rt for 2 h. The reaction was quenched with water, and the mixture was extracted with DCM (50 mL). The organic layer was concentrated, and the residue was dissolved in methanol (20 mL). To the mixture was added ammonium hydroxide (1 mL), and the resulting mixture was stirred for 5 min, then concentrated. The residue was extracted with DCM (50 mL), and the organic layer was washed with saturated aqueous sodium chloride (10 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by

silica gel column chromatography (DCM : EtOAc : MeOH (V : V : V) = 20 : 10 : 1) to give a white solid (0.2 g, 60%).

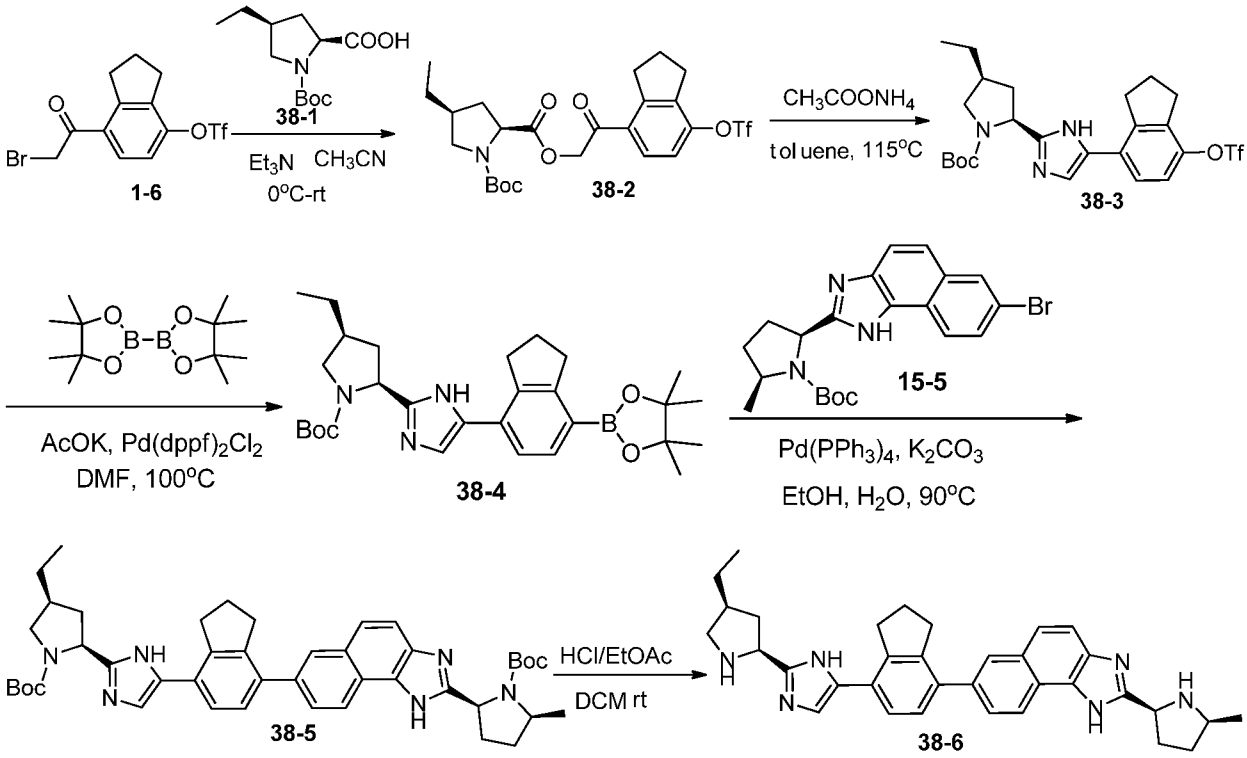
^{1}H NMR (400 MHz, $CDCl_3$): δ 12.82 – 10.07 (m, 2H), 8.86 – 8.40 (m, 1H), 7.86 (dd, J = 22.5, 12.4 Hz, 2H), 7.53 (m, 3H), 7.18 (s, 2H), 7.05 (s, 1H), 5.65 – 5.41 (m, 3H), 5.31 (d, J = 6.7 Hz, 1H), 4.32 (m, 3H), 3.97 – 3.80 (m, 3H), 3.78 – 3.61 (m, 6H), 2.87 (m, 6H), 2.48 – 2.15 (m, 4H),2.06 (s, 1H), 1.45 (s, 3H), 1.28 (m, 6H), 1.21 – 1.07 (m, 6H), 0.99 (t, J = 6.7 Hz, 3H), 0.95 – 0.78 (m, 6H) ppm; MS (ESI, pos.ion) m/z: 871.8[M+H]$^+$.

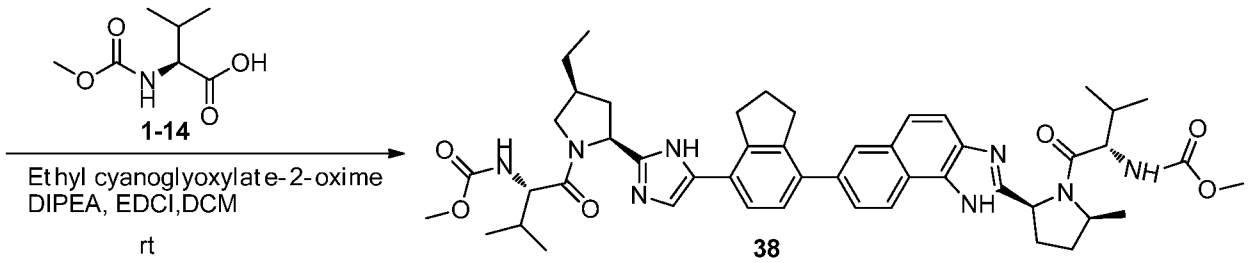
Example 20



38

Synthesis route:





Synthesis steps:

Step 1) synthesis of compound **38-2**

[00333] To the solution of compound **38-1** (0.664 g, 2.73 mmol, 1.05 eq) and compound **1-6** (1.0 g, 2.6 mmol, 1.0 eq) in acetonitrile (10 mL) was added dropwise triethylamine (0.39 g, 3.9 mmol, 1.5 eq) at 0 °C. After the addition, the mixture was stirred at rt for 2 h. The reaction mixture was concentrated to remove the solvent and to the residue was added 20 mL of water. Then the mixture was extracted with DCM (20 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to give the product as brown oil (1.42 g, 100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 5.54 – 5.35 (m, 1H), 5.20 (dd, J = 25.2, 13.6 Hz, 1H), 4.62 (dt, J = 21.6, 8.3 Hz, 1H), 4.06 – 3.52 (m, 3H), 3.40-3.22 (m, 2H), 3.06 (t, J = 7.5 Hz, 2H), 2.83 – 2.64 (m, 1H), 2.58 – 2.33 (m, 1H), 2.20 (dt, J = 14.2, 7.3 Hz, 2H), 1.48 (m, 12H), 0.9 (t, J = 5.6 Hz, 3H) ppm.

Step 2) synthesis of compound **38-3**

[00334] The solution of compound **38-2** (1.42 g, 2.6 mmol, 1.0 eq) and ammonium acetate (1.2 g, 15.6 mmol, 6.0 eq) in toluene (15 mL) was stirred at 115 °C for 20 h. The reaction mixture was concentrated to remove the toluene, and to the residue was added 50 mL of water. The mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give the crude product as a light yellow solid (1.28 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.97 (d, J = 188.0 Hz, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.19 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 5.33 (d, J = 52.9 Hz, 1H), 5.19 (t, J = 7.0 Hz, 1H), 3.98 (dd, J = 21.0, 13.0 Hz, 1H), 3.61 – 3.22 (m, 2H), 3.12 (dt, J = 15.0, 7.1 Hz, 4H), 2.85 – 2.59 (m, 1H), 2.29 – 2.14 (m, 2H), 1.52 (m, 11H), 0.9 (t, J = 5.6 Hz, 3H) ppm; MS-ESI, m/z: 530.2 $[M+H]^+$.

Step 3) synthesis of compound **38-4**

[00335] To DMF (15 mL) were added compound **38-3** (1.26 g, 2.37 mmol, 1.0 eq), bis(pinacolato)diboron (0.63 g, 2.49 mmol, 1.05 eq), potassium acetate (0.70 g, 7.1 mmol, 3.0 eq)

and $Pd(dppf)_2Cl_2$ (69 mg, 0.094 mmol, 0.04 eq). The mixture was stirred at 100 °C for 10 h under nitrogen atomosphere. The reaction mixture was poured into 60 mL of water, then the mixture was filtered by suction to give a gray solid. The gray solid was purfied by silica gel column chromatography (PE : EtOAc (V : V) = 5 : 1) to give a light yellow solid (0.82 g, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.89 (d, J = 186.4 Hz, 1H), 7.78 (s, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.20 (s, 1H), 5.27 (dd, J = 42.7, 30.3 Hz, 2H), 3.97 (dd, J = 20.7, 13.3 Hz, 1H), 3.48 (dd, J = 35.4, 12.0 Hz, 1H), 3.38 – 2.88 (m, 5H), 2.80 – 2.59 (m, 1H), 2.19 – 2.07 (m, 2H), 1.52 (m, 11H), 1.36 (s, 12H), 0.9 (t, J = 5.6 Hz, 3H) ppm; MS-ESI, *m/z*: 508.3 $[M+H]^+$.

Step 4) synthesis of compound **38-5**

[00336] To the mixture of ethanol (10 mL) and water (3 mL) were added compound **38-4** (558 mg, 1.10 mmol, 1.0 eq), compound **15-5** (473 g, 1.10 mmol, 1.0 eq), potassium carbonate (0.30 g, 2.21 mmol, 2.0 eq) and $Pd(PPh_3)_4$ (38 mg, 0.033 mmol, 0.03 eq). The mixture was stirred at 90 °C under nitrogen protection for 6 h. The reaction mixture was poured into 50 mL of water, then the mixture was extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE : EtOAc (V : V) = 1 : 1) to give the crude product as a white solid (0.75 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.88 – 10.35 (m, 2H), 8.67 (d, J = 8.1 Hz, 1H), 8.22 – 7.30 (m, 6H), 7.18 (d, J = 23.9 Hz, 1H), 5.51 – 5.11 (m, 3H), 4.00 (dd, J = 21.1, 13.2 Hz, 1H), 3.57 (dd, J = 32.1, 9.6 Hz, 3H), 3.30-3.11 (m, 5H), 2.44 – 2.21 (m, 2H), 2.20 – 2.08 (m, 2H), 2.00 – 1.86 (m, 2H), 1.55 (m, 20H), 1.32-1.18 (m, 3H), 0.9 (t, J = 5.6 Hz, 3H) ppm; MS-ESI, *m/z*: 731.3 $[M+H]^+$.

Step 5) synthesis of compound **38-6**

[00337] To the mixture of compound **38-5** (0.75 g, 1.03 mmol, 1.0 eq) in DCM (10 mL) was added dropwise HCl/EtOAc (4 N, 3 mL) at 0 °C. After the addition, the mixture was stirred at rt for 10 h. The mixture was concentrated to remove the solvent, and to the residue was added EtOAc (20 mL). The resulting mixture was triturated for 1 h at rt and filtered by suction to give the filter cake as a light yellow solid. The filter cake was dissolved in water (10 mL), then to the solution was added aqueous sodium carbonate to precipitate out the solid. The mixure was filtered and the filter cake was dried to give a yellow solid (502 mg, 92%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (s, 2H), 8.48 (d, J = 7.8 Hz, 1H), 8.03 (s, 1H), 7.96 – 7.49 (m, 4H), 7.45 – 7.08 (m, 2H), 5.37 (d, J = 55.4 Hz, 1H), 4.70 – 4.18 (m, 2H), 3.30 – 3.15 (m, 2H), 3.15 – 2.85 (m, 6H), 2.28 (ddd, J = 39.8, 14.5, 9.4 Hz, 3H), 2.04 (d, J = 5.5 Hz, 2H), 1.94 – 1.65 (m, 4H), 1.32-1.18 (m, 3H), 0.9 (t, J = 5.6 Hz, 3H) ppm; MS-ESI, *m/z*: 531.4 $[M+H]^+$.

Step 6) synthesis of compound **38**

[00338] To DCM (15 mL) were added compound **38-6** (265 mg, 0.5 mmol, 1.0 eq), compound **1-14** (193 mg, 1.1 mmol, 2.2 eq), ethyl cyanoglyoxylate-2-oxime (57 mg, 0.4 mmol, 0.8 eq) and DIPEA (32 mg, 0.25 mmol, 0.5 eq), then EDCI (211 mg, 1.1 mmol, 2.2 eq) was added. The resulting mixture was stirred at rt for 3 h. The reaction mixture was poured into 30 mL of water, then the mixture was extracted with DCM (15 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purfied by silica gel column chromatography (DCM : MeOH (V : V) = 10 : 1) to give the product as a white solid (296 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.09 – 10.24 (m, 2H), 8.63 (s, 1H), 8.19 – 7.54 (m, 4H), 7.42 (d, J = 39.2 Hz, 1H), 7.13 (dd, J = 75.7, 30.2 Hz, 2H), 6.47 – 5.62 (m, 2H), 5.62 – 5.26 (m, 3H), 4.38 (dd, J = 23.1, 15.4 Hz, 3H), 4.14 (q, J = 7.1 Hz, 2H), 3.97 (s, 1H), 3.76 (d, J = 27.7 Hz, 6H), 3.46 – 3.19 (m, 1H), 3.06 (s, 4H), 2.72 (dd, J = 26.7, 14.6 Hz, 1H), 2.59 – 2.07 (m, 4H), 1.94 (d, J = 1.3 Hz, 2H), 1.80 – 1.58 (m, 3H), 1.32-1.18 (m, 3H) 0.89 (m, 15H) ppm; MS-ESI, *m/z*: 845.4 $[M+H]^+$.

Biological assays

Biological example 1: analysis of HCV subgenomic replicon

Experimental purposes:

[00339] To evaluate the inhibitory effect of the compound disclosed herein on HCV GT1a,GT1b and GT2a wild type replicons, HCV GT3a, GT4a, GT5a and GT6a replicon chimeras, and GT1b L31V, GT1b Y93H resistant strains.

Test method

[00340] Detection of activity of GT1a, GT1b and GT2a replicons: HCV GT 1a H77 replicon, GT1b Con1b replicon and GT2a JFH1 replicon containing G418 resistance gene NEO and luciferase reporter gene were transfected respectively and immediately to Huh-7 cell by using an electric shock method. After the addition of G418, the cells were screened for 3 to 4 weeks,

stable and transfected cell line was established. Cell line Huh7-H77 and Huh7- JFH1 was diluted to 5×10^4/mL, 200 μL of which was seeded to a 96 well plate. Cell line Huh7-Con1b was diluted to 1×10^5/mL, 50 μL of which was seeded to a 384 well plate. 16-24 h later, the compound was diluted by 3-fold serially for a total of 11 concentrations to a suitable concentration, the diluted compound was added into the 96 well plate with POD™ 810 plate assembler, the final concentration of DMSO in each well was 0.5%. The plate was incubated in a constant temperature incubator at 37 °C under 5% CO_2 for 72 h, and then to each well was added 40 μL of luciferase assay reagent (Promega Bright-Glo), 5 min later, the plate was detected by chemiluminescence detection system (Envision). The results were processed by using GraphPad Prism software, EC50 of the compound against HCV relipcon was calculated.

[00341] Detection of activity of GT3a, GT4a, GT5a, GT6a chimeric replicons and GT1b L31V, GT1b Y93H resistant strains: HCVGT1b/GT3a-NS5A, HCV GT1b/GT4a-NS5A, HCV GT1b/GT5a-NS5A, HCV GT1b/GT6a-NS5A chimeric replicon RNA, and HCV GT1b L31V, HCV GT1b Y93H resistant replicon RNA was transfered to Huh7 cell by using an electric shock method, and then the cells were seeded to a 96 well plate containing the compound with a corresponding concentration at a density of 10000 cells per well. The compound in DMSO mother solution was diluted, and the diluted solution was added to the 96 well plate, the final concentration of DMSO was 0.5%. The cells were incubated under 5% CO_2 at 37 °C for 72 hours. Luciferase luminescence substrate Bright-Glo was added to each well, 5 min later, the signal value of luminescence was detected by chemiluminescence detection system (Envision), original data (RLU) were used for calculating inhibitory activity of the compound. The corresponding curve of the compound were plotted and the value of the inhibitory activity thereof (EC50) against HCV relipcon were calculated by importing percent inhibition to GraphPad Prism software and nonlinear fitting. The EC50 values of the compound against each HCV genotype replicon were listed in table 2.

Table 2

Example No.	1a (nM)	1b (nM)	2a (nM)	3a (nM)	4a (nM)	5a (nM)	6a (nM)	1b L31V (nM)	1b Y93H (nM)
1	0.007	0.095	0.103	0.453	0.010	0.048	0.157	0.006	0.031
2	0.027	0.213	0.055	0.431	0.009	0.035	0.864	0.007	0.017

3	0.007	0.114	0.026	0.648	0.035	0.044	0.212	0.005	0.010
4	0.012	0.004		0.098	0.007	0.028	0.109	0.004	0.007
5	0.008	0.012	0.009	0.061	0.006	0.029	0.080	0.007	0.019
6	0.064	0.019	0.376		0.029			0.007	0.025
7	0.003	0.007	0.011	0.075	0.005	0.016	0.093	0.003	0.011
8	0.015	0.006	0.515	0.176	0.049	0.103	0.545	0.007	0.042
9	0.054	0.015	0.957		0.038			0.005	0.005
10	0.027	0.035		0.433	0.075	0.078	0.099	0.006	0.021
11	0.031	0.012			0.036			0.006	0.027
12	0.081	0.034		0.883		0.088	0.083	0.005	0.017
13	0.054	0.029	0.028	0.657	0.021	0.036	0.248	0.002	0.007
14	0.037	0.012	0.062	0.968	0.053			0.006	0.021

[00342] Conclusion: The result in table 2 shows that the compounds of the invention have good inhibitory activities against HCVGT1a, GT1b, GT2a, GT3a, GT4b, GT5a, GT6a replicons, and HCV GT1b L31V, HCV GT1b Y93H resistant strains. That is, the compounds of the invention are genome-wide HCV inhibitors.

Biological example 2: PK assay of SD rats

Test method

[00343] Male SD rats were grouped into two groups, each group had 3 rats. One group was administered with test compound by intravenous injection at a dose of 1.0 mg/kg, and the other group was administered with test compound by oral gavage at a dose of 5.0 mg/kg. Blood samples were collected at 8 to 9 time points within 24 hours after administration, and the standard curve was established based on the concentrations of the samples in a suitable range; the concentration of test compound in plasma sample was detected by using AB SCIEX API4000 LC-MS/MS in a MRM mode. Pharmacokinetic parameters were calculated according to drug concentration -time curve using a noncompartmental method by WinNonLin 6.3 software.

Table 3

Example No.	Rat%F
1	35.6

3	25.8
7	31.1
13	28.4

[00344] Conclusion: The result in table 3 shows that the compounds of the invention have good bioavailability.

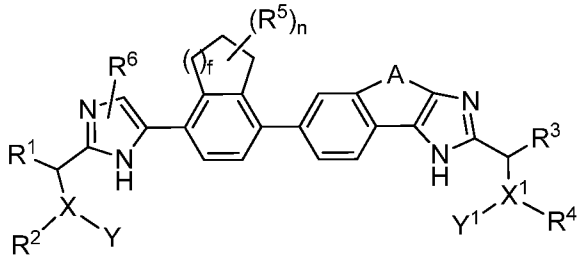
[00345] It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

[00346] Reference throughout this specification to "an embodiment," "some embodiments," "one embodiment", "another example," "an example," "a specific examples," or "some examples," means that a particular feature, structure, material, or characteristic described in connection with the embodiment or example is included in at least one embodiment or example of the present disclosure. Thus, the appearances of the phrases such as "in some embodiments," "in one embodiment", "in an embodiment", "in another example, "in an example," "in a specific examples," or "in some examples," in various places throughout this specification are not necessarily referring to the same embodiment or example of the present disclosure. Furthermore, the particular features, structures, materials or characteristics may be combined in any suitable manner in one or more embodiments or examples.

[00347] Although explanatory embodiments have been shown and described, it would be appreciated by those skilled in the art that the above embodiments cannot be construed to limit the present disclosure, and changes, alternatives, and modifications can be made in the embodiments without departing from spirit, principles and scope of the present disclosure. The scope of the invention is limited by the claims and equivalent thereof.

What is claimed is:

1. A compound having Formula (I) or a stereoisomer, a geometric isomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



(I),

wherein A is $-(CR^7R^{7a})_m-$, $-CR^7=CR^{7a}-$, $-(CH_2)_nO-$, $-N=CR^7-$, $-NR^7-CR^7R^{7a}-$, $-CR^7R^{7a}-NR^7-$, $-O(CH_2)_n-$, $-CR^7=N-$, $-S(CH_2)_n-$, $-(CH_2)_nS-$ or $-NR^{9a}-$;

each of X and X^1 is independently N or CR^{7b};

each of Y and Y^1 is independently H, deuterium, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, $-C(=O)-(CR^8R^{8a})_t-N(R^9)-R^{10}$ or an α-amino acid group; and wherein the *α*-amino acid group is derived from isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophane, valine, alanine, asparagine, aspartic acid, glutamic acid, glutamine, proline, serine, *p*-tyrosine, arginine, histidine, cysteine, glycine, sarcosine, *N*,*N*-dimethylglycine, homoserine, norvaline, norleucine, ornithine, homocysteine, homophenylalanine, phenylglycine, *o*-tyrosine, *m*-tyrosine or hydroxyproline;

each of R^1, R^2, R^3 and R^4 is independently H, deuterium, alkyl, arylalkyl, cycloalkyl, heterocyclyl, heteroaryl or aryl; or R^1 and R^2, together with the X-CH to which they are attached, optionally form a 3-8 membered heterocyclic ring, 3-8 membered carbocyclic ring, fused bicyclic ring, fused heterobicyclic ring, spiro bicyclic ring or spiro heterobicyclic ring; or R^3 and R^4, together with the X^1-CH to which they are attached, optionally form a 3-8 membered heterocyclic ring, 3-8 membered carbocyclic ring, fused bicyclic ring, fused heterobicyclic ring, spiro bicyclic ring or spiro heterobicyclic ring;

each R^5 and R^6 is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, alkyl, haloalkyl, alkenyl, alkynyl, heterocyclyl, cycloalkyl, mercapto, nitro, aryl, heteroaryl, arylalkyl, alkoxyalkyl, alkoxy, arylamino, heteroarylamino, arylalkylamino, heteroarylalkylamino, heteroaryloxy, heteroarylalkyl, arylalkoxy, heteroarylalkoxy,

heterocyclyloxy, heterocyclylalkoxy, heterocyclylamino, alkylacyl, alkylacyloxy, alkoxyacyl, heterocyclylalkylamino or aryloxy;

each R^7, R^{7a}, R^{7b}, R^8, R^{8a} and R^{9a} is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, deuterated alkyl, alkyl, haloalkyl, alkoxy, alkenyl, alkynyl, heterocyclyl, cycloalkyl, mercapto, nitro, aryl, heteroaryl, arylalkyl, alkoxyalkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl, arylamino, heteroarylamino, arylalkylamino, heteroarylalkylamino, heteroaryloxy, arylalkoxy, heteroarylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylamino, alkyl-OC(=O)-, alkyl-C(=O)-, carbamoyl, alkyl-OS(=O)$_r$-, alkyl-S(=O)$_r$O-, alkyl-OS(=O)$_r$O-, alkyl-S(=O)$_r$-, heterocyclylalkylamino or aryloxy;

each of R^9 and R^{10} is independently H, deuterium, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, alkyl-OC(=O)-, alkyl-C(=O)-, carbamoyl, alkyl-OS(=O)$_r$-, alkyl-S(=O)$_r$O-, alkyl-S(=O)$_r$- or aminosulfonyl;

each f, n and t is independently 0, 1, 2, 3 or 4;

m is 1, 2, 3 or 4;

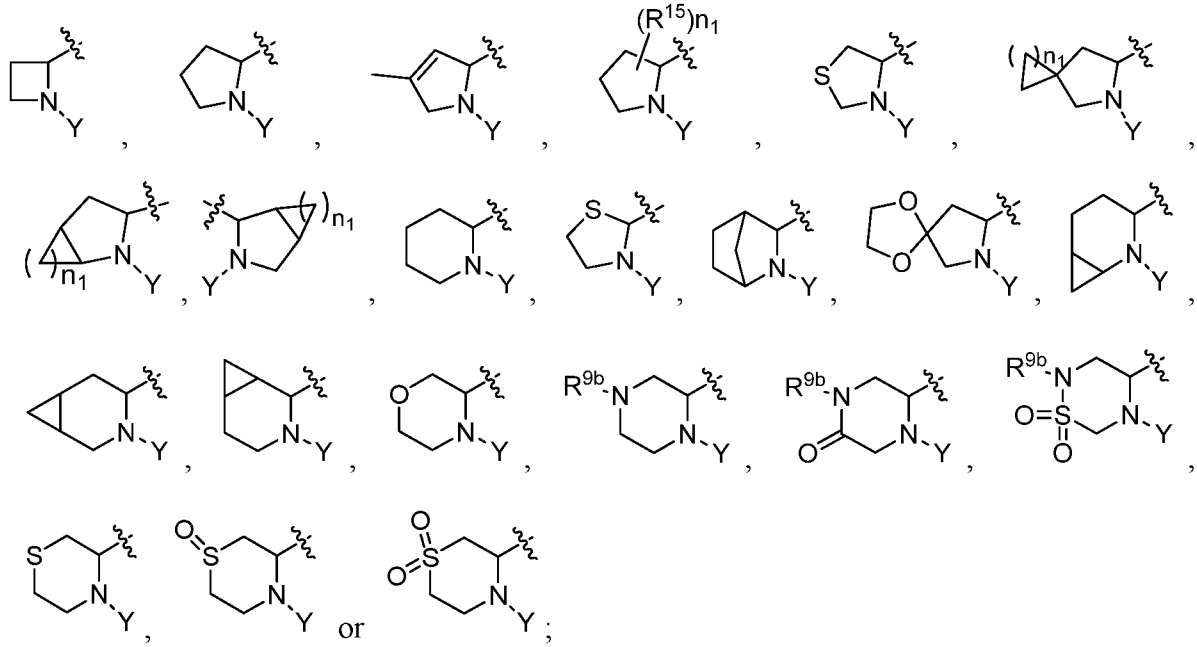
each r is independently 0, 1 or 2; and

wherein each alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, -C(=O)-(CR^{8}R^{8a})$_t$-N(R^9)-R^{10}, α-amino acid group, 3-8 membered heterocyclic ring, 3-8 membered carbocyclic ring, fused bicyclic ring, fused heterobicyclic ring, spiro bicyclic ring, spiro heterobicyclic ring, haloalkyl, alkenyl, alkynyl, alkoxyalkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl, arylamino, heteroarylamino, arylalkylamino, heteroarylalkylamino, aryloxy, heteroaryloxy, arylalkoxy, heteroarylalkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylamino, alkyl-OC(=O)-, alkyl-C(=O)-, carbamoyl, alkyl-OS(=O)$_r$-, alkyl-S(=O)$_r$O-, alkyl-S(=O)$_r$- and aminosulfonyl is independently and optionally substituted with one, two, three or four substituents selected from hydroxy, deuterium, amino, halogen, cyano, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, mercapto, nitro, aryloxy, arylamino, heteroaryloxy, heteroarylalkyl, oxo (=O), carboxy, hydroxy substituted alkoxy, hydroxy substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-S(=O)$_2$-, hydroxy substituted alkyl-S(=O)-, hydroxy substitued alkyl-S(=O)$_2$- or

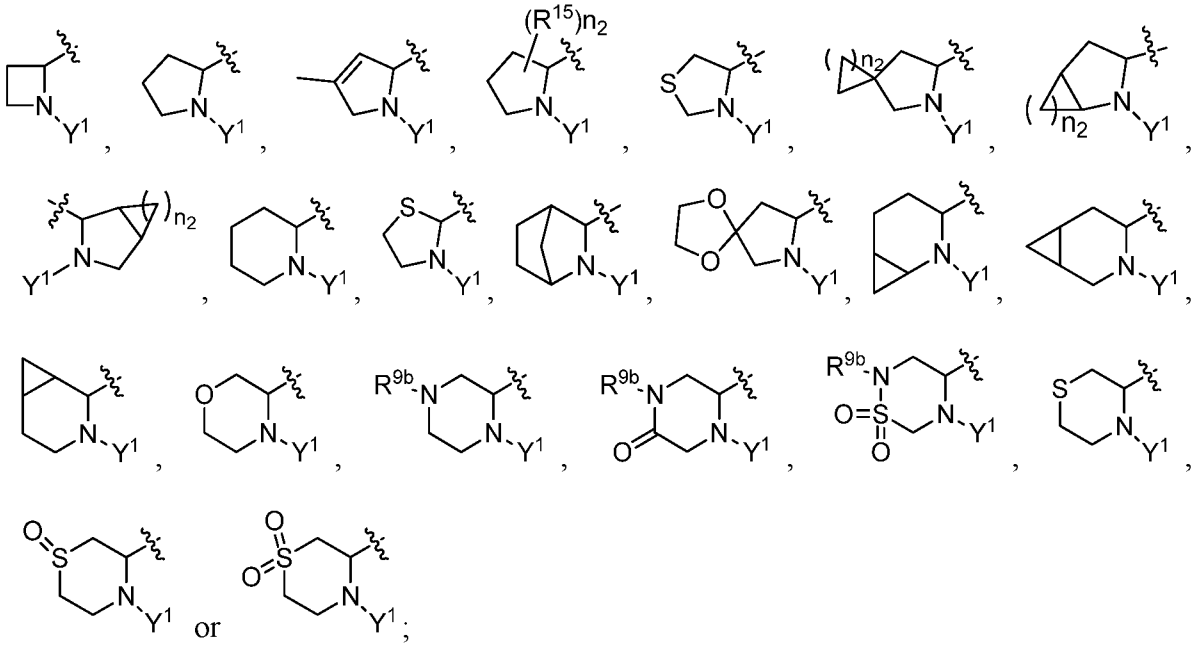
carboxy substituted alkoxy.

2. The compound of claim 1, wherein each of R^1, R^2, R^3 and R^4 is independently H, C_{1-6} alkyl, C_{6-10} aryl-C_{1-6}-alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocyclyl, C_{1-9} heteroaryl or C_{6-10} aryl; or R^1 and R^2, together with the X-CH to which they are attached, optionally form a 3-8 membered heterocyclic ring, 3-8 membered carbocyclic ring, C_{5-12} fused bicyclic ring, C_{5-12} fused heterobicyclic ring, C_{5-12} spiro bicyclic ring or C_{5-12} spiro heterobicyclic ring; or R^3 and R^4, together with the X^1-CH to which they are attached, optionally form a 3-8 membered heterocyclic ring, 3-8 membered carbocyclylic ring, C_{5-12} fused bicyclic ring, C_{5-12} fused heterobicyclic ring, C_{5-12} spiro bicyclic ring or C_{5-12} spiro heterobicyclic ring; and wherein the 3-8 membered heterocyclic ring, 3-8 membered carbocyclic ring, C_{5-12} fused bicyclic ring, C_{5-12} fused heterobicyclic ring, C_{5-12} spiro bicyclic ring or C_{5-12} spiro heterobicyclic ring is independently and optionally substituted with one, two, three or four substituents selected from H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} haloalkoxy-C_{1-6}-alkyl, C_{1-6} alkylamino, C_{1-6} alkylthio, C_{6-10} arylamino, C_{6-10} aryloxy, C_{1-9} heteroaryl, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{2-10} heterocyclyl.

3. The compound of claim 1 or 2, wherein R^1 and R^2, together with Y-X-CH to which they are attached, form one of the following groups:



wherein R^3 and R^4, together with Y^1-X^1-CH to which they are attached, form one of the following groups:



wherein each R^{15} is independently H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} haloalkoxy-C_{1-6}-alkyl, C_{1-6} alkylamino, C_{1-6} alkylthio, C_{6-10} arylamino, C_{6-10} aryloxy, C_{1-9} heteroaryl, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-8} cycloalkyl or C_{2-10} heterocyclyl;

each R^{9b} is independently H, deuterium, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} alkylamino-C_{1-6}-alkyl, C_{1-6} alkylthio-C_{1-6}-alkyl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-9} heteroaryl, C_{6-10} aryl, C_{2-10} heterocyclyl or C_{3-8} cycloalkyl; and

each n_1 and n_2 is independently 1, 2, 3 or 4.

4. The compound of claim 3, wherein each R^{15} is independently H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} alkoxy-C_{1-3}-alkyl, C_{1-3} haloalkoxy-C_{1-3}-alkyl, C_{1-3} alkylamino, C_{1-3} alkylthio, C_{6-10} arylamino, C_{6-10} aryloxy, C_{1-9} heteroaryl, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-3}-alkyl, C_{3-8} cycloalkyl or C_{2-10} heterocyclyl; and

each R^{9b} is independently H, deuterium, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} aminoalkyl, C_{1-3} alkoxy-C_{1-3}-alkyl, C_{1-3} alkylamino-C_{1-3}-alkyl, C_{1-3} alkylthio-C_{1-3}-alkyl, C_{6-10} aryl-C_{1-3}-alkyl, C_{1-9} heteroaryl, C_{6-10} aryl, C_{2-10} heterocyclyl or C_{3-8} cycloalkyl.

5. The compound of claim 3, wherein each R^{15} is independently H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, methyl, ethyl, propyl, isopropyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, methoxymethyl, difluoromethoxymethyl, trifluoromethoxymethyl, ethoxymethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylamino, ethylamino, phenylamino,

phenoxy, pyrrolyl, morpholinyl or piperazinyl; and

each R^{9b} is independently H, deuterium, methyl, ethyl, propyl, isopropyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxymethyl, ethoxymethyl, phenylmethyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

6. The compound of any one of claims 1-5, wherein each R^7, R^{7a}, R^{7b} and R^{9a} is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-10} heterocyclyl, C_{3-8} cycloalkyl, mercapto, nitro, C_{6-10} aryl, C_{1-9} heteroaryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6} alkyl, C_{3-8} cycloalkyl-C_{1-6} alkyl, C_{2-10} heterocyclyl-C_{1-6} alkyl, C_{6-10} arylamino, C_{1-9} heteroarylamino, C_{6-10} aryl-C_{1-6}-alkylamino, C_{1-9} heteroaryl-C_{1-6}-alkylamino, C_{1-9} heteroaryloxy, C_{6-10} aryl-C_{1-6}-alkoxy, C_{1-9} heteroaryl-C_{1-6}-alkoxy, C_{2-10} heterocyclyloxy, C_{2-10} heterocyclyl-C_{1-6}-alkoxy, C_{2-10} heterocyclylamino, C_{1-6} alkyl-OC(=O)-, C_{1-6} alkyl-C(=O)-, carbamoyl, C_{1-6} alkyl-OS(=O)$_r$-, C_{1-6} alkyl-S(=O)$_r$O-, C_{1-6} alkyl-OS(=O)$_r$O-, C_{1-6} alkyl-S(=O)$_r$-, C_{2-10} heterocyclyl-C_{1-6}-alkylamino or C_{6-10} aryloxy; and

each r is independently 0, 1 or 2.

7. The compound of any one of claims 1-6, wherein each of Y and Y^1 is independently H, deuterium, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl, C_{1-9} heteroaryl, C_{6-10} aryl-C_{1-6}-alkyl or -C(=O)-(CR^8R^{8a})$_t$-N(R^9)-R^{10};

each R^8 and R^{8a} is independently H, deuterium, hydroxy, amino, F, Cl, Br, I, cyano, C_{1-6} alkyl, C_{1-6} deuterated alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-10} heterocyclyl, C_{3-8} cycloalkyl, mercapto, nitro, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-8} cycloalkyl-C_{1-6}-alkyl, C_{2-10} heterocyclyl-C_{1-6}-alkyl, C_{6-10} arylamino, C_{1-9} heteroarylamino, C_{6-10} aryl-C_{1-6}-alkylamino, C_{1-9} heteroaryl-C_{1-6}-alkylamino, C_{1-9} heteroaryloxy, C_{6-10} aryl-C_{1-6}-alkoxy, C_{1-9} heteroaryl-C_{1-6}-alkoxy, C_{2-10} heterocyclyloxy, C_{2-10} heterocyclyl-C_{1-6}-alkoxy, C_{2-10} heterocyclylamino, C_{1-6} alkyl-OC(=O)-, C_{1-6} alkyl-C(=O)-, carbamoyl, C_{1-6} alkyl-OS(=O)$_r$-, C_{1-6} alkyl-S(=O)$_r$O-, C_{1-6} alkyl-OS(=O)$_r$O-, C_{1-6} alkyl-S(=O)$_r$-, C_{2-10} heterocyclyl-C_{1-6}-alkylamino or C_{6-10} aryloxy;

each of R^9 and R^{10} is independently H, deuterium, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl, C_{1-9} heteroaryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-6} alkyl-OC(=O)-, C_{1-6} alkyl-C(=O)-, carbamoyl, C_{1-6} alkyl-OS(=O)$_r$-, C_{1-6} alkyl-S(=O)$_r$O-, C_{1-6} alkyl-S(=O)$_r$- or

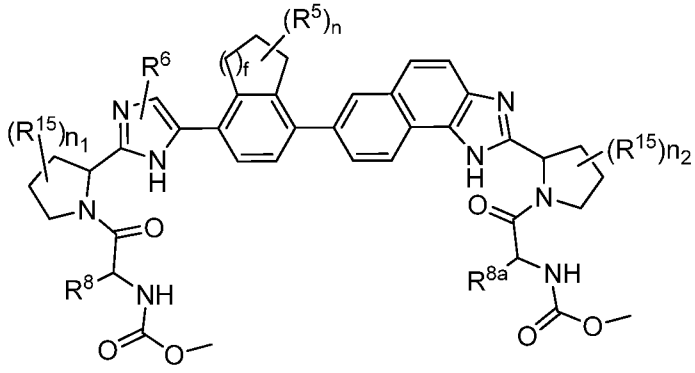
aminosulfonyl;

t is 0, 1, 2, 3 or 4; and

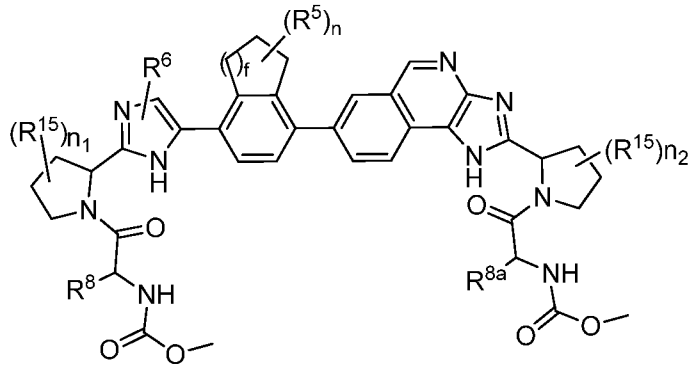
each r is independently 0, 1 or 2.

8. The compound of claim 7, wherein each of R^9 and R^{10} is independently H, deuterium, methyl, ethyl, isopropyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, methyl-OC(=O)-, ethyl-OC(=O)-, propyl-OC(=O)-, isopropyl-OC(=O)-, *t*-butyl-OC(=O)-, methyl-C(=O)-, ethyl-C(=O)-, isopropyl-C(=O)-, *n*-butyl-C(=O)-, *i*-butyl-C(=O)-, carbamoyl, methylaminoformyl, ethylaminoformyl, methyl-$OS(=O)_2$-, cyclopropyl-$OS(=O)_2$-, methyl-$S(=O)_2O$-, cyclopropyl-$S(=O)_2O$- or aminosulfonyl.

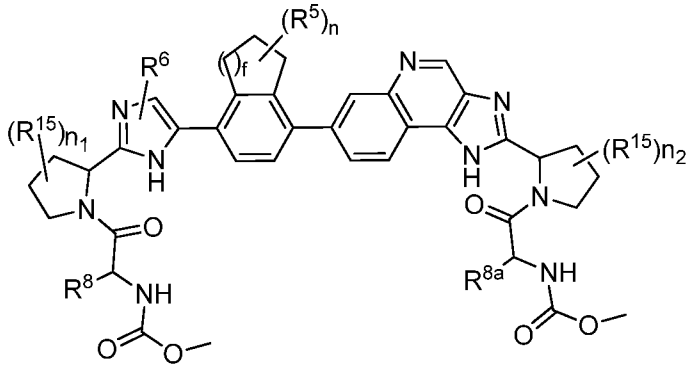
9. The compound of claim 1 having Formula (II), (IIa), (IIb) or (III), or a stereoisomer, a geometric isomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof,



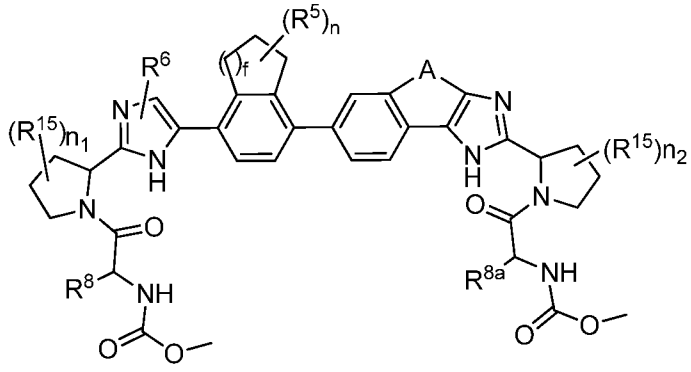
(II),



(IIa),



(IIb) or



(III),

wherein A is -O-, -S-, -NH-, $-CH_2-S-$, $-CH_2-O-$, $-CH_2-NH-$, $-O-CH_2-$, $-NH-CH_2-$, $-S-CH_2-$ or $-CH_2-CH_2-$;

each R^{15} is independently H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} alkoxy-C_{1-3}-alkyl, C_{1-3} haloalkoxy-C_{1-3}-alkyl, C_{1-3} alkylamino, C_{1-3} alkylthio, C_{6-10} arylamino, C_{6-10} aryloxy, C_{1-9} heteroaryl, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-3}-alkyl, C_{3-8} cycloalkyl or C_{2-10} heterocyclyl; and

each n_1 and n_2 is independently 1, 2, 3 or 4.

10. The compound of claim 9, wherein each R^8 and R^{8a} is independently H, deuterium, hydroxy, amino, F, Cl, Br, I, cyano, C_{1-6} alkyl, C_{1-6} deuterated alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-10} heterocyclyl, C_{3-8} cycloalkyl, mercapto, nitro, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{3-8} cycloalkyl-C_{1-6}-alkyl, C_{2-10} heterocyclyl-C_{1-6}-alkyl, C_{6-10} arylamino, C_{1-9} heteroarylamino, C_{6-10} aryl-C_{1-6}-alkylamino, C_{1-9} heteroaryl-C_{1-6}-alkylamino, C_{1-9} heteroaryloxy, C_{6-10} aryl-C_{1-6}-alkoxy, C_{1-9} heteroaryl-C_{1-6}-alkoxy, C_{2-10} heterocyclyloxy, C_{2-10} heterocyclyl-C_{1-6}-alkoxy, C_{2-10} heterocyclylamino, C_{1-6} alkyl-OC(=O)-, C_{1-6} alkyl-C(=O)-, carbamoyl, C_{1-6} alkyl-$OS(=O)_r$-, C_{1-6} alkyl-$S(=O)_rO$-, C_{1-6} alkyl-$OS(=O)_rO$-, C_{1-6} alkyl-$S(=O)_r$-, C_{2-10} heterocyclyl-C_{1-6}-alkylamino or C_{6-10} aryloxy.

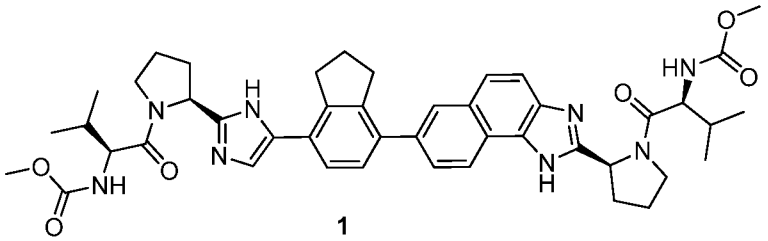
11. The compound of claim 9, wherein each R^{15} is independently H, deuterium, oxo (=O), F, Cl, Br, I, cyano, hydroxy, methyl, ethyl, propyl, isopropyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, methoxymethyl, difluoromethoxymethyl, trifluoromethoxymethyl, ethoxymethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylamino, ethylamino, phenylamino, phenoxy, pyrrolyl, morpholinyl or piperazinyl.

12. The compound of any one of claims 1 to 11, wherein each of R^5 and R^6 is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-10} heterocyclyl, C_{3-8} cycloalkyl, mercapto, nitro, C_{6-10} aryl, C_{1-9} heteroaryl, C_{6-10} aryl-C_{1-6}-alkyl, C_{1-6} alkoxy-C_{1-6}-alkyl, C_{1-6} alkoxy, C_{6-10} arylamino, C_{1-9} heteroarylamino, C_{6-10} aryl-C_{1-6}-alkylamino, C_{1-9} heteroaryl-C_{1-6}-alkylamino, C_{1-9} heteroaryloxy, C_{1-9} heteroaryl-C_{1-6}-alkyl, C_{6-10} aryl-C_{1-6}-alkoxy, C_{1-9} heteroaryl-C_{1-6}-alkoxy, C_{2-10} heterocyclyloxy, C_{2-10} heterocyclyl-C_{1-6}-alkoxy, C_{2-10} heterocyclylamino, C_{1-6} alkylacyl, C_{1-6} alkylacyloxy, C_{1-6} alkoxyacyl, C_{2-10} heterocyclyl-C_{1-6}-alkylamino or C_{6-10} aryloxy.

13. The compound of claim of 12, wherein each of R^5 and R^6 is independently H, deuterium, oxo (=O), hydroxy, amino, F, Cl, Br, I, cyano, methyl, ethyl, propyl, isopropyl, *n*-butyl, *t*-butyl, trifluoromethyl, methoxymethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, phenoxy, phenylamino, mercapto or nitro.

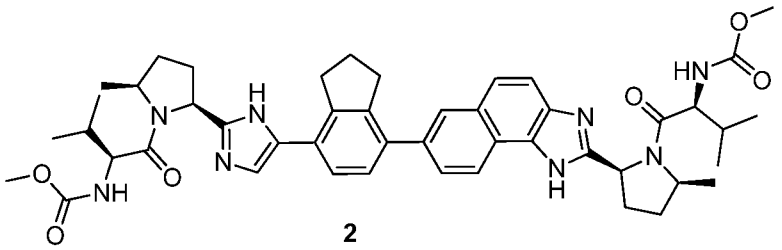
14. The compound of any one of claims 1 to 13, wherein each R^8 and R^{8a} is independently H, deuterium, hydroxy, amino, F, Cl, Br, I, cyano, methyl, ethyl, isopropyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, deuterated methyl, deuterated ethyl, deuterated propyl, deuterated isopropoxy, methoxy, ethoxy, isopropoxy, methoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 1-methoxypropyl, 2-methoxypropyl, 3-methoxypropyl, phenyl, pyranyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, trifluoromethyl, vinyl, allyl, ethynyl, morpholinyl, mercapto, nitro, phenylmethyl or phenylamino.

15. The compound of claim 1 having one of the following structures, or a stereoisomer, a geometric isomer, a tautomer, an enantiomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a pharmaceutically acceptable salt or a prodrug thereof:



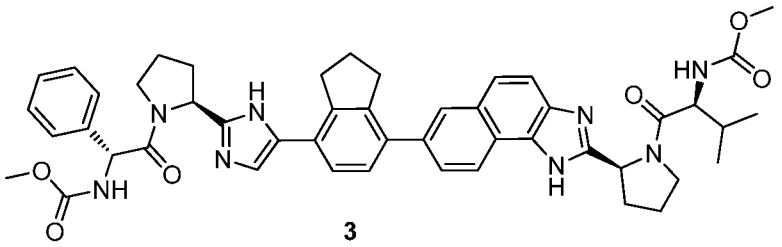
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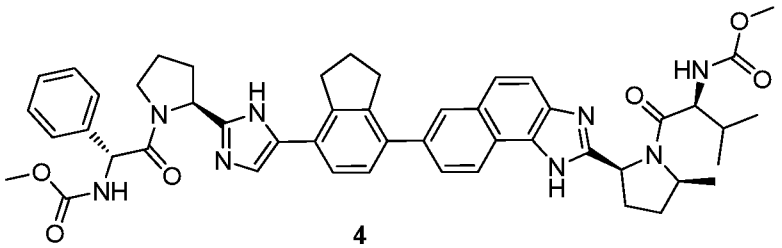
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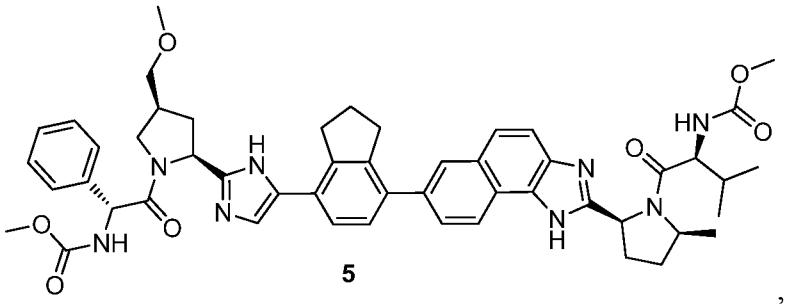
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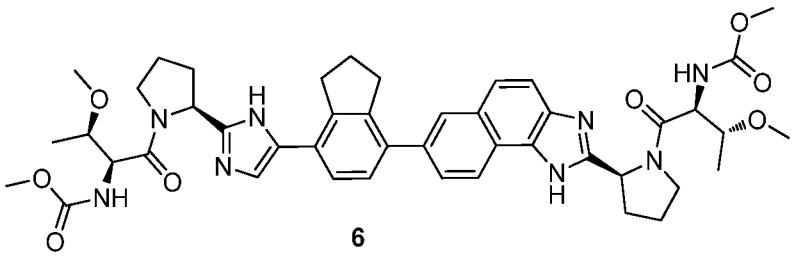
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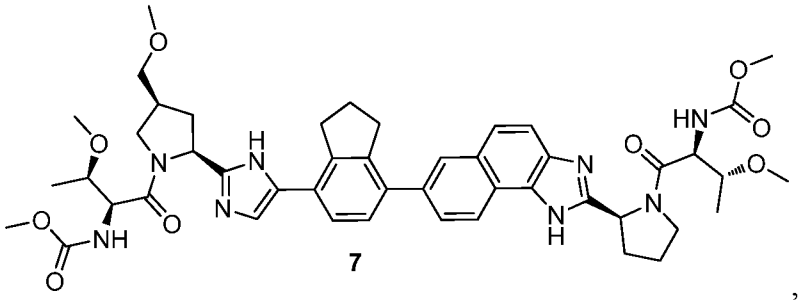
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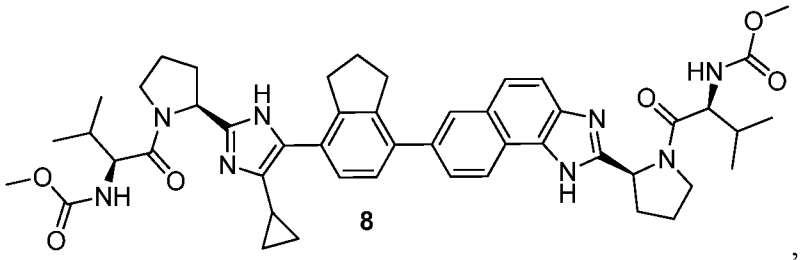


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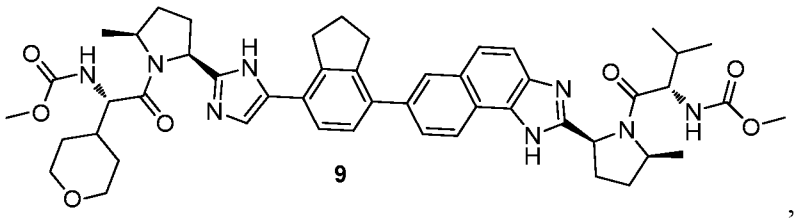
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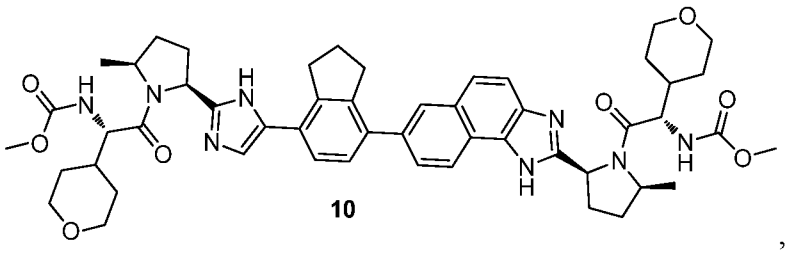
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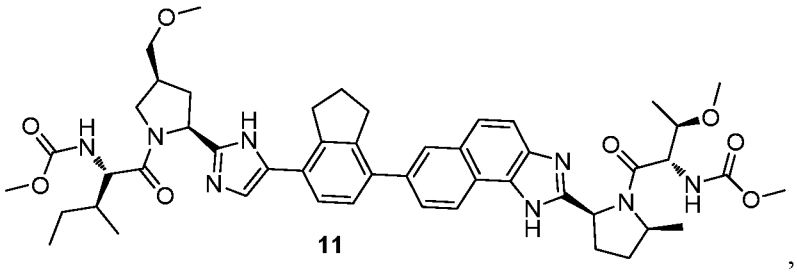
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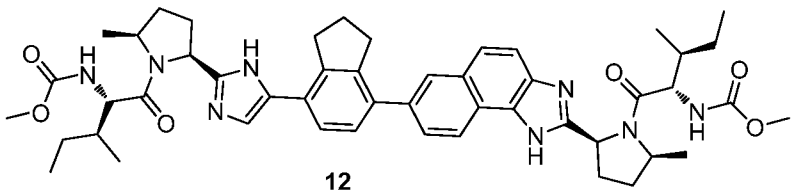
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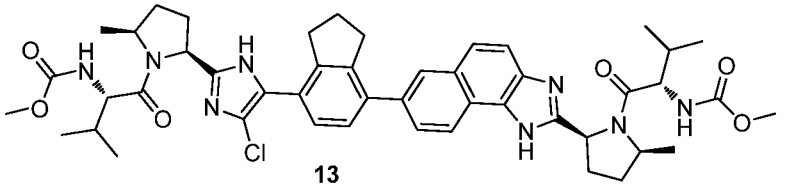
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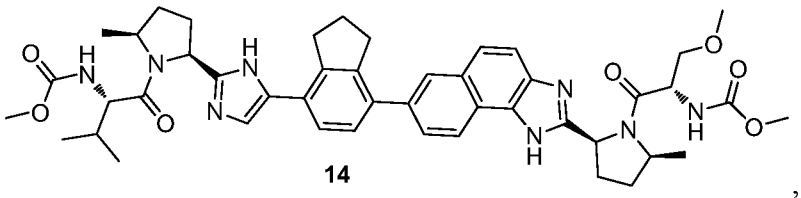
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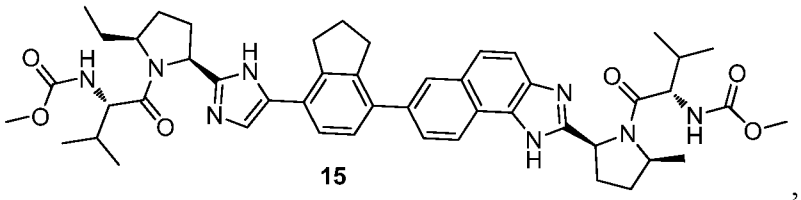
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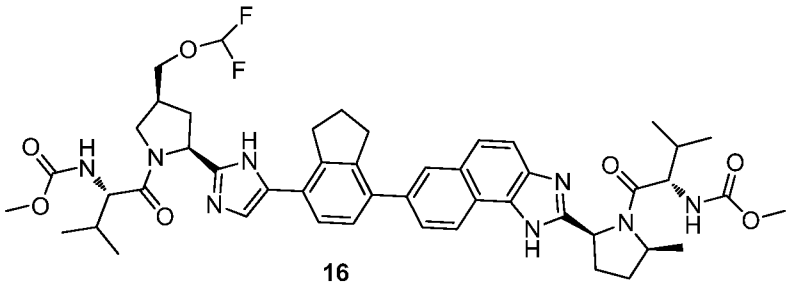
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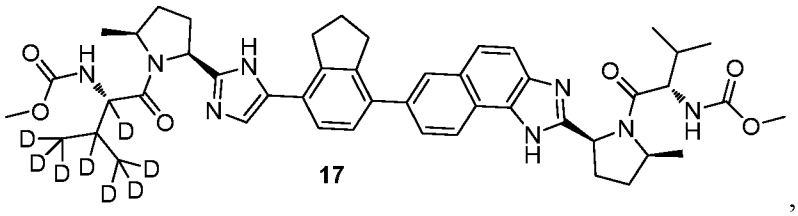
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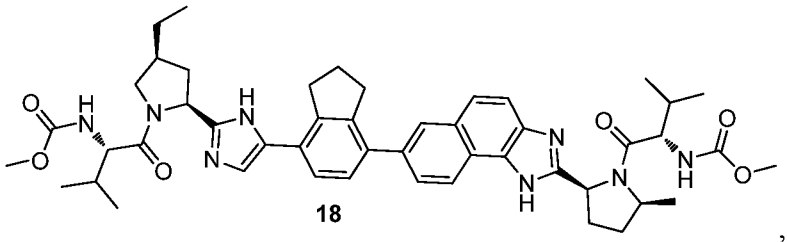
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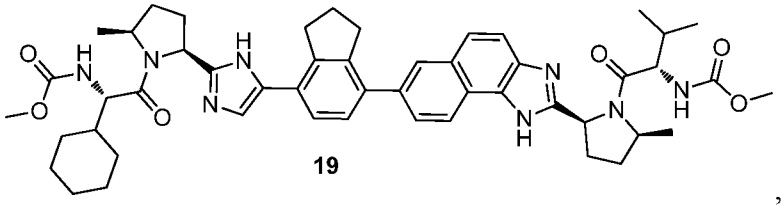
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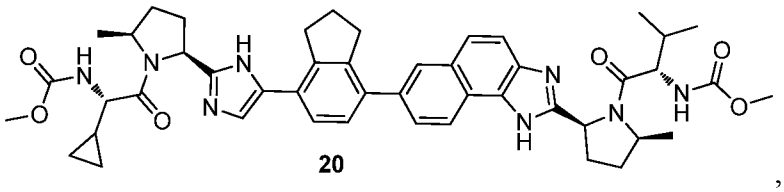
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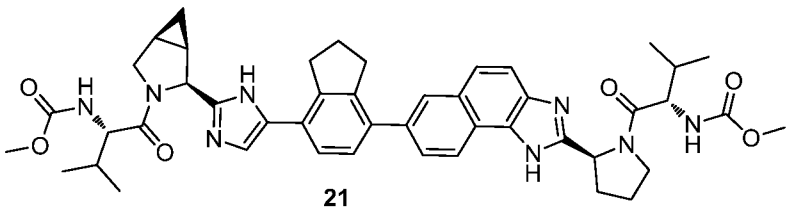
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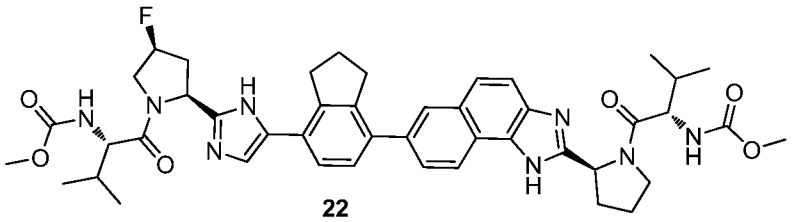
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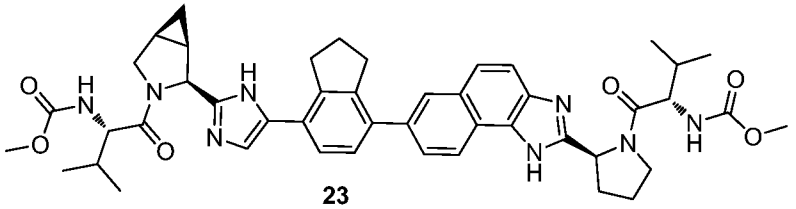
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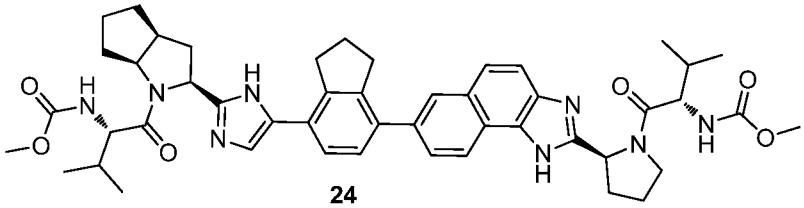
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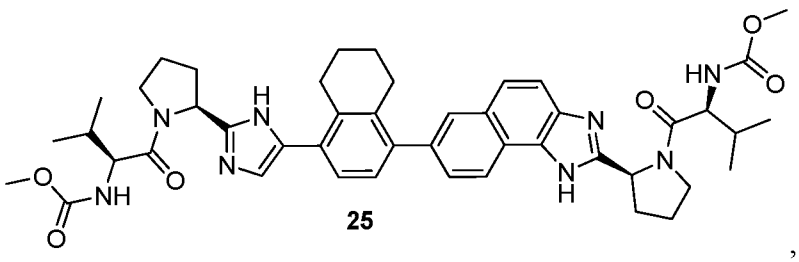
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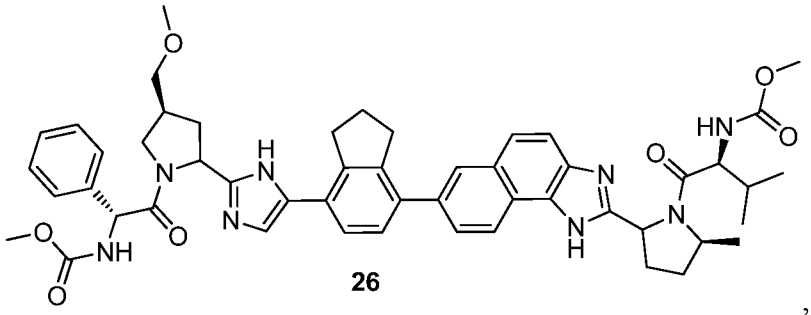
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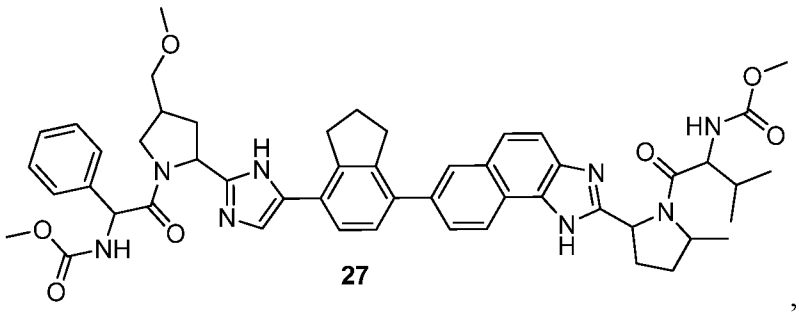
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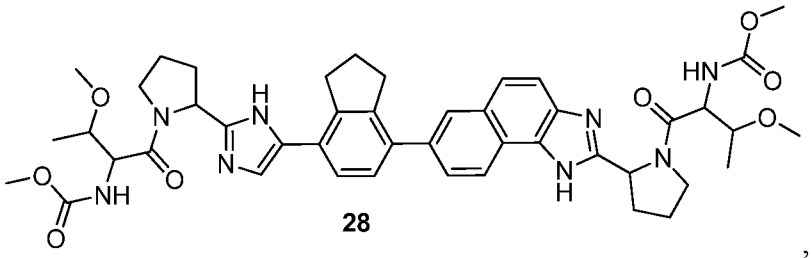
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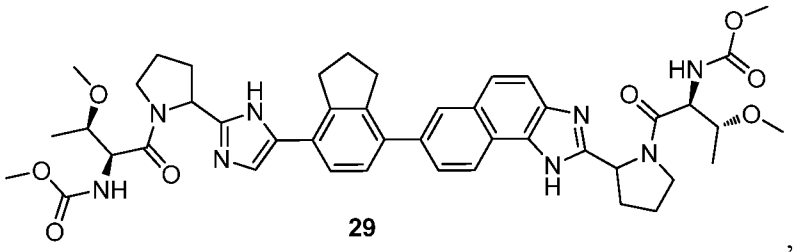


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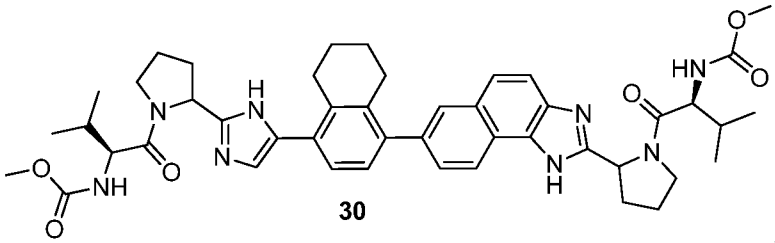
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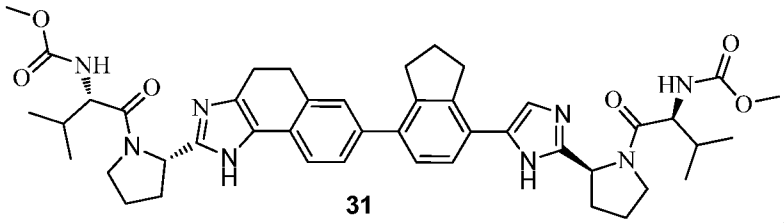
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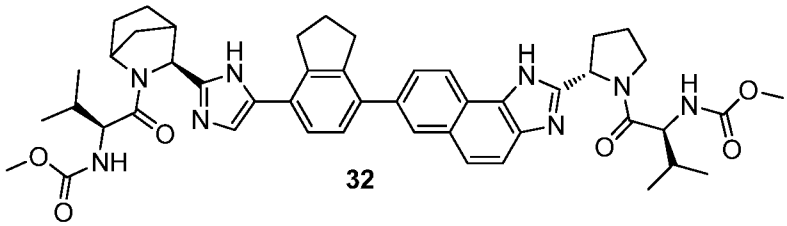
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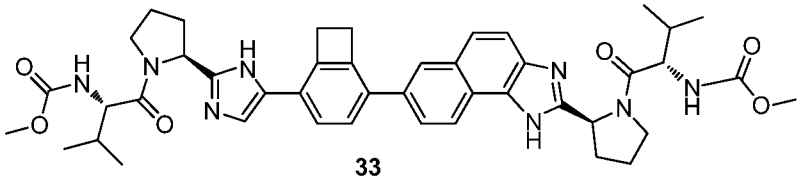
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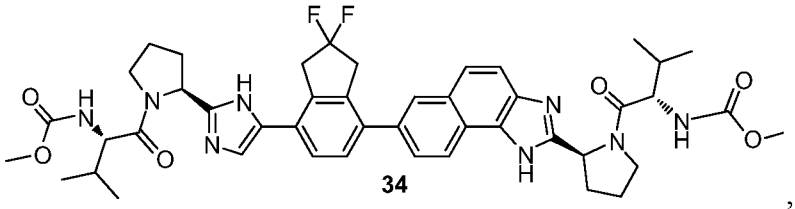
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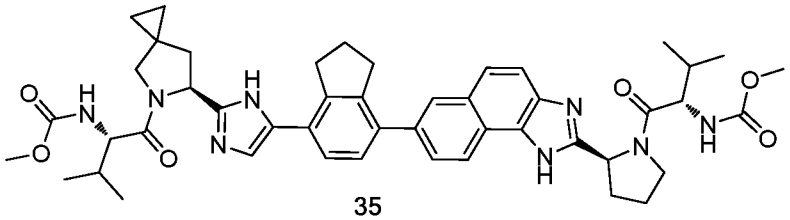
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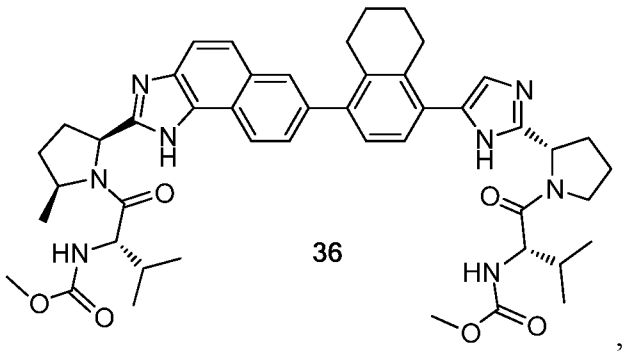
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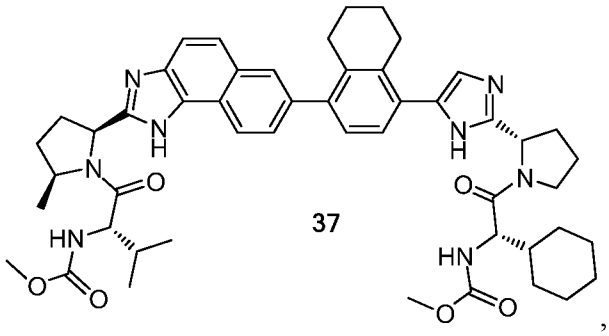
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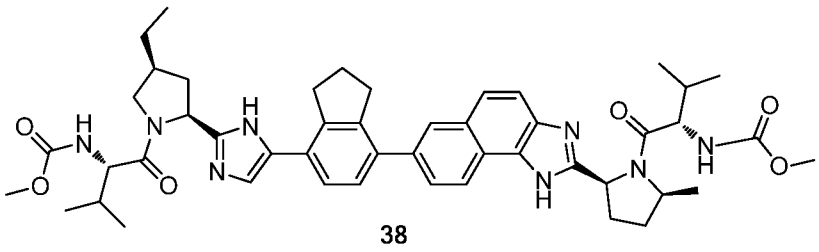
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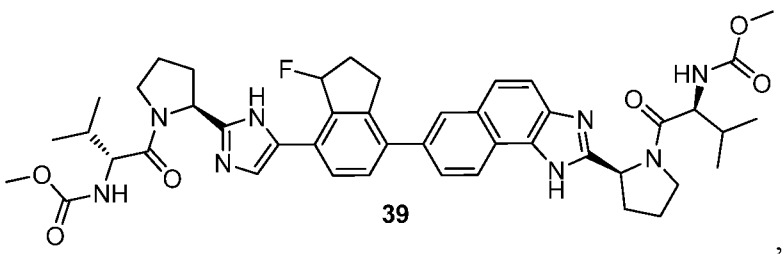
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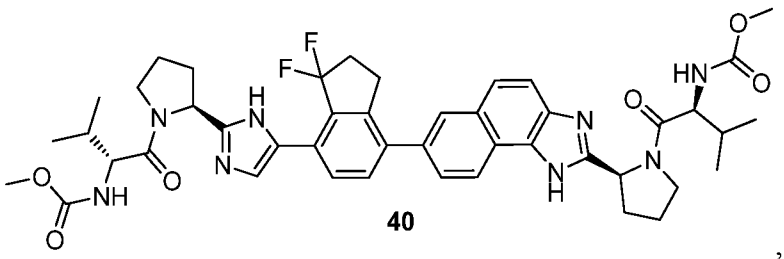
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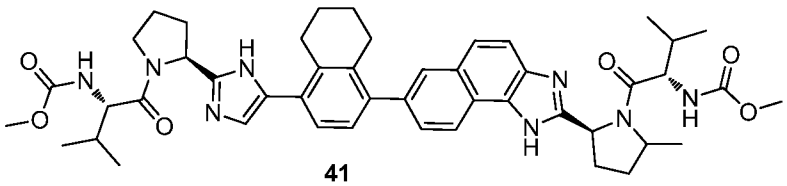
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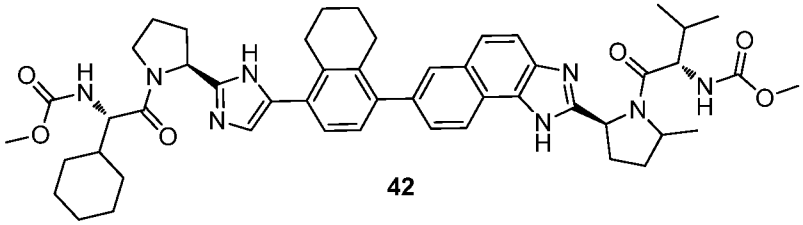
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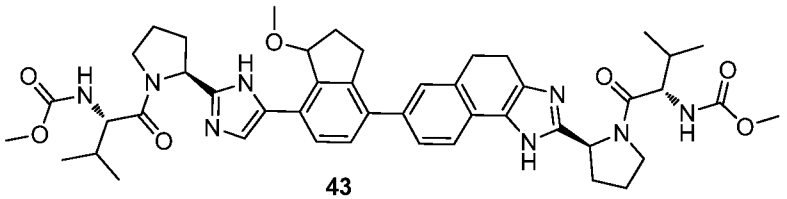
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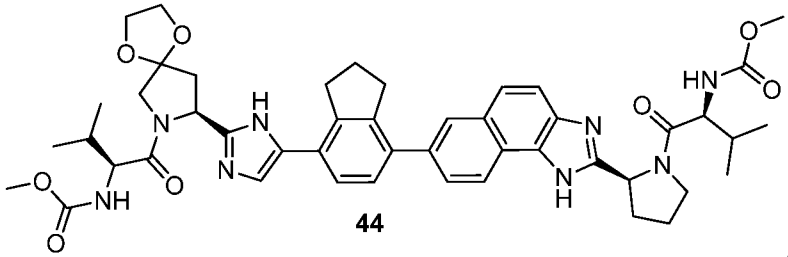
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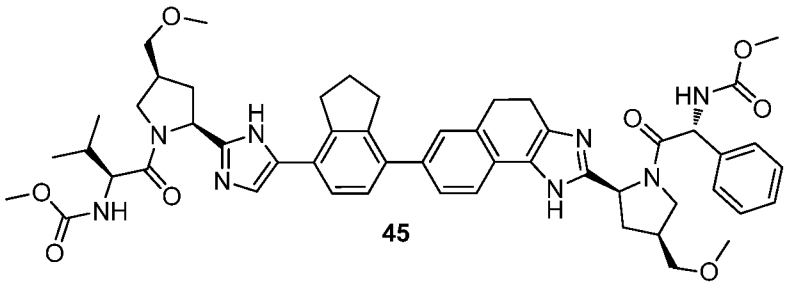
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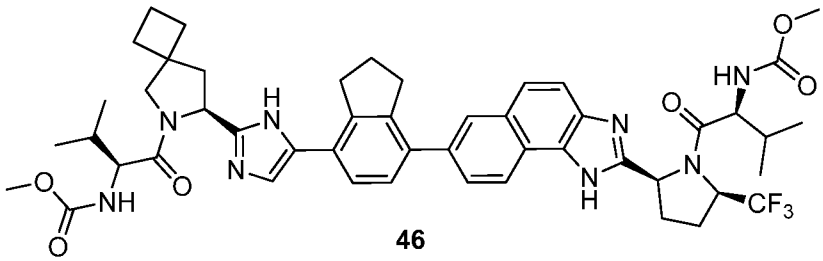
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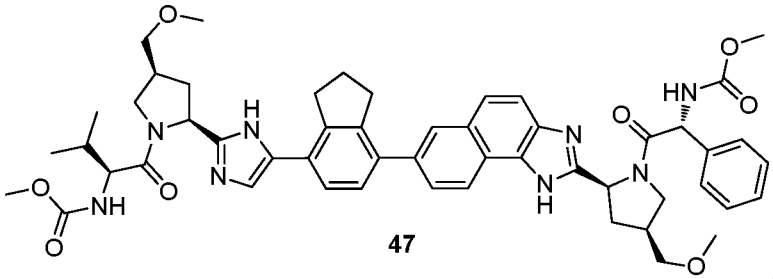
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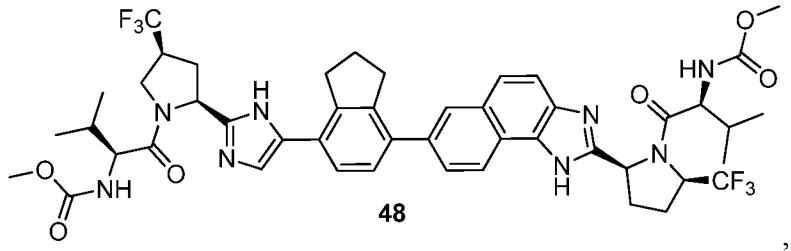
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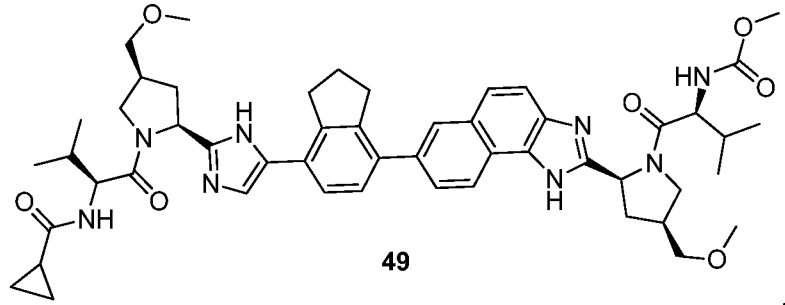


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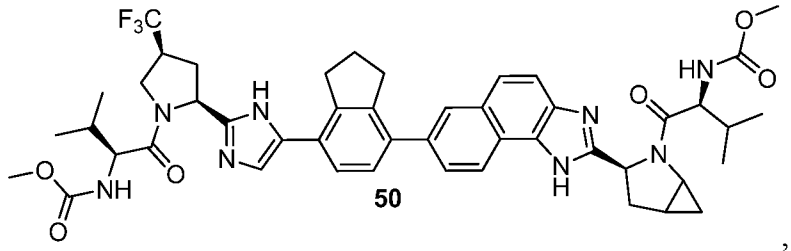
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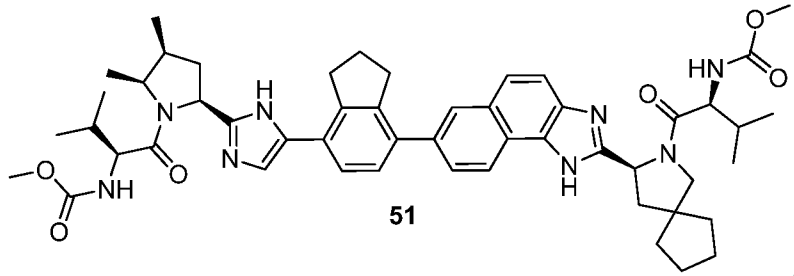
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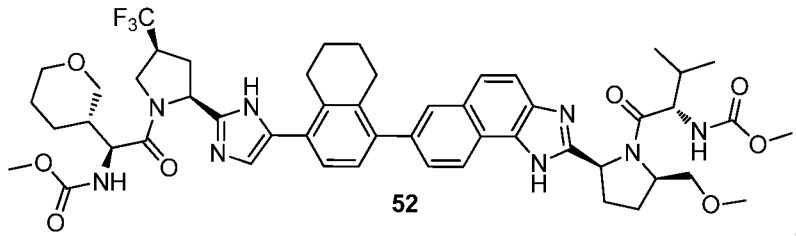
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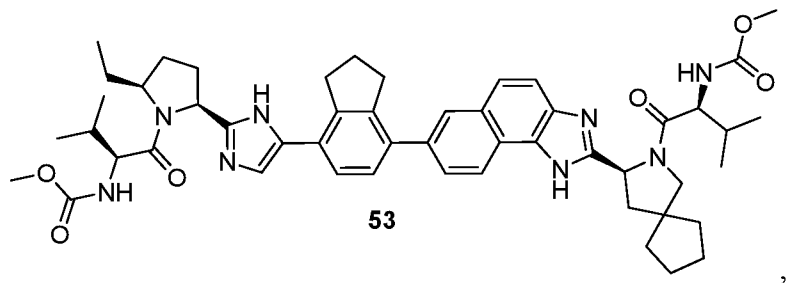
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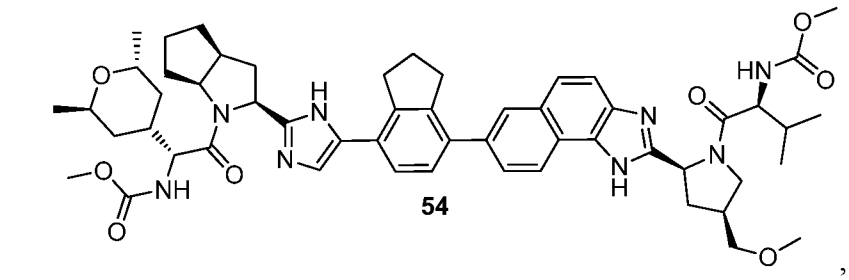
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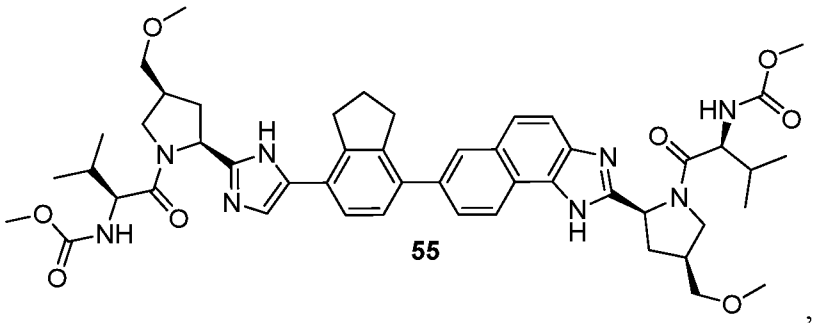
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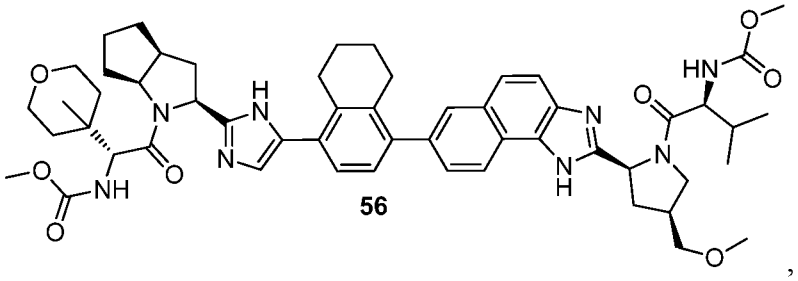
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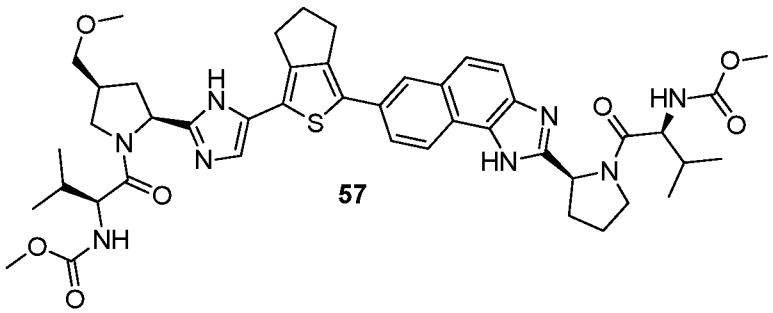
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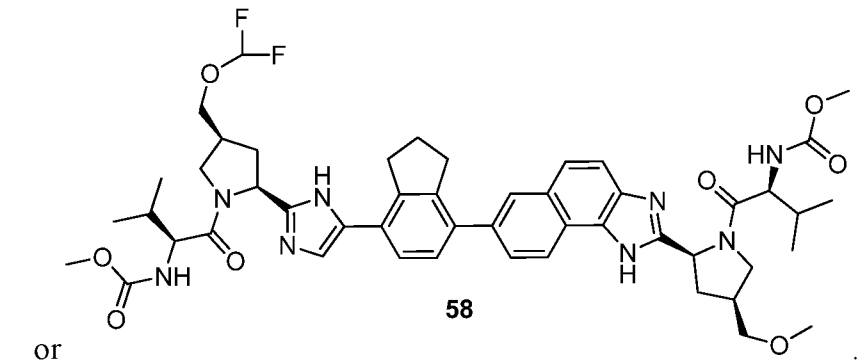
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or .

16. A pharmaceutical composition comprising the compound of any one of claims 1 to 15, and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

17. The pharmaceutical composition of claim 16 further comprising an anti-HCV agent other

than the said compound.

18. The pharmaceutical composition of claim 17, wherein the anti-HCV agent is interferon, ribavirin, IL-2, IL-6, IL-12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, imiquimod, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, rimantadine, bavituximab, hepatitis C immunogloblin, Civacir^{TM}, boceprevir, telaprevir, erlotinib, daclatasvir, simeprevir, asunaprevir, vaniprevir, faldaprevir, paritaprevir, danoprevir, sovaprevir, grazoprevir, vedroprevir, BZF-961, GS-9256, narlaprevir, ANA975, ombitasvir, EDP239, ravidasvir, velpatasvir, samatasvir, elbasvir, MK-8325, GSK-2336805, PPI-461, ciluprevir, sovaprevir, ACH-1095, VX-985, IDX-375, VX-500, VX-813, PHX-1766, PHX-2054, IDX-136, IDX-316, modithromycin, VBY-376, TMC-649128, mericitabine, sofosbuvir, INX-189, IDX-184, IDX102, R-1479, UNX-08189, PSI-6130, PSI-938, PSI-879, nesbuvir, HCV-371, VCH-916, lomibuvir, MK-3281, dasabuvir, ABT-072, filibuvir, deleobuvir, tegobuvir, A-837093, JKT-109, Gl-59728, GL-60667, AZD-2795, TMC647055, ledipasvir, odalasvir, ritonavir, furaprevir, setrobuvir, alisporivir, BIT-225, AV-4025, ACH-3422, MK-2748, MK-8325, JNJ-47910382, ABP-560, TD-6450, TVB-2640, ID-12, PPI-383, A-848837, RG-7795, BC-2125, alloferon, nivolumab, WF-10, nitazoxanide, multiferon, nevirapine, ACH-3422, alisporivir, MK-3682, MK-8408, GS-9857, CD-AdNS3, pibrentasvir, RG-101, glecaprevir, BZF-961, INO-8000, MBL-HCV1, CIGB-230, TG-2349, procvax, CB-5300, miravirsen, chronvac-C, MK-1075, ACH-0143422, WS-007, MK-7680, MK-2248, MK-8408, IDX-21459, AV-4025, MK-8876, GSK-2878175, MBX-700, AL-335, JNJ-47910382, AL-704, ABP-560, TD-6450, EDP-239, SB-9200, ITX-5061, ID-12 or a combination thereof; wherein the interferon is interferon α-2b, pegylated interferon α, interferon α-2a, pegylated interferon α-2a, consensus interferon-α, interferon γ or a combination thereof.

19. The pharmaceutical composition of claim 17, wherein the anti-HCV agent is used for inhibiting HCV replication process and/or at least a function of a HCV viral protein; and wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral protein comprises metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase

(IMPDH) required in the HCV viral replication.

20. Use of the compound of any one of claims 1 to 15 or the pharmaceutical composition of any one of claims 16 to 19 in the manufacture of a medicament for inhibiting HCV replication process and/or at least a function of a HCV viral protein; wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral protein comprises metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in the HCV viral replication.
21. Use of the compound of any one of claims 1 to 15 or the pharmaceutical composition of any one of claims 16 to 19 in the manufacture of a medicament for preventing, managing, treating or lessening the severity of HCV infection or a HCV disorder in a subject.
22. The compound of any one of claims 1 to 15 or the pharmaceutical composition of any one of claims 16 to 19 for use in inhibiting HCV replication process and/or at least a function of a HCV viral protein; wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral protein comprises metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in the HCV viral replication.
23. The compound of any one of claims 1 to 15 or the pharmaceutical composition of any one of claims 16 to 19 for use in preventing, managing, treating or lessening the severity of HCV infection or a HCV disorder in a subject.
24. A method of inhibiting HCV replication process and/or at least a function of a HCV viral protein in a subject comprising administering to the subject the compound of any one of claims 1 to 15 or the pharmaceutical composition of any one of claims 16 to 19; wherein the HCV replication process is a whole viral cycle consisting of HCV entry, uncoating, translation, replication, assembly and egress; and wherein the HCV viral protein comprises metalloproteinase, non-structural protein NS2, NS3, NS4A, NS4B, NS5A or NS5B, an internal ribosome entry site (IRES) and inosine-5'-monophosphate dehydrogenase (IMPDH) required in the HCV viral replication.

25. A method of preventing, managing, treating or lessening the severity of HCV infection or a HCV disorder in a subject, comprising administering to the subject the compound of any one of claims 1 to 15 or the pharmaceutical composition of any one of claims 16 to 19.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2016/076131

A. CLASSIFICATION OF SUBJECT MATTER

C07D 403/14(2006.01)i; A61K 31/4184(2006.01)i; A61P 31/14(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D; A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

VEN, CNABS, CPRSABS, CNKI, CA: HCV, Hepatitis, virus, +benz+, +midazol+

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 102143959 A (BRISTOL-MYERS SQUIBB CO) 03 August 2011 (2011-08-03) claims 1-22, examples 22-22i, 22m, 22r-22r.3, 22s-22u.1, 22v-22x.1a, 23, 23.3, 24-24.b, 24.3	1-23
A	CN 102741242 A (BRISTOL-MYERS SQUIBB CO) 17 October 2012 (2012-10-17) the whole document	1-23
A	CN 104302290 A (BRISTOL-MYERS SQUIBB CO) 21 January 2015 (2015-01-21) the whole document	1-23

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 June 2016	**20 June 2016**

Name and mailing address of the ISA/CN	Authorized officer
STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China**	**HAN, Yating**
Facsimile No. **(86-10)62019451**	Telephone No. **(86-10)62086315**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2016/076131

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **24 and 25**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 24 and 25 are directed to a method for the treatment or prophylaxis of the human body. Thus, the subject-matter of claims 24 and 25 is not required to be searched by this Authority. (Rule 39.1(iv) PCT).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2016/076131

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	102143959	A	03 August 2011	EP	2245027	B1	25 April 2012
				HR	P20120523	T1	31 July 2012
				US	8147818	B2	03 April 2012
				MX	2010008749	A	31 August 2010
				CA	2715559	A1	20 August 2009
				NZ	587322	A	27 April 2012
				CO	6290682	A2	20 June 2011
				IL	207459	D0	30 December 2010
				AU	2009214997	A1	20 August 2009
				SI	2245027	T1	31 August 2012
				EA	201001273	A1	30 August 2011
				AT	555109	T	15 May 2012
				DK	2245027	T3	06 August 2012
				TW	I458482	B	01 November 2014
				IL	207459	A	30 June 2015
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				JP	2011511840	A	14 April 2011
				PT	2245027	E	04 July 2012
				KR	20100124290	A	26 November 2010
				AU	2009214997	B2	26 September 2013
				EP	2245027	A1	03 November 2010
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				HK	1143812	A1	07 September 2012
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				WO	2009102633	A1	20 August 2009
				US	2009202478	A1	13 August 2009
				ES	2384911	T3	13 July 2012
				PE	13812009	A1	18 September 2009
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				JP	2013514359	A	25 April 2013
				AU	2010332034	B2	14 April 2016
				BR	112012014677	A2	15 September 2015
				AR	079634	A1	08 February 2012
				KR	20120107991	A	04 October 2012
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				EA	201270656	A1	30 November 2012
				MA	33806	B1	03 December 2012
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				NZ	601220	A	25 July 2014
				EP	2513091	A1	24 October 2012
				CO	6561788	A2	15 November 2012
				WO	2011075439	A1	23 June 2011
				CA	2784662	A1	23 June 2011
				EA	020815	B1	30 January 2015
				PE	14792012	A1	07 November 2012
				US	8377980	B2	19 February 2013

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2016/076131

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
		SG 181700 A1	30 July 2012
		MX 2012006635 A	21 June 2012
		JP 5785189 B2	24 September 2015
		CN 102741242 B	01 July 2015
CN 104302290 A	21 January 2015	WO 2013106520 A1	18 July 2013
		IN 4845CHN2014 A	18 September 2015
		TW 201408649 A	01 March 2014
		UY 34570 A	31 July 2013
		AR 089711 A1	10 September 2014
		US 2013183269 A1	18 July 2013
		MX 2014008227 A	08 August 2014
		EA 201491361 A1	28 November 2014
		CA 2863268 A1	18 July 2013
		EP 2802326 A1	19 November 2014
		JP 2015503617 A	02 February 2015