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(54) Title: NOVEL INHIBITORS OF HEPATITIS C VIRUS REPLICATION

(57) Abstract: The embodiments provide compounds of the general Formulae XV, XVI, XVII and XVIII as well as compositions, including pharmaceutical compositions, comprising a subject compound. The embodiments further provide treatment methods, including methods of treating a hepatitis C virus infection and methods of treating liver fibrosis, the methods generally involving administering to an individual in need thereof an effective amount of a subject compound or composition.



WO 2012/087976 A2

NOVEL INHIBITORS OF HEPATITIS C VIRUS REPLICATION

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Nos. 61/425,718, filed December 21, 2010; and 61/ 454,438, filed March 18, 2011; both of which are incorporated herein by reference in their entirety.

BACKGROUND

Field of the Invention

[0002] The embodiments described herein relate to compounds, processes for their synthesis, compositions and methods for the therapeutic use of the compounds, such as for treating hepatitis C virus (HCV) infection.

Description of the Related Art

[0003] Hepatitis C virus (HCV) infection is the most common chronic blood borne infection in the United States. Although the numbers of new infections have declined, the burden of chronic infection is substantial, with Centers for Disease Control estimates of 3.9 million (1.8%) infected persons in the United States. Chronic liver disease is the tenth leading cause of death among adults in the United States, and accounts for approximately 25,000 deaths annually, or approximately 1% of all deaths. Studies indicate that 40% of chronic liver disease is HCV-related, resulting in an estimated 8,000-10,000 deaths each year. HCV-associated end-stage liver disease is the most frequent indication for liver transplantation among adults.

[0004] Antiviral therapy of chronic hepatitis C has evolved rapidly over the last decade, with significant improvements seen in the efficacy of treatment. Nevertheless, even with combination therapy using pegylated IFN- α plus ribavirin, 40% to 50% of patients fail therapy; they are nonresponders or relapsers. These patients currently have no effective therapeutic alternative. In particular, patients who have advanced fibrosis or cirrhosis on liver biopsy are at significant risk of developing complications of advanced liver disease, including ascites, jaundice, variceal bleeding, encephalopathy, and progressive liver failure, as well as a markedly increased risk of hepatocellular carcinoma.

[0005] The high prevalence of chronic HCV infection has important public health implications for the future burden of chronic liver disease in the United States.

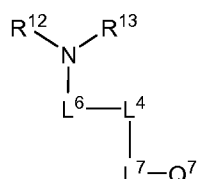
Data derived from the National Health and Nutrition Examination Survey (NHANES III) indicate that a large increase in the rate of new HCV infections occurred from the late 1960s to the early 1980s, particularly among persons between 20 to 40 years of age. It is estimated that the number of persons with long-standing HCV infection of 20 years or longer could more than quadruple from 1990 to 2015, from 750,000 to over 3 million. The proportional increase in persons infected for 30 or 40 years would be even greater. Since the risk of HCV-related chronic liver disease is related to the duration of infection, with the risk of cirrhosis progressively increasing for persons infected for longer than 20 years, this will result in a substantial increase in cirrhosis-related morbidity and mortality among patients infected between the years of 1965-1985.

[0006] HCV is an enveloped positive strand RNA virus in the Flaviviridae family. The single strand HCV RNA genome is believed to be 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, it is believed that this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS) proteins of the virus. In the case of HCV, the generation of mature nonstructural proteins (NS2, NS3, NS4, NS4A, NS4B, NS5A, and NS5B) is believed to be effected by two viral proteases. The first viral protease is believed to cleave at the NS2-NS3 junction of the polyprotein. The second viral protease is believed to be a serine protease contained within the N-terminal region of NS3 (herein referred to as "NS3 protease"). NS3 protease is believed to mediate all of the subsequent cleavage events at sites downstream relative to the position of NS3 in the polyprotein (i.e., sites located between the C-terminus of NS3 and the C-terminus of the polyprotein). NS3 protease exhibits activity both in cis, at the NS3-NS4 cleavage site, and in trans, for the remaining NS4A-NS4B, NS4B-NS5A, and NS5A-NS5B sites. The NS4A protein is believed 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. Apparently, the formation of the complex between NS3 and NS4A may be necessary for NS3-mediated processing events and enhances proteolytic efficiency at all sites recognized by NS3. The NS3 protease also appears to exhibit nucleoside triphosphatase and RNA helicase activities. NS5B is believed to be an RNA-dependent RNA polymerase involved in the replication of HCV RNA. In addition, compounds that

inhibit the action of NS5A in viral replication are potentially useful for the treatment of HCV.

SUMMARY

[0007] Some embodiments provide a compound having the structure of Formula XV:



XV

or a pharmaceutically acceptable salt thereof,

wherein:

each $\text{R}^{12}\text{R}^{13}\text{N}$ is separately selected, wherein R^{12} and R^{13} are each separately selected from hydrogen, $-\text{[(Y}^{14})(\text{C}(\text{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\text{R}^2)_2)_r]-$, $[\text{Y}^{14}(\text{C}(\text{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\text{R}^2)_2)_r]_s-(\text{Y}^{14})_s-\text{R}^{80}$, $-\text{[(Y}^{14})(\text{C}(\text{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\text{R}^2)_2)_r]-$, $\text{Y}^{14}(\text{C}(\text{R}^2)_2)_r\text{O}(\text{C}(\text{R}^2)_2)_r-(\text{Y}^{14})_s-\text{R}^{80}$, alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, $(\text{R}^e\text{R}^f\text{N})$ alkyl, $(\text{R}^e\text{R}^f\text{N})$ alkylC(=O)–, and $(\text{R}^e\text{R}^f\text{N})\text{C}(=\text{O})-$,

said alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, and alkyl in $(\text{R}^e\text{R}^f\text{N})$ alkyl and $(\text{R}^e\text{R}^f\text{N})$ alkylC(=O)– are each optionally substituted with one or more R^{1ab} ;

or $\text{R}^{12}\text{R}^{13}\text{N}$ is a heterocyclyl linked through a ring nitrogen atom optionally substituted with one or more of oxo, $-\text{[(Y}^{14})(\text{C}(\text{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\text{R}^2)_2)_r]-$, $[\text{Y}^{14}(\text{C}(\text{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\text{R}^2)_2)_r]_s-(\text{Y}^{14})_s-\text{R}^{80}$, $-\text{[(Y}^{14})(\text{C}(\text{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\text{R}^2)_2)_r]-$

$Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, (R^eR^fN) alkyl, (R^eR^fN) alkylC(=O)–, and $(R^eR^fN)C(=O)–$,

said alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, and alkyl in (R^eR^fN) alkyl and (R^eR^fN) alkylC(=O)– are each optionally substituted with one or more R^{1ab} ;

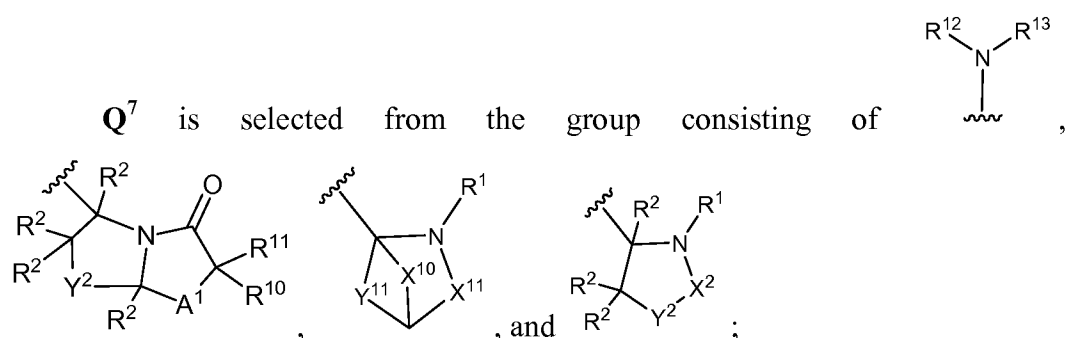
each R^{1ab} is separately selected from the group consisting of $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, $-C(R^{2a})_2NR^{3a}R^{3b}$, alkoxyalkyl, C_{1-6} alkylOC(=O)–, C_{1-6} alkylOC(=O) C_{1-6} alkyl, C_{1-6} alkylC(=O) C_{1-6} alkyl, aryl, aryl(CH₂)_n–, aryl(CH₂)_nO–, aryl(CH=CH)_m–, arylalkylO–, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)(CH=CH)_m–, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclyl, heterocyclyl(CH=CH)_m–, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, R^cR^dN –, $R^cR^dN(CH_2)_n$ –, $(R^cR^dN)(CH=CH)_m$ –, (R^cR^dN) alkyl, $(R^cR^dN)C(=O)–$, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9 halo;

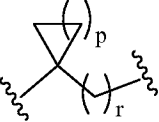
each R^{80} is separately selected from the group consisting of hydrogen, alkoxyalkyl, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and (R^eR^fN) alkyl, said alkoxyalkyl, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylalkyl,

heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and alkyl in $(\mathbf{R}^e\mathbf{R}^f\mathbf{N})$ alkyl are each optionally substituted with one or more $\mathbf{R}^{1ac}$;

each $\mathbf{R}^{1ac}$ is separately selected from the group consisting of $-\mathbf{C}(\mathbf{R}^{2a})_2\mathbf{NR}^{3a}\mathbf{R}^{3b}$, alkoxyalkyl, $\text{C}_{1-6}\text{alkylOC(=O)-}$, $\text{C}_{1-6}\text{alkylOC(=O)C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylC(=O)C}_{1-6}\text{alkyl}$, aryl, $\text{aryl(CH}_2)_n-$, $\text{aryl(CH}_2)_n\text{O-}$, aryl(CH=CH)_m- , arylalkylO- , arylalkyl , arylOalkyl , cycloalkyl, $(\text{cycloalkyl})(\text{CH=CH})_m-$, $(\text{cycloalkyl})\text{alkyl}$, cycloalkylOalkyl , heterocyclyl, $\text{heterocyclyl(CH=CH)}_m-$, $\text{heterocyclylalkoxy}$, heterocyclylalkyl , $\text{heterocyclylOalkyl}$, hydroxyalkyl, $\mathbf{R}^c\mathbf{R}^d\mathbf{N-}$, $\mathbf{R}^c\mathbf{R}^d\mathbf{N(CH}_2)_n-$, $(\mathbf{R}^c\mathbf{R}^d\mathbf{N})(\text{CH=CH})_m-$, $(\mathbf{R}^c\mathbf{R}^d\mathbf{N})\text{alkyl}$, $(\mathbf{R}^c\mathbf{R}^d\mathbf{N})\text{C(=O)-}$, $\text{C}_{1-6}\text{alkoxy}$ optionally substituted with up to 9 halo, and $\text{C}_{1-6}\text{alkyl}$ optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, $\text{C}_{1-6}\text{alkoxy}$ optionally substituted with up to 9 halo, and $\text{C}_{1-6}\text{alkyl}$ optionally substituted with up to 9 halo;

each $\mathbf{Y}^{14}$ is separately selected from the group consisting of $-\text{C(=O)-}$, $-\text{S(=O)-}$, $-\text{C(=S)-}$, $-\text{S(=O)}_2-$, $-\text{C(=O)O-}$, $-\text{C(=O)NR}^{2c}-$, $-\text{S(=O)}_2\mathbf{NR}^{2c}-$, $-\text{C(=O)NR}^{2c}\text{C(=O)-}$, and $-\text{C(CF}_3)_2\mathbf{NR}^{2c}-$,

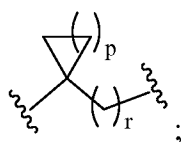


$\mathbf{X}^2$ is $(\text{C}(\mathbf{R}^2)_2)_q$, , or $\mathbf{X}^2$ is null;

$\mathbf{Y}^2$ is selected from O (oxygen), S (sulfur), S(O), SO_2 , $\mathbf{NR}^2$, and $\text{C}(\mathbf{R}^2)_2$ with the proviso that when $\mathbf{X}^2$ is null $\mathbf{Y}^2$ is $\text{C}(\mathbf{R}^2)_2$;

each $\mathbf{X}^{10}$ is $(\text{C}(\mathbf{R}^2)_2)_q$;

each $\mathbf{X}^{11}$ is separately selected from the group consisting of $(\text{C}(\mathbf{R}^2)_2)_q$, and



each Y^{11} is separately selected from the group consisting of $-O(C(R^2)_2)_n-$, $-S(C(R^2)_2)_n-$, $-S(O)(C(R^2)_2)_n-$, $-SO_2(C(R^2)_2)_n-$, $-NR^2(C(R^2)_2)_n-$, and $(C(R^2)_2)_q$;

R^1 is selected from the group consisting of R^{1aa} , $R^{1a}C(=O)-$ and $R^{1a}C(=S)-$;

each R^{1a} is separately selected from the group consisting of $-C(R^{2a})_2NR^{3a}R^{3b}$, alkoxyalkyl, $C_{1-6}alkylOC(=O)-$, $C_{1-6}alkylOC(=O)C_{1-6}alkyl$, $C_{1-6}alkylC(=O)C_{1-6}alkyl$, aryl, $aryl(CH_2)_n-$, $aryl(CH_2)_nO-$, $aryl(CH=CH)_m-$, $arylalkylO-$, $arylalkyl$, $arylOalkyl$, cycloalkyl, $(cycloalkyl)(CH=CH)_m-$, $(cycloalkyl)alkyl$, $cycloalkylOalkyl$, heterocyclyl, $heterocyclyl(CH=CH)_m-$, $heterocyclylalkoxy$, $heterocyclylalkyl$, $heterocyclylOalkyl$, hydroxyalkyl, R^cR^dN- , $R^cR^dN(CH_2)_n-$, $(R^cR^dN)(CH=CH)_m-$, $(R^cR^dN)alkyl$, $(R^cR^dN)C(=O)-$, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo;

R^{1aa} is $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-$ $(Y^{14})_s-R^{80}$, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, $alkoxyC(=O)-$, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{3-7}cycloalkyl$, $C_{1-6}alkylC(=O)-$, $C_{3-7}cycloalkylC(=O)-$, $C_{1-6}alkylsulfonyl$, $arylalkylOC(=O)-$, aryl, $arylalkyl$, $arylalkylC(=O)-$, $arylC(=O)-$, $arylsulfonyl$, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, $(R^eR^fN)alkyl$, $(R^eR^fN)alkylC(=O)-$, and $(R^eR^fN)C(=O)-$,

said alkoxyalkyl, $alkoxyC(=O)-$, $C_{1-6}alkyl$, $C_{3-7}cycloalkyl$, $C_{1-6}alkylC(=O)-$, $C_{3-7}cycloalkylC(=O)-$, $C_{1-6}alkylsulfonyl$, $arylalkylOC(=O)-$, aryl, $arylalkyl$, $arylalkylC(=O)-$, $arylC(=O)-$, $arylsulfonyl$, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, and alkyl in $(R^eR^fN)alkyl$ and $(R^eR^fN)alkylC(=O)-$ are each optionally substituted with one or more R^{1ab} ;

each R^{10} is R^cR^dN- ;

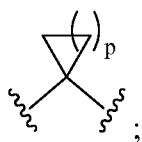
each R^{11} is separately selected from the group consisting of H (hydrogen), alkoxyalkyl, $C_{1-6}alkylOC(=O)C_{1-6}alkyl$, $C_{1-6}alkylC(=O)C_{1-6}alkyl$, $aryl(CH_2)_n-$, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclalkyl, heterocyclOalkyl, hydroxyalkyl, $R^eR^dN(CH_2)_n-$, $(R^eR^dN)alkyl$, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo;

each R^eR^dN is separately selected, wherein R^e and R^d are each separately selected from hydrogen, $alkoxyC(=O)-$, $C_{1-6}alkyl$, $C_{1-6}alkylC(=O)-$, $C_{1-6}alkylsulfonyl$, $arylalkylOC(=O)-$, arylalkyl, $arylalkylC(=O)-$, $arylC(=O)-$, arylsulfonyl, heterocyclalkyl, heterocyclalkylC(=O)-, heterocyclC(=O)-, $(R^eR^fN)alkyl$, $(R^eR^fN)alkylC(=O)-$, and $(R^eR^fN)C(=O)-$, wherein the alkyl part of arylalkyl, $arylalkylC(=O)-$, heterocyclalkyl, and heterocyclalkylC(=O)- are each optionally substituted with one R^eR^fN- group; and wherein the aryl part of arylalkyl, $arylalkylC(=O)-$, $arylC(=O)-$, and arylsulfonyl, and the heterocycl part of heterocyclalkyl, heterocyclalkylC(=O)-, and heterocyclC(=O)- are each optionally substituted with up to three substituents each independently selected from the group consisting of cyano, halo, nitro, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo;

each R^eR^fN is separately selected, wherein R^e and R^f are each separately selected from hydrogen, $C_{1-6}alkyl$, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycl, heterocyclalkyl, $(R^xR^yN)alkyl$, and $(R^xR^yN)C(=O)-$;

each R^xR^yN is separately selected, wherein R^x and R^y are each separately selected from hydrogen, $C_{1-6}alkylOC(=O)-$, $C_{1-6}alkyl$, $C_{1-6}alkylC(=O)-$, aryl, arylalkyl, cycloalkyl, and heterocycl;

each $C(R^{2a})_2$ is separately selected, wherein each R^{2a} is separately selected from the group consisting of hydrogen, $C_{1-6}alkyl$ optionally substituted with up to 9 halo, $aryl(CH_2)_n-$, and heteroaryl $(CH_2)_n-$, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9

halo, or optionally $C(R^{2a})_2$ is ;

each R^{3a} is separately selected from the group consisting of hydrogen, and optionally substituted C_{1-6} alkyl;

each R^{3b} is separately selected from the group consisting of optionally substituted C_{1-6} alkyl, heteroaryl, $-(CH_2)_nC(=O)NR^{4a}R^{4b}$, $-(CH_2)_nC(=O)OR^{5a}$, and $-(CH_2)_nC(=O)R^{6a}$ said heteroaryl optionally substituted with cyano, halo, nitro, hydroxyl, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9 halo;

each $R^{4a}R^{4b}N$ is separately selected, wherein R^{4a} and R^{4b} are each separately selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, and aryl $(CH_2)_n-$;

each R^{5a} is separately selected from the group consisting of optionally substituted C_{1-6} alkyl, and aryl $(CH_2)_n-$;

each R^{6a} is separately selected from the group consisting of optionally substituted C_{1-6} alkyl, and aryl $(CH_2)_n-$;

each A^1 is separately selected from the group consisting of C_{2-6} alkenyl, C_{1-6} alkyl, and $-(CH_2)_n-O-(CH_2)_m-$, each optionally substituted with one or more R^2 ;

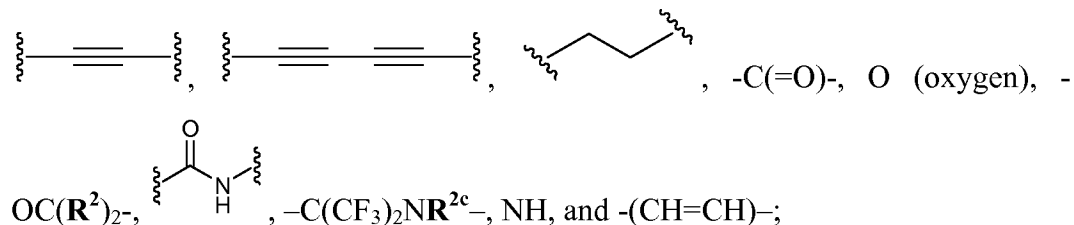
each R^2 is separately selected, wherein R^2 is selected from the group consisting of hydrogen, halo, hydroxy, C_{1-6} alkoxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, alkoxyalkyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, (R^eR^fN) alkyl, and R^aR^bN- , said C_{1-6} alkyl optionally substituted with one or more halo, $-OR^{2b}$, $-C(=O)OR^{2b}$, $-C(=O)NHR^{2b}$, $-NHC(=NH)NHR^{2b}$, $-NHR^{2b}$, SR^{2b} , imidazolyl, indolyl, $-SCH_3$, phenyl, and 4-hydroxyphenyl, said C_{1-6} alkoxy, alkoxyalkyl, aryl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and alkyl in (R^eR^fN) alkyl each optionally substituted with one or more R^4 , or optionally two vicinal R^2 and the carbons to which they are attached are together a fused three- to six-membered carbocyclic ring optionally substituted with up to two C_{1-6} alkyl groups;

R^{2b} is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

each **R**^{2c} is selected from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, said alkyl optionally substituted with **R**^e**R**^fN-, alkoxy, or C₁₋₆alkylS-;

each $\mathbf{R}^a\mathbf{R}^b\mathbf{N}$ is separately selected, wherein $\mathbf{R}^a$ and $\mathbf{R}^b$ are each separately selected from the group consisting of hydrogen, C_{2-6} alkenyl, and C_{1-6} alkyl;

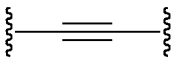
$\mathbf{L}^4$ is selected from the group consisting of $-(\mathbf{J}^2)_s-(\mathbf{L}^5)_s-(\mathbf{J}^2)_s-(\mathbf{L}^5)_s-\mathbf{J}^2$.

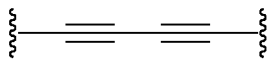
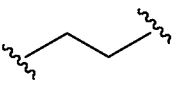
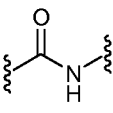
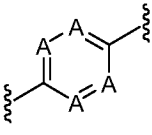


J² is aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, or polycyclic hydrocarbon, each optionally substituted with one or more **R**¹⁵;

each **R**¹⁴ is separately selected from the group consisting of hydroxy, C₁₋₆alkoxy optionally substituted with up to 9 fluoro, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC(=O)–, arylalkylOC(=O)–, –COOH, halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each **R**¹⁵ is separately selected from the group consisting of halo, hydroxy, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC(=O)–, arylalkylOC(=O)–, –COOH, **R**⁹, **R**^x**R**^yN, **R**^x**R**^yNC(=O), **R**^x**R**^yNC₁₋₆alkyl, heteroaryl, aryl, C₁₋₆alkyl optionally substituted with up to 9 halo, C₁₋₆alkyl substituted with up to 5 hydroxy, C₁₋₆alkoxy optionally substituted with up to 9 halo, C₁₋₆haloalkyl, **R**^a**R**^bN–, (**R**^a**R**^bN)alkyl, (**R**^a**R**^bN)C(=O)–, C₁₋₆alkyl substituted with up to 5 hydroxy, said substituent aryl and heteroaryl are each optionally substituted with one or more **R**¹⁴, or optionally two vicinal **R**¹⁵ and the carbons to which they are attached are together a fused three– to six–membered carbocyclic ring optionally substituted with up to two C₁₋₆alkyl groups, or optionally two geminal **R**¹⁵ and the carbon to which they are attached are together a three– to six–membered carbocyclic ring optionally substituted with up to two C₁₋₆alkyl groups, or optionally two geminal **R**¹⁵ are together oxo;

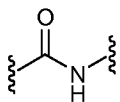
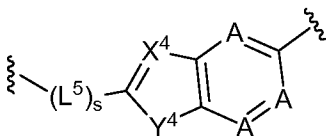
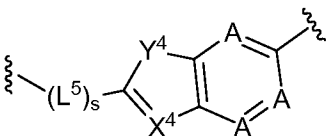
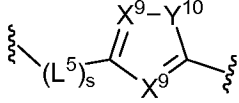
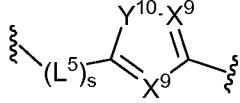
each L^5 is separately selected from the group consisting of ,

, , , $-\text{C}(\text{CF}_3)_2\text{NR}^{2c}-$, , $-\text{C}(\text{R}^2)_2$, $-\text{C}(\text{R}^2)_2\text{O}-$, $-\text{C}(=\text{O})-$, O (oxygen), NH, and $-(\text{CH}=\text{CH})-$;

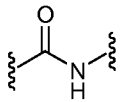
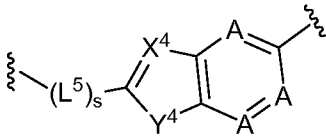
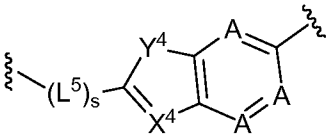
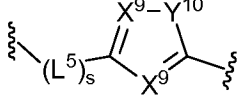
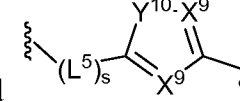
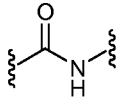
each A is separately selected from the group consisting of CR^3 and N (nitrogen);

each R^3 is separately selected from the group consisting of hydrogen, C_{1-6} alkoxy, C_{1-6} alkyl OC_{1-6} alkyl, C_{1-6} alkyl $\text{OC}(=\text{O})-$, arylalkyl $\text{OC}(=\text{O})-$, $-\text{COOH}$, halo, hydroxy, $\text{R}^a\text{R}^b\text{N}-$, $(\text{R}^a\text{R}^b\text{N})$ alkyl, $(\text{R}^a\text{R}^b\text{N})\text{C}(=\text{O})-$, C_{1-6} alkyl optionally substituted with up to 9 halo and up to 5 hydroxy;

L^6 is selected from the group consisting of

, $-\text{C}(\text{CF}_3)_2\text{NR}^{2c}-$, , , , and ;

L^7 is selected from the group consisting of

, $-\text{C}(\text{CF}_3)_2\text{NR}^{2c}-$, , , , and , wherein at least one of L^6 and L^7 is not ;

each X^4 is separately selected from the group consisting of CR^4 and N (nitrogen);

each Y^4 is separately selected from the group consisting of $\text{C}(\text{R}^4)_2$, NR^4 , O (oxygen), and S (sulfur);

each X^9 is separately selected from the group consisting of CH and N (nitrogen);

each Y^{10} is separately selected from the group consisting of $-\text{CH}_2-$ and $-\text{NH}-$;

each **m** separately is 1 or 2;
 each **n** separately is 0, 1 or 2;
 each **p** separately is 1, 2, 3 or 4;
 each **q** separately is 1, 2, 3, 4 or 5;
 each **r** separately is 0, 1, 2, 3, or 4;
 each **s** separately is 0 or 1;

each **R⁴** is separately selected from the group consisting of H (hydrogen), C₁₋₆alkoxy, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC(=O)–, arylalkylOC(=O)–, –COOH, halo, C₁₋₆haloalkyl, hydroxy, **R^aR^bN**–, (**R^aR^bN**)alkyl, (**R^aR^bN**)C(=O)–, C₁₋₆alkyl optionally substituted with up to 9 halo and up to 5 hydroxy, or optionally two geminal **R⁴** are together oxo;

R⁹ is selected from the group consisting of hydrogen and –C(=O)**R^{9a}**;

R^{9a} is selected from the group consisting of –**NR^{9b}R^{9c}**, –**OR^{9d}**, C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl;

R^{9b} is selected from the group consisting of hydrogen, C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl;

R^{9c} is selected from the group consisting of C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl; and

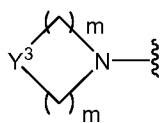
R^{9d} is selected from the group consisting of C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl.

[0008] In some embodiments of Formula **XV**, at least one **R¹²R¹³N** is a nitrogen containing heterocyclyl optionally including one or more –C(=O)–, O (oxygen), S (sulfur), S(O), SO₂, or NH groups in the heterocyclyl ring and optionally substituted with one or more of –[(**Y¹⁴**)(C(**R²**)₂)_r(**NR²**)_s(C(**R²**)₂)_r)]–[**Y¹⁴**(C(**R²**)₂)_r(**NR²**)_s(C(**R²**)₂)_r)]–(**Y¹⁴**)_s–**R⁸⁰**, –[(**Y¹⁴**)(C(**R²**)₂)_r(**NR²**)_s(C(**R²**)₂)_r)]–**Y¹⁴**(C(**R²**)₂)_rO(C(**R²**)₂)_r–(**Y¹⁴**)_s–**R⁸⁰**, alkoxyalkyl, alkoxyC(=O)–, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)–, C₃₋₇cycloalkylC(=O)–, C₁₋₆alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, (**R^eR^fN**)alkyl, (**R^eR^fN**)alkylC(=O)–, and (**R^eR^fN**)C(=O)–,

said alkoxyalkyl, alkoxyC(=O)–, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)–, C₃₋₇cycloalkylC(=O)–, C₁₋₆alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl,

arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, and alkyl in $(R^e R^f N)$ alkyl and $(R^e R^f N)$ alkylC(=O)– are each optionally substituted with one or more R^1 .

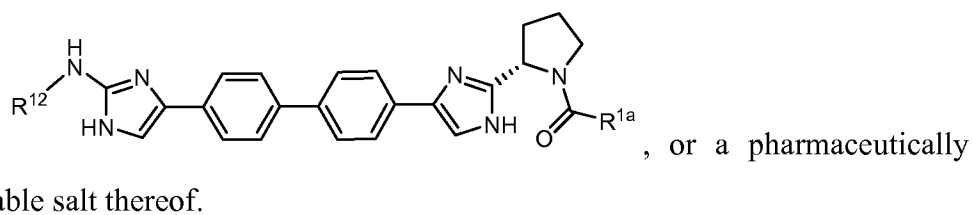
[0009] In some embodiments of Formula **XV**, at least one $R^{12} R^{13} N$ is



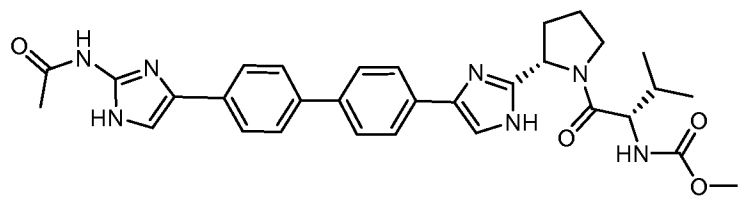
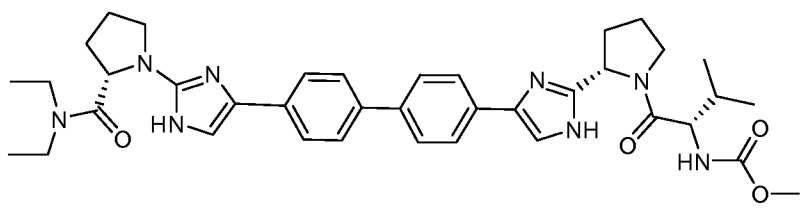
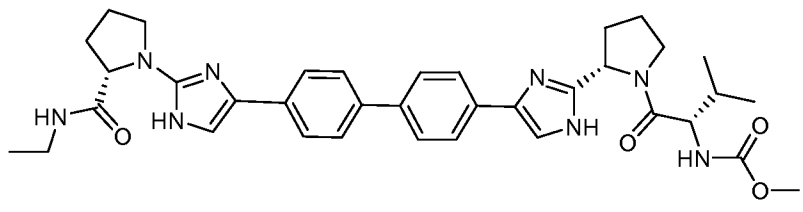
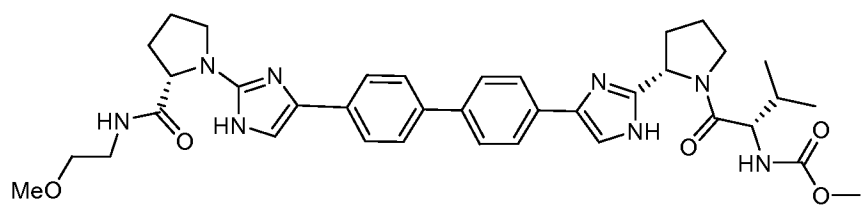
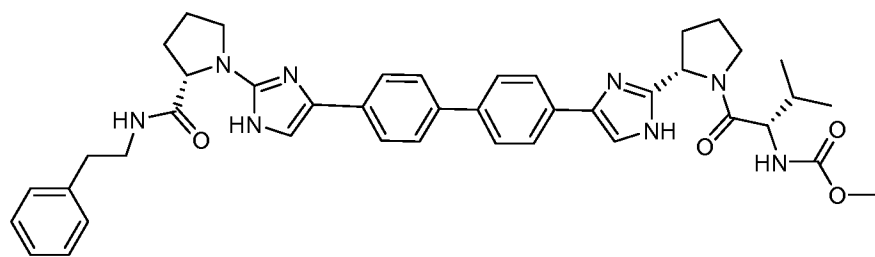
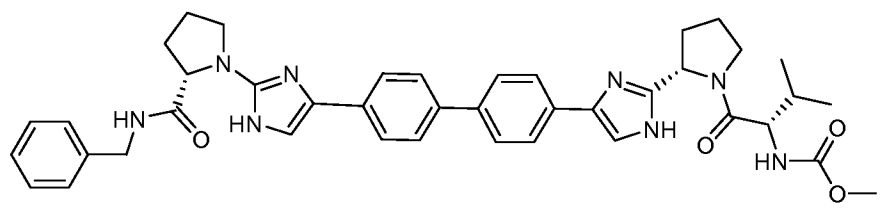
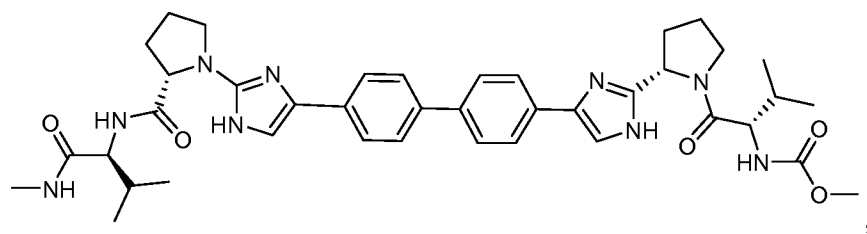
optionally substituted with one or more of $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-$, $[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-$, $Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, $(R^e R^f N)$ alkyl, $(R^e R^f N)$ alkylC(=O)–, and $(R^e R^f N)C(=O)–$,

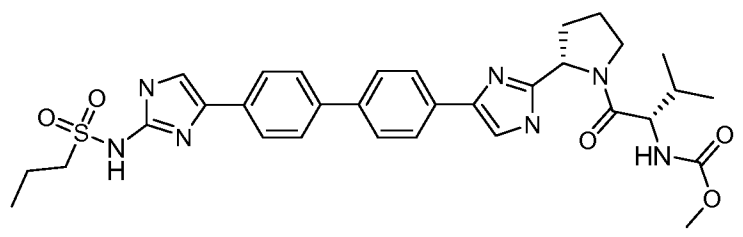
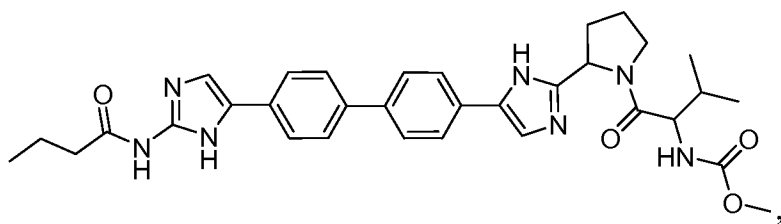
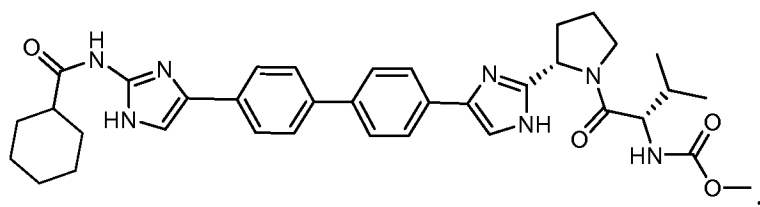
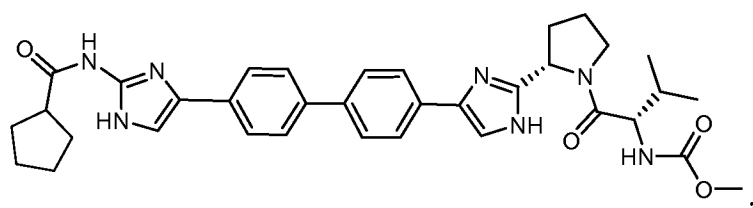
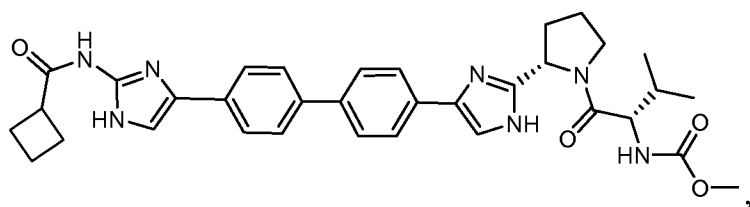
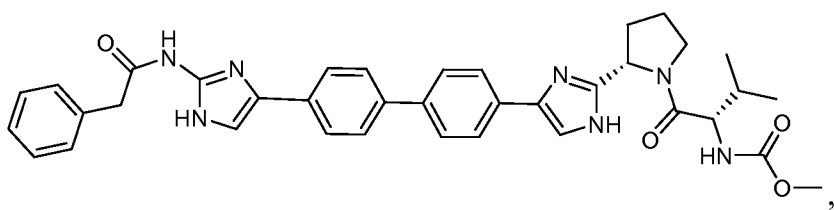
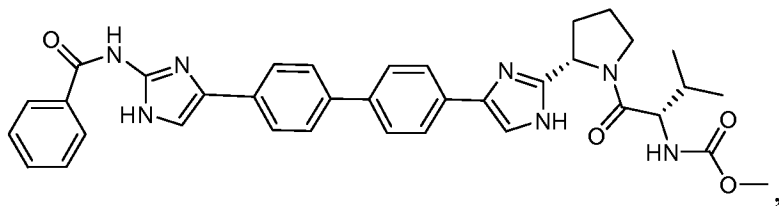
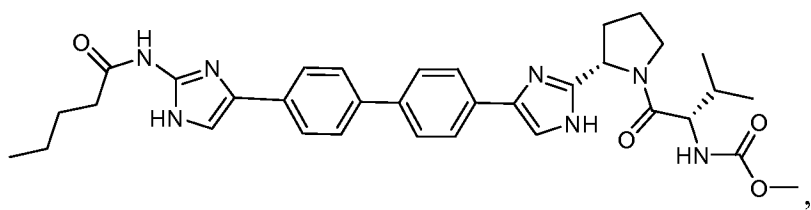
said alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, and alkyl in $(R^e R^f N)$ alkyl and $(R^e R^f N)$ alkylC(=O)– are each optionally substituted with one or more R^1 ; wherein Y^3 is O (oxygen), S (sulfur), S(O), SO_2 , $-C(=O)-$, $-NH-$, $-CH_2-$, $-NHCH_2-$, $-OCH_2-$, $-SCH_2-$, $-NHCH_2-$, $-NHC(=O)-$, or $-NHSO_2-$.

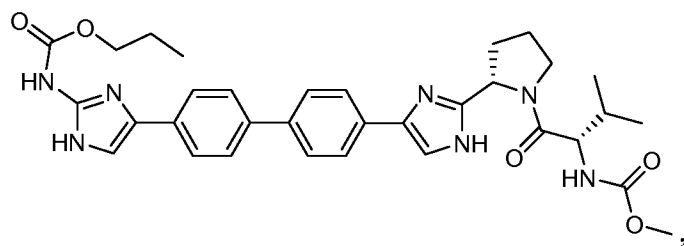
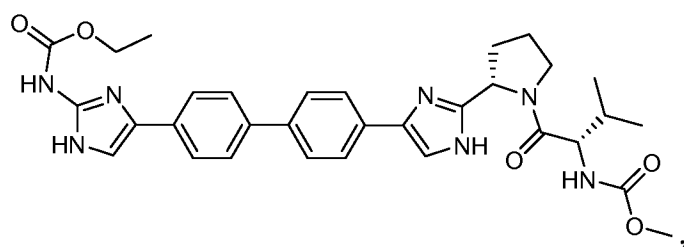
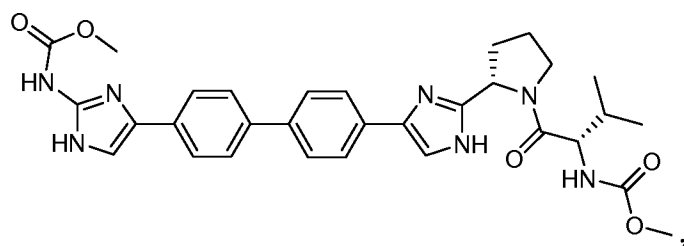
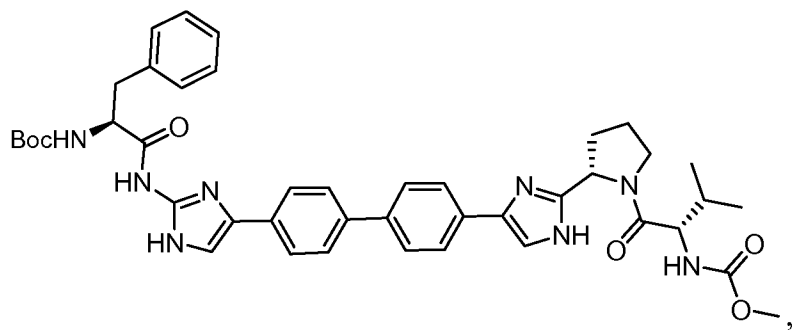
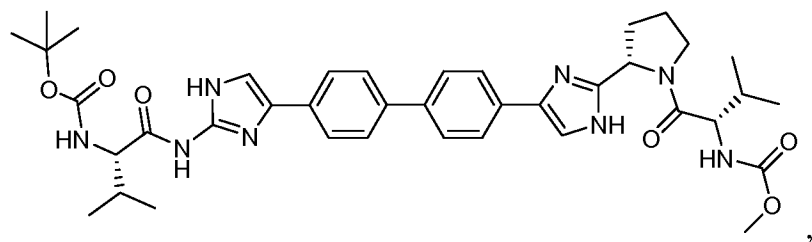
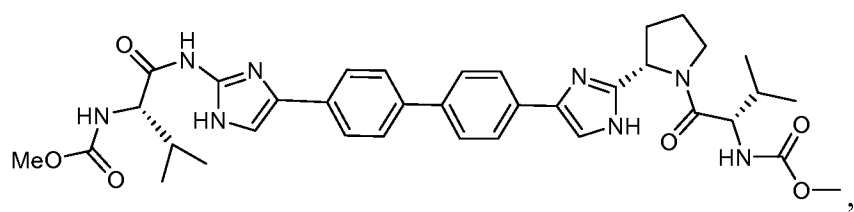
[0010] In some embodiments, the compound of Formula **XV** has the structure of Formula **XVa**:

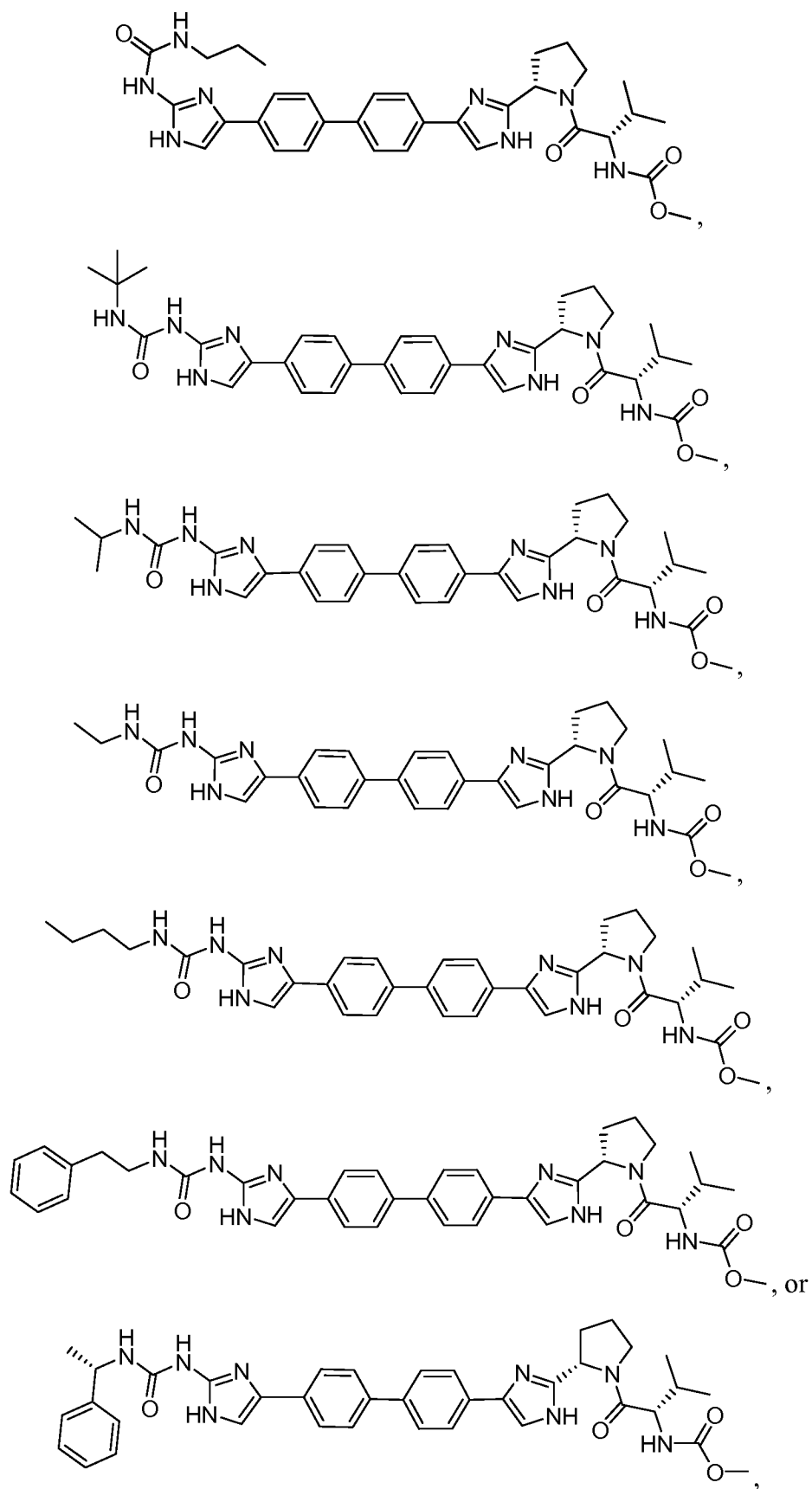


[0011] In some embodiments, the compound of Formula **XV** has the structure:



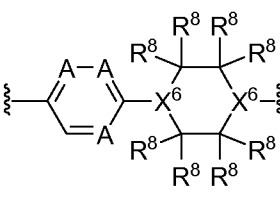


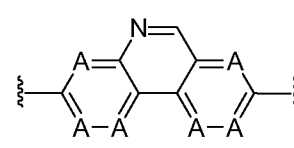


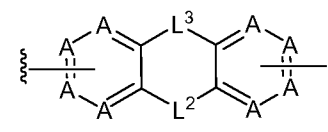


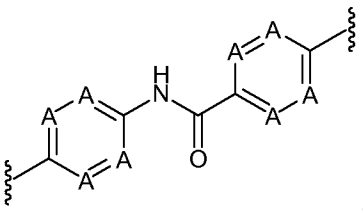
or a pharmaceutically acceptable salt thereof.

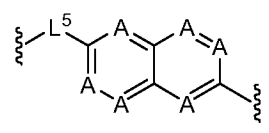
group consisting of

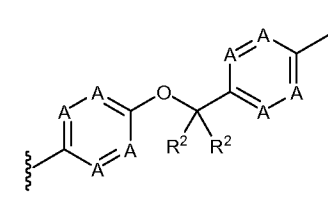


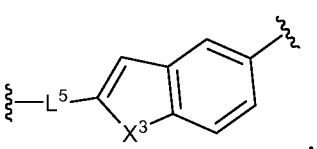


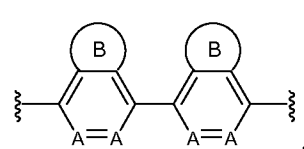


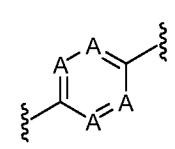


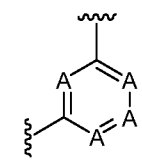


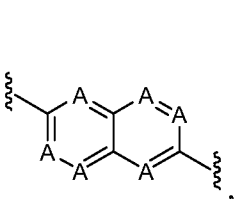


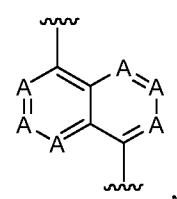


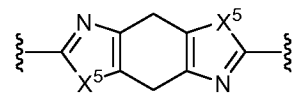


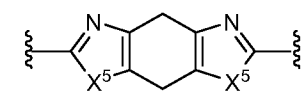


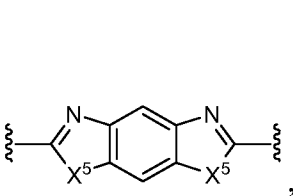


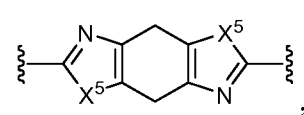


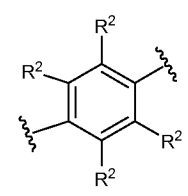


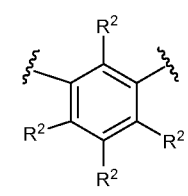


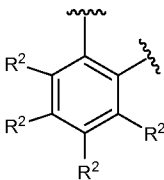


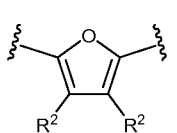


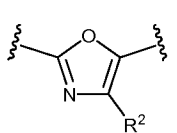


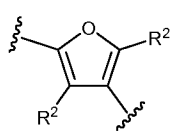


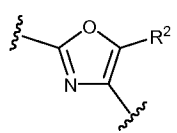


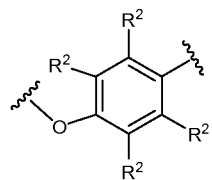


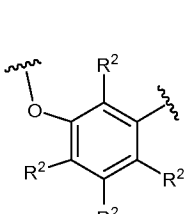


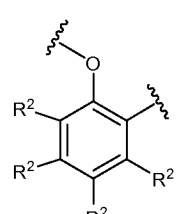










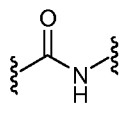


and ;

-17-

a fused optionally substituted saturated or unsaturated three- to seven-membered heterocyclic ring, each optionally substituted with one or more R^4 ;

L^2 can be selected from the group consisting of $-C(=O)-$, $-(CH_2CH_2)-$, $-(CH_2O)-$, $-(CH_2S)-$, $-(CH=CH)-$, $-(CH=N)-$, $-NH-$, O (oxygen), S (sulfur), and $-CH_2-$;

L^3 can be selected from the group consisting of , $-(NR^9)-$, O (oxygen), S (sulfur), and $-CH_2-$;

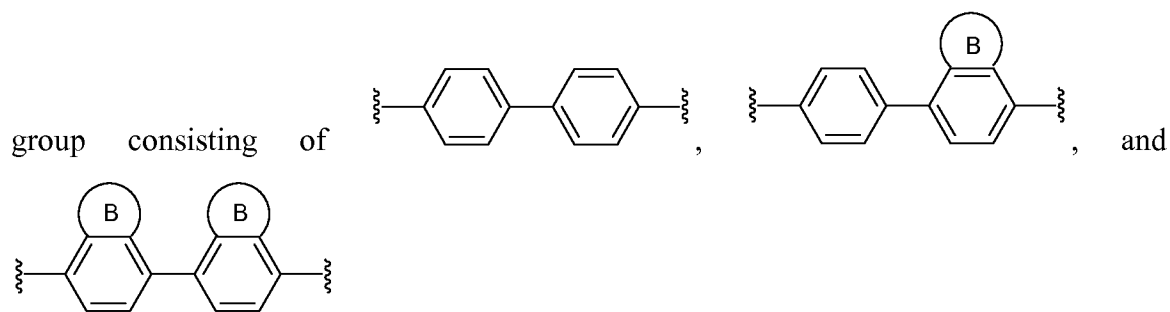
X^3 can be selected from the group consisting of NH, O (oxygen), and S (sulfur);

each X^5 can be separately selected from the group consisting of $-NH-$, O (oxygen), S (sulfur), and $-CH_2-$;

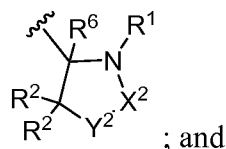
each X^6 can be separately selected from the group consisting of N (nitrogen), and CR^8 ; and

each R^8 can be separately selected from the group consisting of hydrogen, $C_{1-6}alkylOC_{1-6}alkyl$, $C_{1-6}alkylOC(=O)-$, arylalkyl $OC(=O)-$, halo, $(R^aR^bN)alkyl$, $(R^aR^bN)C(=O)-$, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo and up to 5 hydroxy.

[0013] In some embodiments of Formula XV, L^4 can be selected from the



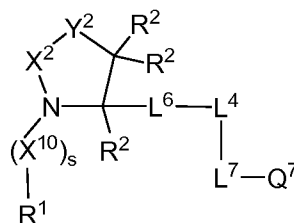
[0014] In some embodiments of Formula XV, Q^7 can be:



R^6 can be $C_{1-6}alkyl$ optionally substituted with up to 9 halo.

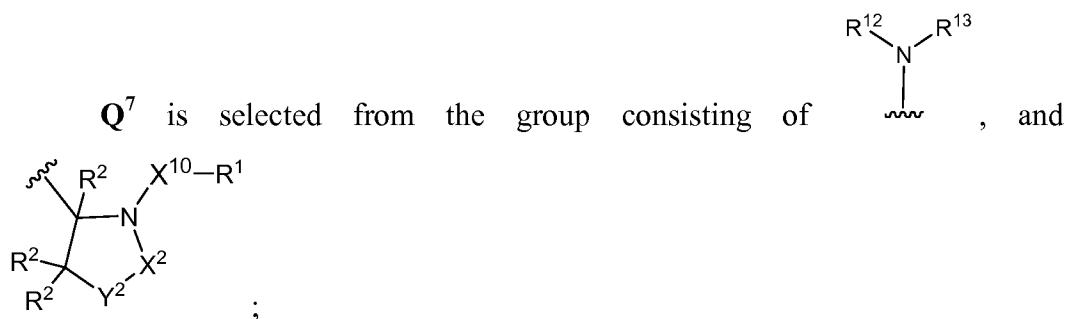
[0015] In some embodiments of Formula XV, R^6 can be methyl.

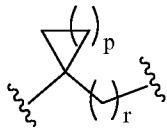
[0016] Some embodiments provide a compound having the structure of Formula XVI:



XVI

or a pharmaceutically acceptable salt thereof,
wherein:

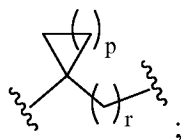


each X^2 is $(C(R^2)_2)_q$, , or X^2 is null;

each Y^2 is selected from O (oxygen), S (sulfur), S(O), SO₂, NR², and C(R²)₂ with the proviso that when X^2 is null Y^2 is C(R²)₂;

each X^{10} is $(C(R^2)_2)_q$;

each X^{11} is separately selected from the group consisting of $(C(R^2)_2)_q$, and



each Y^{11} is separately selected from the group consisting of -O(C(R²)₂)_n-, -S(C(R²)₂)_n-, -S(O)(C(R²)₂)_n-, -SO₂(C(R²)₂)_n-, -NR²(C(R²)₂)_n-, and (C(R²)₂)_q;

each $R^{12}R^{13}N$ is separately selected, wherein R^{12} and R^{13} are each separately selected from hydrogen, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-$, $[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-$, $Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-,

arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, ($R^e R^f N$)alkyl, ($R^e R^f N$)alkylC(=O)–, and ($R^e R^f N$)C(=O)–,

said alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, and alkyl in ($R^e R^f N$)alkyl and ($R^e R^f N$)alkylC(=O)– are each optionally substituted with one or more R^{1ab} ;

or $R^{12} R^{13} N$ is a heterocyclyl linked through a ring nitrogen atom optionally substituted with one or more of oxo, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, ($R^e R^f N$)alkyl, ($R^e R^f N$)alkylC(=O)–, and ($R^e R^f N$)C(=O)–,

said alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, and alkyl in ($R^e R^f N$)alkyl and ($R^e R^f N$)alkylC(=O)– are each optionally substituted with one or more R^{1ab} ;

each R^{1ab} is separately selected from the group consisting of $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$,

$-\text{C}(\text{R}^{2a})_2\text{NR}^{3a}\text{R}^{3b}$, alkoxyalkyl, $\text{C}_{1-6}\text{alkylOC}(=\text{O})-$, $\text{C}_{1-6}\text{alkylOC}(=\text{O})\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylC}(=\text{O})\text{C}_{1-6}\text{alkyl}$, aryl, $\text{aryl}(\text{CH}_2)_n-$, $\text{aryl}(\text{CH}_2)_n\text{O}-$, $\text{aryl}(\text{CH}=\text{CH})_m-$, $\text{arylalkylO}-$, arylalkyl , arylOalkyl , cycloalkyl , $(\text{cycloalkyl})(\text{CH}=\text{CH})_m-$, $(\text{cycloalkyl})\text{alkyl}$, cycloalkylOalkyl , heterocyclyl , $\text{heterocyclyl}(\text{CH}=\text{CH})_m-$, $\text{heterocyclylalkoxy}$, heterocyclylalkyl , $\text{heterocyclylOalkyl}$, hydroxyalkyl , $\text{R}^c\text{R}^d\text{N}-$, $\text{R}^c\text{R}^d\text{N}(\text{CH}_2)_n-$, $(\text{R}^c\text{R}^d\text{N})(\text{CH}=\text{CH})_m-$, $(\text{R}^c\text{R}^d\text{N})\text{alkyl}$, $(\text{R}^c\text{R}^d\text{N})\text{C}(=\text{O})-$, $\text{C}_{1-6}\text{alkoxy}$ optionally substituted with up to 9 halo, and $\text{C}_{1-6}\text{alkyl}$ optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, $\text{C}_{1-6}\text{alkoxy}$ optionally substituted with up to 9 halo, and $\text{C}_{1-6}\text{alkyl}$ optionally substituted with up to 9 halo;

each R^{80} is separately selected from the group consisting of hydrogen, alkoxyalkyl, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{3-7}\text{cycloalkyl}$, aryl, arylalkyl , heterocyclyl , heterocyclylalkyl , heteroaryl , heteroarylalkyl , heterocyclylalkyl , and $(\text{R}^e\text{R}^f\text{N})\text{alkyl}$, said alkoxyalkyl, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{3-7}\text{cycloalkyl}$, aryl, arylalkyl , heterocyclyl , heterocyclylalkyl , heteroaryl , heteroarylalkyl , heterocyclylalkyl , and alkyl in $(\text{R}^e\text{R}^f\text{N})\text{alkyl}$ are each optionally substituted with one or more R^{1ac} ;

each R^{1ac} is separately selected from the group consisting of $-\text{C}(\text{R}^{2a})_2\text{NR}^{3a}\text{R}^{3b}$, alkoxyalkyl, $\text{C}_{1-6}\text{alkylOC}(=\text{O})-$, $\text{C}_{1-6}\text{alkylOC}(=\text{O})\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylC}(=\text{O})\text{C}_{1-6}\text{alkyl}$, aryl, $\text{aryl}(\text{CH}_2)_n-$, $\text{aryl}(\text{CH}_2)_n\text{O}-$, $\text{aryl}(\text{CH}=\text{CH})_m-$, $\text{arylalkylO}-$, arylalkyl , arylOalkyl , cycloalkyl , $(\text{cycloalkyl})(\text{CH}=\text{CH})_m-$, $(\text{cycloalkyl})\text{alkyl}$, cycloalkylOalkyl , heterocyclyl , $\text{heterocyclyl}(\text{CH}=\text{CH})_m-$, $\text{heterocyclylalkoxy}$, heterocyclylalkyl , $\text{heterocyclylOalkyl}$, hydroxyalkyl , $\text{R}^c\text{R}^d\text{N}-$, $\text{R}^c\text{R}^d\text{N}(\text{CH}_2)_n-$, $(\text{R}^c\text{R}^d\text{N})(\text{CH}=\text{CH})_m-$, $(\text{R}^c\text{R}^d\text{N})\text{alkyl}$, $(\text{R}^c\text{R}^d\text{N})\text{C}(=\text{O})-$, $\text{C}_{1-6}\text{alkoxy}$ optionally substituted with up to 9 halo, and $\text{C}_{1-6}\text{alkyl}$ optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, $\text{C}_{1-6}\text{alkoxy}$ optionally substituted with up to 9 halo, and $\text{C}_{1-6}\text{alkyl}$ optionally substituted with up to 9 halo;

each Y^{14} is separately selected from the group consisting of $-\text{C}(=\text{O})-$, $-\text{S}(=\text{O})-$, $-\text{C}(=\text{S})-$, $-\text{S}(=\text{O})_2-$, $-\text{C}(=\text{O})\text{O}-$, $-\text{C}(=\text{O})\text{NR}^{2c}-$, $-\text{S}(=\text{O})_2\text{NR}^{2c}-$, $-\text{C}(=\text{O})\text{NR}^{2c}\text{C}(=\text{O})-$, and $-\text{C}(\text{CF}_3)_2\text{NR}^{2c}-$,

R^1 is selected from the group consisting of R^{1aa} , $\text{R}^{1a}\text{C}(=\text{O})-$ and $\text{R}^{1a}\text{C}(=\text{S})-$;

each R^{1a} is separately selected from the group consisting of $-C(R^{2a})_2NR^{3a}R^{3b}$, alkoxyalkyl, $C_{1-6}alkylOC(=O)-$, $C_{1-6}alkylOC(=O)C_{1-6}alkyl$, $C_{1-6}alkylC(=O)C_{1-6}alkyl$, aryl, $aryl(CH_2)_n-$, $aryl(CH_2)_nO-$, $aryl(CH=CH)_m-$, $arylalkylO-$, $arylalkyl$, $arylOalkyl$, cycloalkyl, $(cycloalkyl)(CH=CH)_m-$, $(cycloalkyl)alkyl$, $cycloalkylOalkyl$, heterocyclyl, $heterocyclyl(CH=CH)_m-$, $heterocyclylalkoxy$, $heterocyclylalkyl$, $heterocyclylOalkyl$, hydroxyalkyl, R^cR^dN- , $R^cR^dN(CH_2)_n-$, $(R^cR^dN)(CH=CH)_m-$, $(R^cR^dN)alkyl$, $(R^cR^dN)C(=O)-$, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo;

R^{1aa} is selected from the group consisting of $-C(R^{2a})_2NR^{3a}R^{3b}$, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxy $C(=O)-$, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{3-7}cycloalkyl$, $C_{1-6}alkylC(=O)-$, $C_{3-7}cycloalkylC(=O)-$, $C_{1-6}alkylsulfonyl$, $arylalkylOC(=O)-$, aryl, $arylalkyl$, $arylalkylC(=O)-$, $arylC(=O)-$, $arylsulfonyl$, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, $heterocyclylalkylC(=O)-$, $heterocyclylC(=O)-$, heteroaryl $C(=O)-$, heteroarylalkyl $C(=O)-$, $(R^eR^fN)alkyl$, $(R^eR^fN)alkylC(=O)-$, and $(R^eR^fN)C(=O)-$,

said alkoxyalkyl, alkoxy $C(=O)-$, $C_{1-6}alkyl$, $C_{3-7}cycloalkyl$, $C_{1-6}alkylC(=O)-$, $C_{3-7}cycloalkylC(=O)-$, $C_{1-6}alkylsulfonyl$, $arylalkylOC(=O)-$, aryl, $arylalkyl$, $arylalkylC(=O)-$, $arylC(=O)-$, $arylsulfonyl$, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, $heterocyclylalkylC(=O)-$, $heterocyclylC(=O)-$, heteroaryl $C(=O)-$, heteroarylalkyl $C(=O)-$, and alkyl in $(R^eR^fN)alkyl$ and $(R^eR^fN)alkylC(=O)-$ are each optionally substituted with one or more R^{1ab} ;

each R^{10} is R^cR^dN- ;

each R^{11} is separately selected from the group consisting of H (hydrogen), alkoxyalkyl, $C_{1-6}alkylOC(=O)C_{1-6}alkyl$, $C_{1-6}alkylC(=O)C_{1-6}alkyl$, $aryl(CH_2)_n-$, $arylalkyl$, $arylOalkyl$, cycloalkyl, $(cycloalkyl)alkyl$, $cycloalkylOalkyl$,

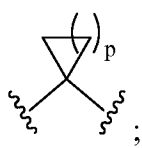
heterocyclalkyl, heterocyclalkoxy, hydroxyalkyl, $R^cR^dN(CH_2)_n-$, $(R^cR^dN)alkyl$, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo;

each R^cR^dN is separately selected, wherein R^c and R^d are each separately selected from hydrogen, alkoxyC(=O)-, $C_{1-6}alkyl$, $C_{1-6}alkylC(=O)-$, $C_{1-6}alkylsulfonyl$, arylalkylOC(=O)-, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclalkyl, heterocyclalkylC(=O)-, heterocyclalkylC(=O)-, $(R^eR^fN)alkyl$, $(R^eR^fN)alkylC(=O)-$, and $(R^eR^fN)C(=O)-$, wherein the alkyl part of arylalkyl, arylalkylC(=O)-, heterocyclalkyl, and heterocyclalkylC(=O)- are each optionally substituted with one R^eR^fN- group; and wherein the aryl part of arylalkyl, arylalkylC(=O)-, arylC(=O)-, and arylsulfonyl, and the heterocycl part of heterocyclalkyl, heterocyclalkylC(=O)-, and heterocyclalkylC(=O)- are each optionally substituted with up to three substituents each independently selected from the group consisting of cyano, halo, nitro, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo;

each R^eR^fN is separately selected, wherein R^e and R^f are each separately selected from hydrogen, $C_{1-6}alkyl$, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycl, heterocyclalkyl, $(R^xR^yN)alkyl$, and $(R^xR^yN)C(=O)-$;

each R^xR^yN is separately selected, wherein R^x and R^y are each separately selected from hydrogen, $C_{1-6}alkylOC(=O)-$, $C_{1-6}alkyl$, $C_{1-6}alkylC(=O)-$, aryl, arylalkyl, cycloalkyl, and heterocycl;

each $C(R^{2a})_2$ is separately selected, wherein each R^{2a} is separately selected from the group consisting of hydrogen, $C_{1-6}alkyl$ optionally substituted with up to 9 halo, aryl $(CH_2)_n-$, and heteroaryl $(CH_2)_n-$, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9

halo, or optionally $C(R^{2a})_2$ is ;

each R^{3a} is separately selected from the group consisting of hydrogen, and optionally substituted $C_{1-6}alkyl$;

each R^{3b} is separately selected from the group consisting of optionally substituted $C_{1-6}alkyl$, heteroaryl, $-(CH_2)_nC(=O)NR^{4a}R^{4b}$, $-(CH_2)_nC(=O)OR^{5a}$,

and $-(\text{CH}_2)_n\text{C}(=\text{O})\text{R}^{6a}$ said heteroaryl optionally substituted with cyano, halo, nitro, hydroxyl, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9 halo;

each $\text{R}^{4a}\text{R}^{4b}\text{N}$ is separately selected, wherein R^{4a} and R^{4b} are each separately selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, and $\text{aryl}(\text{CH}_2)_n-$;

each R^{5a} is separately selected from the group consisting of optionally substituted C_{1-6} alkyl, and $\text{aryl}(\text{CH}_2)_n-$;

each R^{6a} is separately selected from the group consisting of optionally substituted C_{1-6} alkyl, and $\text{aryl}(\text{CH}_2)_n-$;

each A^1 is separately selected from the group consisting of C_{2-6} alkenyl, C_{1-6} alkyl, and $-(\text{CH}_2)_n\text{O}-(\text{CH}_2)_m-$, each optionally substituted with one or more R^2 ;

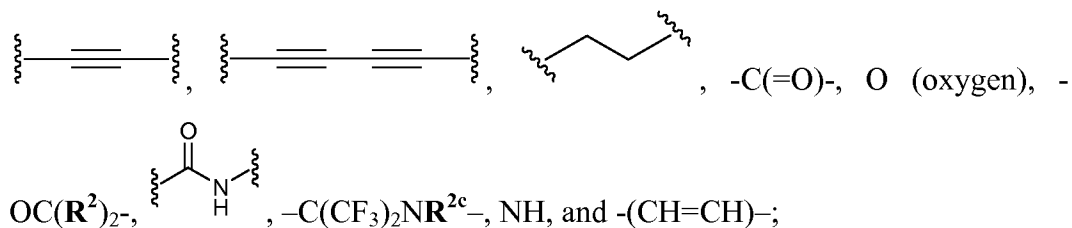
each R^2 is separately selected, wherein R^2 is selected from the group consisting of hydrogen, halo, hydroxy, C_{1-6} alkoxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, alkoxyalkyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, $(\text{R}^e\text{R}^f\text{N})\text{alkyl}$, $\text{R}^a\text{R}^b\text{N}-$, said C_{1-6} alkyl optionally substituted with one or more halo, $-\text{OR}^{2b}$, $-\text{C}(=\text{O})\text{OR}^{2b}$, $-\text{C}(=\text{O})\text{NHR}^{2b}$, $-\text{NHC}(=\text{NH})\text{NHR}^{2b}$, $-\text{NHR}^{2b}$, SR^{2b} , imidazolyl, indolyl, $-\text{SCH}_3$, phenyl, and 4-hydroxyphenyl, said C_{1-6} alkoxy, alkoxyalkyl, aryl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and alkyl in $(\text{R}^e\text{R}^f\text{N})\text{alkyl}$ each optionally substituted with one or more R^4 , or optionally two vicinal R^2 and the carbons to which they are attached are together a fused three- to six-membered carbocyclic ring optionally substituted with up to two C_{1-6} alkyl groups;

R^{2b} is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

each R^{2c} is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, said alkyl optionally substituted with $\text{R}^e\text{R}^f\text{N}-$, alkoxy, or C_{1-6} alkylS-;

each $\mathbf{R^aR^bN}$ is separately selected, wherein $\mathbf{R^a}$ and $\mathbf{R^b}$ are each separately selected from the group consisting of hydrogen, C_{2-6} alkenyl, and C_{1-6} alkyl;

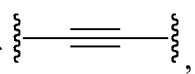
$\mathbf{L^4}$ is selected from the group consisting of $-(\mathbf{J^2})_s-(\mathbf{L^5})_s-(\mathbf{J^2})_s-(\mathbf{L^5})_s-\mathbf{J^2}-$,

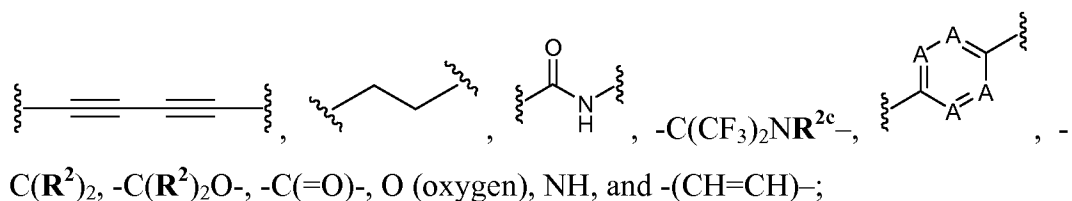


$\mathbf{J^2}$ is aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, or polycyclic hydrocarbon, each optionally substituted with one or more $\mathbf{R^{15}}$;

each $\mathbf{R^{14}}$ is separately selected from the group consisting of hydroxy, C_{1-6} alkoxy optionally substituted with up to 9 fluoro, C_{1-6} alkyl OC_{1-6} alkyl, C_{1-6} alkyl $\text{OC}(=\text{O})-$, arylalkyl $\text{OC}(=\text{O})-$, $-\text{COOH}$, halo, and C_{1-6} alkyl optionally substituted with up to 9 halo;

each $\mathbf{R^{15}}$ is separately selected from the group consisting of halo, hydroxy, C_{1-6} alkyl OC_{1-6} alkyl, C_{1-6} alkyl $\text{OC}(=\text{O})-$, arylalkyl $\text{OC}(=\text{O})-$, $-\text{COOH}$, $\mathbf{R^9}$, $\mathbf{R^xR^yN}$, $\mathbf{R^xR^yNC}(=\text{O})$, $\mathbf{R^xR^yNC}_{1-6}$ alkyl, heteroaryl, aryl, C_{1-6} alkyl optionally substituted with up to 9 halo, C_{1-6} alkyl substituted with up to 5 hydroxy, C_{1-6} alkoxy optionally substituted with up to 9 halo, C_{1-6} haloalkyl, $\mathbf{R^aR^bN}-$, $(\mathbf{R^aR^bN})\text{alkyl}$, $(\mathbf{R^aR^bN})\text{C}(=\text{O})-$, C_{1-6} alkyl substituted with up to 5 hydroxy, said substituent aryl and heteroaryl are each optionally substituted with one or more $\mathbf{R^{14}}$, or optionally two vicinal $\mathbf{R^{15}}$ and the carbons to which they are attached are together a fused three- to six-membered carbocyclic ring optionally substituted with up to two C_{1-6} alkyl groups, or optionally two geminal $\mathbf{R^{15}}$ and the carbon to which they are attached are together a three- to six-membered carbocyclic ring optionally substituted with up to two C_{1-6} alkyl groups, or optionally two geminal $\mathbf{R^{15}}$ are together oxo;

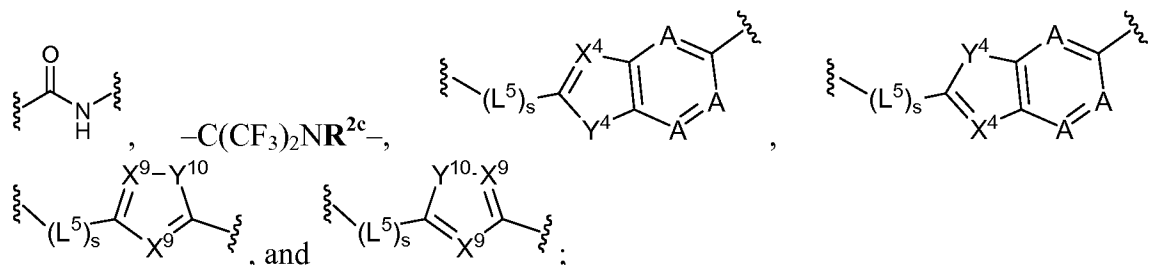
each $\mathbf{L^5}$ is separately selected from the group consisting of ,



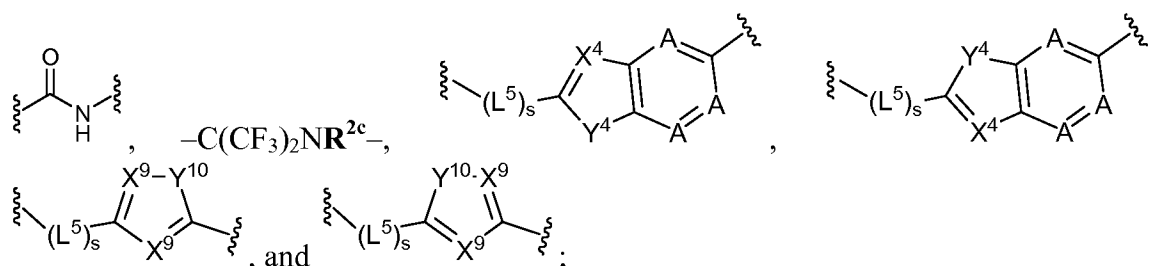
each **A** is separately selected from the group consisting of CR^3 and N (nitrogen);

each R^3 is separately selected from the group consisting of hydrogen, C_{1-6} alkoxy, C_{1-6} alkylOC $_{1-6}$ alkyl, C_{1-6} alkylOC(=O)–, arylalkylOC(=O)–, –COOH, halo, hydroxy, $\text{R}^a\text{R}^b\text{N}$ –, $(\text{R}^a\text{R}^b\text{N})$ alkyl, $(\text{R}^a\text{R}^b\text{N})\text{C}(=\text{O})$ –, C_{1-6} alkyl optionally substituted with up to 9 halo and up to 5 hydroxy;

L^6 is selected from the group consisting of



L^7 is selected from the group consisting of



each X^4 is separately selected from the group consisting of CR^4 and N (nitrogen);

each Y^4 is separately selected from the group consisting of $\text{C}(\text{R}^4)_2$, NR^4 , O (oxygen), and S (sulfur);

each X^9 is separately selected from the group consisting of CH and N (nitrogen);

each Y^{10} is separately selected from the group consisting of $-\text{CH}_2-$ and $-\text{NH}-$;

each **m** separately is 1 or 2;

each **n** separately is 0, 1 or 2;

each **p** separately is 1, 2, 3 or 4;

each **q** separately is 1, 2, 3, 4 or 5;

each **r** separately is 0, 1, 2, 3, or 4;

each **s** separately is 0 or 1;

each R^4 is separately selected from the group consisting of H (hydrogen), C_{1-6} alkoxy, C_{1-6} alkylOC $_{1-6}$ alkyl, C_{1-6} alkylOC(=O)–, arylalkylOC(=O)–, –COOH, halo, C_{1-6} haloalkyl, hydroxy, R^aR^bN –, (R^aR^bN) alkyl, $(R^aR^bN)C(=O)$ –, C_{1-6} alkyl optionally substituted with up to 9 halo and up to 5 hydroxy, or optionally two geminal R^4 are together oxo;

R^9 is selected from the group consisting of hydrogen and $-C(=O)R^{9a}$;

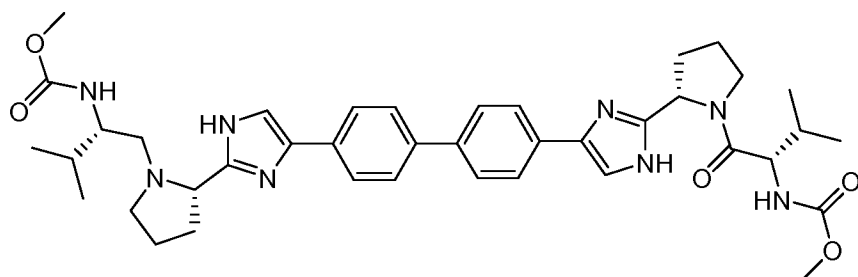
R^{9a} is selected from the group consisting of $-NR^{9b}R^{9c}$, $-OR^{9d}$, C_{1-6} alkyl optionally substituted with up to 9 halo, and optionally substituted aryl;

R^{9b} is selected from the group consisting of hydrogen, C_{1-6} alkyl optionally substituted with up to 9 halo, and optionally substituted aryl;

R^{9c} is selected from the group consisting of C_{1-6} alkyl optionally substituted with up to 9 halo, and optionally substituted aryl; and

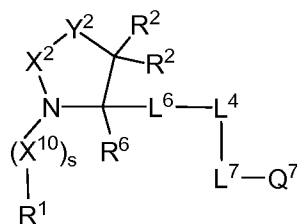
R^{9d} is selected from the group consisting of C_{1-6} alkyl optionally substituted with up to 9 halo, and optionally substituted aryl.

[0017] In some embodiments, the compound of Formula **XVI** has the structure:



[0018] In some embodiments of Formula **XVI**, R^6 can be methyl.

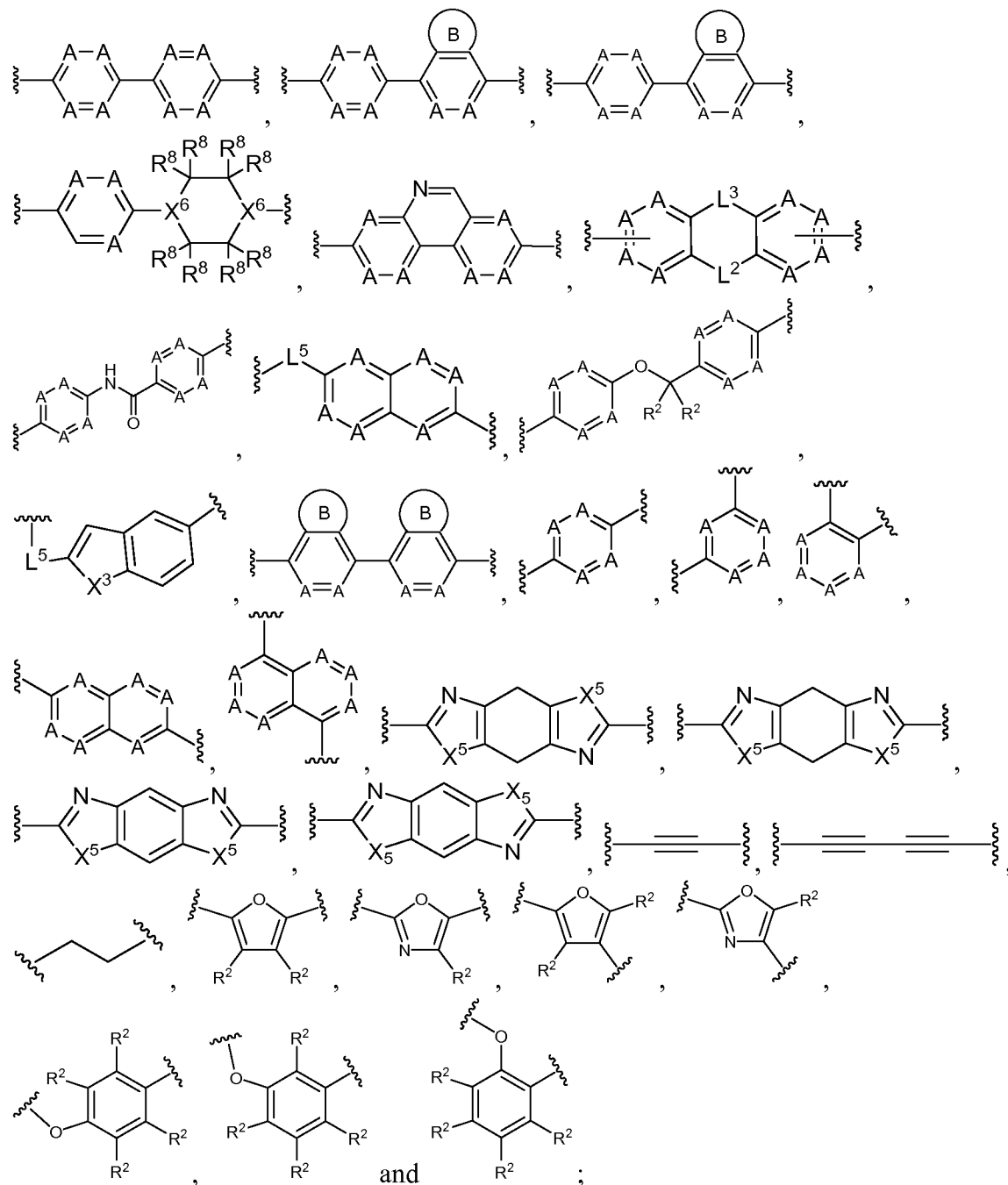
[0019] In some embodiments, the compound of Formula **XVI** has the structure of Formula **XVIa**:



XVIa

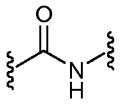
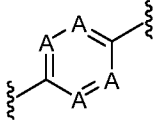
or a pharmaceutically acceptable salt thereof, wherein R^6 can be C_{1-6} alkyl optionally substituted with up to 9 halo.

[0020] In some embodiments of Formula **XVIa**, **L⁴** can be selected from the group consisting of



$\mathbf{L}^2$ can be selected from the group consisting of $-\text{C}(=\text{O})-$, $-(\text{CH}_2\text{CH}_2)-$, $-(\text{CH}_2\text{O})-$, $-(\text{CH}_2\text{S})-$, $-(\text{CH}=\text{CH})-$, $-(\text{CH}=\text{N})-$, $-\text{NH}-$, O (oxygen), S (sulfur), and $-\text{CH}_2-$;

L^3 can be selected from the group consisting of , $-(NR^9)-$, O (oxygen), S (sulfur), and $-CH_2-$;

L^5 can be selected from the group consisting of , , O (oxygen), NH, and $-(CH=CH)-$;

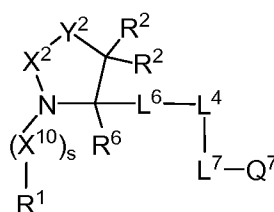
each X^3 can separately be selected from the group consisting of NH, O (oxygen), and S (sulfur);

each X^5 can separately be selected from the group consisting of $-NH-$, O (oxygen), S (sulfur), and $-CH_2-$;

each X^6 can separately be selected from the group consisting of N (nitrogen), and CR^8 ; and

each **B** can separately be selected, wherein **B** can be a fused optionally substituted saturated or unsaturated three- to seven-membered carbocyclic ring or a fused optionally substituted saturated or unsaturated three- to seven-membered heterocyclic ring, each optionally substituted with one or more R^4 .

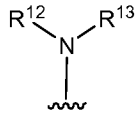
[0021] Some embodiments provide a compound having the structure of Formula **XVII**:

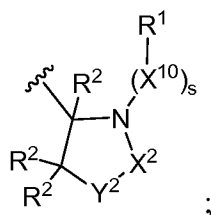


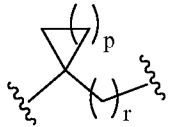
XVII

or a pharmaceutically acceptable salt thereof,

wherein:

Q^7 is selected from the group consisting of , and

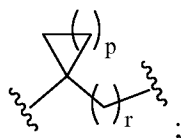


each X^2 is $(C(R^2)_2)_q$, , or X^2 is null;

each Y^2 is selected from O (oxygen), S (sulfur), S(O), SO_2 , NR^2 , and $C(R^2)_2$ with the proviso that when X^2 is null Y^2 is $C(R^2)_2$;

each X^{10} is $(C(R^2)_2)_q$;

each X^{11} is separately selected from the group consisting of $(C(R^2)_2)_q$, and



each Y^{11} is separately selected from the group consisting of $-O(C(R^2)_2)_n$, $-S(C(R^2)_2)_n$, $-S(O)(C(R^2)_2)_n$, $-SO_2(C(R^2)_2)_n$, $-NR^2(C(R^2)_2)_n$, and $(C(R^2)_2)_q$;

each $R^{12}R^{13}N$ is separately selected, wherein R^{12} and R^{13} are each separately selected from hydrogen, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r$ -, $[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r$ -, $Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxyC(=O)-, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)-, C_{3-7} cycloalkylC(=O)-, C_{1-6} alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, (R^eR^fN) alkyl, (R^eR^fN) alkylC(=O)-, and $(R^eR^fN)C(=O)-$,

said alkoxyalkyl, alkoxyC(=O)-, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)-, C_{3-7} cycloalkylC(=O)-, C_{1-6} alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, and alkyl in (R^eR^fN) alkyl and (R^eR^fN) alkylC(=O)- are each optionally substituted with one or more R^{1ab} ;

or $R^{12}R^{13}N$ is a heterocyclyl linked through a ring nitrogen atom optionally substituted with one or more of oxo, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r$ -, $[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r$ -, $Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxyC(=O)-, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)-, C_{3-7} cycloalkylC(=O)-, C_{1-6} alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-,

arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, ($R^e R^f N$)alkyl, ($R^e R^f N$)alkylC(=O)–, and ($R^e R^f N$)C(=O)–,

said alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, and alkyl in ($R^e R^f N$)alkyl and ($R^e R^f N$)alkylC(=O)– are each optionally substituted with one or more R^{1ab} ;

each R^{1ab} is separately selected from the group consisting of $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, $-C(R^{2a})_2NR^{3a}R^{3b}$, alkoxyalkyl, C_{1-6} alkylOC(=O)–, C_{1-6} alkylOC(=O) C_{1-6} alkyl, C_{1-6} alkylC(=O) C_{1-6} alkyl, aryl, aryl(CH₂)_n–, aryl(CH₂)_nO–, aryl(CH=CH)_m–, arylalkylO–, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)(CH=CH)_m–, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclyl, heterocyclyl(CH=CH)_m–, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, $R^e R^d N$ –, $R^e R^d N(CH_2)_n$ –, ($R^e R^d N$)(CH=CH)_m–, ($R^e R^d N$)alkyl, ($R^e R^d N$)C(=O)–, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9 halo;

each R^{80} is separately selected from the group consisting of hydrogen, alkoxyalkyl, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and ($R^e R^f N$)alkyl, said alkoxyalkyl, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and alkyl in ($R^e R^f N$)alkyl are each optionally substituted with one or more R^{1ac} ;

each R^{1ac} is separately selected from the group consisting of $-C(R^{2a})_2NR^{3a}R^{3b}$, alkoxyalkyl, C_{1-6} alkylOC(=O)–, C_{1-6} alkylOC(=O) C_{1-6} alkyl,

C₁₋₆alkylC(=O)C₁₋₆alkyl, aryl, aryl(CH₂)_n-, aryl(CH₂)_nO-, aryl(CH=CH)_m-, arylalkylO-, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)(CH=CH)_m-, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclyl, heterocyclyl(CH=CH)_m-, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, **R^cR^dN**-, **R^cR^dN**(CH₂)_n-, (**R^cR^dN**)(CH=CH)_m-, (**R^cR^dN**)alkyl, (**R^cR^dN**)C(=O)-, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each **Y¹⁴** is separately selected from the group consisting of -C(=O)-, -S(=O)-, -C(=S)-, -S(=O)₂-, -C(=O)O-, -C(=O)NR^{2c}-, -S(=O)₂NR^{2c}-, -C(=O)NR^{2c}C(=O)-, and -C(CF₃)₂NR^{2c}-,

R¹ is selected from the group consisting of **R^{1aa}**, **R^{1a}C(=O)-** and **R^{1a}C(=S)-**;

each **R^{1a}** is separately selected from the group consisting of -C(**R^{2a}**)₂NR^{3a}R^{3b}, alkoxyalkyl, C₁₋₆alkylOC(=O)-, C₁₋₆alkylOC(=O)C₁₋₆alkyl, C₁₋₆alkylC(=O)C₁₋₆alkyl, aryl, aryl(CH₂)_n-, aryl(CH₂)_nO-, aryl(CH=CH)_m-, arylalkylO-, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)(CH=CH)_m-, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclyl, heterocyclyl(CH=CH)_m-, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, **R^cR^dN**-, **R^cR^dN**(CH₂)_n-, (**R^cR^dN**)(CH=CH)_m-, (**R^cR^dN**)alkyl, (**R^cR^dN**)C(=O)-, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

R^{1aa} is selected from the group consisting of -C(**R^{2a}**)₂NR^{3a}R^{3b}, -[(**Y¹⁴**)(C(**R²**)₂)_r(NR²)_s(C(**R²**)₂)_r]-[**Y¹⁴**(C(**R²**)₂)_r(NR²)_s(C(**R²**)₂)_r]-(**Y¹⁴**)_s-**R⁸⁰**, -[(**Y¹⁴**)(C(**R²**)₂)_r(NR²)_s(C(**R²**)₂)_r]-**Y¹⁴**(C(**R²**)₂)_rO(C(**R²**)₂)_r-(**Y¹⁴**)_s-**R⁸⁰**, alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-,

heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, ($R^e R^f N$)alkyl, ($R^e R^f N$)alkylC(=O)–, and ($R^e R^f N$)C(=O)–,

said alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, and alkyl in ($R^e R^f N$)alkyl and ($R^e R^f N$)alkylC(=O)– are each optionally substituted with one or more R^{1ab} ;

each R^{10} is $R^c R^d N$ –;

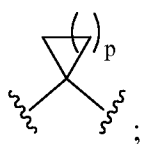
each R^{11} is separately selected from the group consisting of H (hydrogen), alkoxyalkyl, C_{1-6} alkylOC(=O) C_{1-6} alkyl, C_{1-6} alkylC(=O) C_{1-6} alkyl, aryl(CH₂)_n–, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, $R^c R^d N(CH_2)_n$ –, ($R^c R^d N$)alkyl, and C_{1-6} alkyl optionally substituted with up to 9 halo;

each $R^c R^d N$ is separately selected, wherein R^c and R^d are each separately selected from hydrogen, alkoxyC(=O)–, C_{1-6} alkyl, C_{1-6} alkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, ($R^e R^f N$)alkyl, ($R^e R^f N$)alkylC(=O)–, and ($R^e R^f N$)C(=O)–, wherein the alkyl part of arylalkyl, arylalkylC(=O)–, heterocyclylalkyl, and heterocyclylalkylC(=O)– are each optionally substituted with one $R^e R^f N$ – group; and wherein the aryl part of arylalkyl, arylalkylC(=O)–, arylC(=O)–, and arylsulfonyl, and the heterocyclyl part of heterocyclylalkyl, heterocyclylalkylC(=O)–, and heterocyclylC(=O)– are each optionally substituted with up to three substituents each independently selected from the group consisting of cyano, halo, nitro, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9 halo;

each $R^e R^f N$ is separately selected, wherein R^e and R^f are each separately selected from hydrogen, C_{1-6} alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, heterocyclylalkyl, ($R^x R^y N$)alkyl, and ($R^x R^y N$)C(=O)–;

each $\mathbf{R}^x\mathbf{R}^y\mathbf{N}$ is separately selected, wherein $\mathbf{R}^x$ and $\mathbf{R}^y$ are each separately selected from hydrogen, $\text{C}_{1-6}\text{alkylOC(=O)-}$, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylC(=O)-}$, aryl, arylalkyl, cycloalkyl, and heterocyclyl;

each $\text{C}(\mathbf{R}^{2a})_2$ is separately selected, wherein each $\mathbf{R}^{2a}$ is separately selected from the group consisting of hydrogen, $\text{C}_{1-6}\text{alkyl}$ optionally substituted with up to 9 halo, $\text{aryl}(\text{CH}_2)_n-$, and $\text{heteroaryl}(\text{CH}_2)_n-$, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, $\text{C}_{1-6}\text{alkoxy}$ optionally substituted with up to 9 halo, and $\text{C}_{1-6}\text{alkyl}$ optionally substituted with up to 9

halo, or optionally $\text{C}(\mathbf{R}^{2a})_2$ is ;

each $\mathbf{R}^{3a}$ is separately selected from the group consisting of hydrogen, and optionally substituted $\text{C}_{1-6}\text{alkyl}$;

each $\mathbf{R}^{3b}$ is separately selected from the group consisting of optionally substituted $\text{C}_{1-6}\text{alkyl}$, heteroaryl, $-(\text{CH}_2)_n\text{C(=O)NR}^{4a}\mathbf{R}^{4b}$, $-(\text{CH}_2)_n\text{C(=O)OR}^{5a}$, and $-(\text{CH}_2)_n\text{C(=O)R}^{6a}$ said heteroaryl optionally substituted with cyano, halo, nitro, hydroxyl, $\text{C}_{1-6}\text{alkoxy}$ optionally substituted with up to 9 halo, and $\text{C}_{1-6}\text{alkyl}$ optionally substituted with up to 9 halo;

each $\mathbf{R}^{4a}\mathbf{R}^{4b}\mathbf{N}$ is separately selected, wherein $\mathbf{R}^{4a}$ and $\mathbf{R}^{4b}$ are each separately selected from the group consisting of hydrogen, optionally substituted $\text{C}_{1-6}\text{alkyl}$, and $\text{aryl}(\text{CH}_2)_n-$;

each $\mathbf{R}^{5a}$ is separately selected from the group consisting of optionally substituted $\text{C}_{1-6}\text{alkyl}$, and $\text{aryl}(\text{CH}_2)_n-$;

each $\mathbf{R}^{6a}$ is separately selected from the group consisting of optionally substituted $\text{C}_{1-6}\text{alkyl}$, and $\text{aryl}(\text{CH}_2)_n-$;

each $\mathbf{A}^1$ is separately selected from the group consisting of $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{1-6}\text{alkyl}$, and $-(\text{CH}_2)_n\text{-O-(CH}_2)_m-$, each optionally substituted with one or more $\mathbf{R}^2$;

each $\mathbf{R}^2$ is separately selected, wherein $\mathbf{R}^2$ is selected from the group consisting of protium, halo, hydroxy, $\text{C}_{1-6}\text{alkoxy}$, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, alkoxyalkyl, $\text{C}_{3-7}\text{cycloalkyl}$, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, $(\mathbf{R}^e\mathbf{R}^f\mathbf{N})\text{alkyl}$, $\mathbf{R}^a\mathbf{R}^b\mathbf{N}-$, said $\text{C}_{1-6}\text{alkyl}$ optionally substituted with one or more halo, $-\text{OR}^{2b}$, $-\text{C(=O)OR}^{2b}$, -

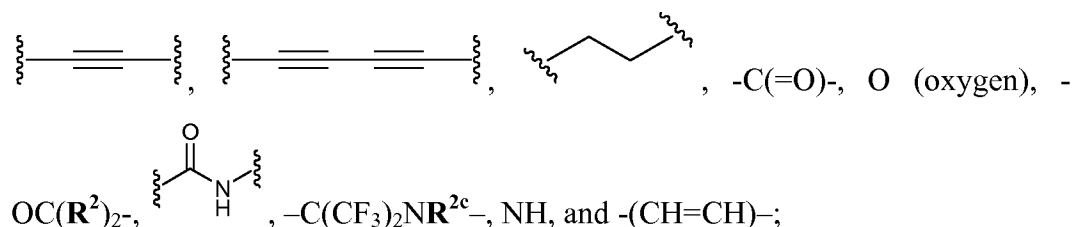
$C(=O)NHR^{2b}$, $-NHC(=NH)NHR^{2b}$, $-NHR^{2b}$, SR^{2b} , imidazolyl, indolyl, $-SCH_3$, phenyl, and 4-hydroxyphenyl, said C_{1-6} alkoxy, alkoxyalkyl, aryl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclalkyl, and alkyl in $(R^e R^f N)$ alkyl each optionally substituted with one or more R^4 , or optionally two vicinal R^2 and the carbons to which they are attached are together a fused three- to six-membered carbocyclic ring optionally substituted with up to two C_{1-6} alkyl groups;

R^{2b} is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclalkyl;

each R^{2c} is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclalkyl, said alkyl optionally substituted with $R^e R^f N$ -, alkoxy, or C_{1-6} alkylS-;

each $R^a R^b N$ is separately selected, wherein R^a and R^b are each separately selected from the group consisting of hydrogen, C_{2-6} alkenyl, and C_{1-6} alkyl;

L^4 is selected from the group consisting of $-J^2-(L^5)_s-(J^2)_s-(L^5)_s-J^2-$, $-J^2-$,

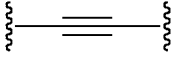
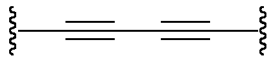
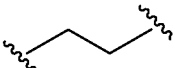


each J^2 is phenyl optionally substituted with one or more R^{15} ;

each R^{14} is separately selected from the group consisting of hydroxy, C_{1-6} alkoxy optionally substituted with up to 9 fluoro, C_{1-6} alkylOC C_{1-6} alkyl, C_{1-6} alkylOC(=O)-, arylalkylOC(=O)-, $-COOH$, halo, and C_{1-6} alkyl optionally substituted with up to 9 halo;

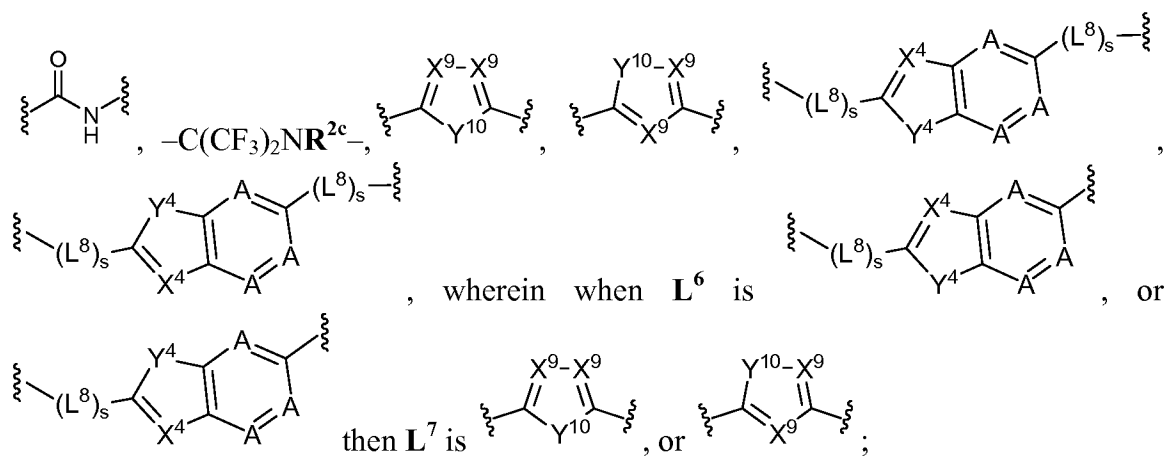
each R^{15} is separately selected from the group consisting of halo, hydroxy, C_{1-6} alkylOC C_{1-6} alkyl, C_{1-6} alkylOC(=O)-, arylalkylOC(=O)-, $-COOH$, R^9 , $R^x R^y N$, $R^x R^y NC(=O)$, $R^x R^y NC_{1-6}$ alkyl, heteroaryl, aryl, C_{1-6} alkyl optionally substituted with up to 9 halo, C_{1-6} alkyl substituted with up to 5 hydroxy, C_{1-6} alkoxy optionally substituted with up to 9 halo, C_{1-6} haloalkyl, $R^a R^b N$ -, $(R^a R^b N)$ alkyl, $(R^a R^b N)C(=O)-$, C_{1-6} alkyl substituted with up to 5 hydroxy, said substituent aryl and heteroaryl are each optionally substituted with one or more R^{14} , or optionally

two vicinal R^{15} and the carbons to which they are attached are together a fused three- to six-membered carbocyclic ring optionally substituted with up to two C_{1-6} alkyl groups, or optionally two geminal R^{15} and the carbon to which they are attached are together a three- to six-membered carbocyclic ring optionally substituted with up to two C_{1-6} alkyl groups, or optionally two geminal R^{15} are together oxo;

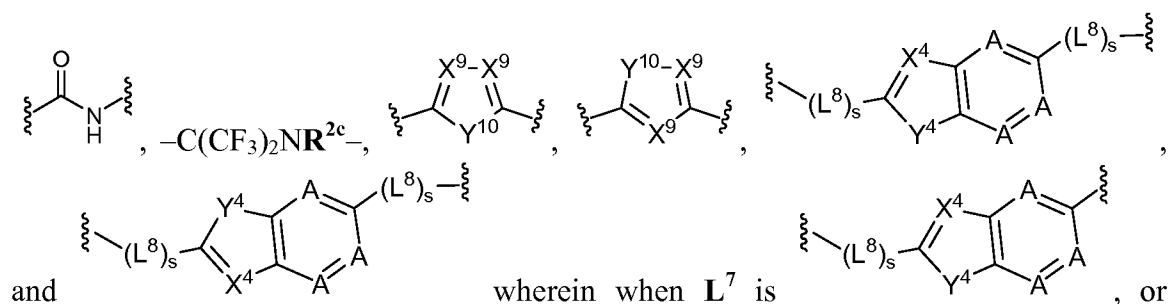
each L^5 is separately selected from the group consisting of , , , $-C(CF_3)_2NR^{2c}-$, $-C(R^2)_2-$, $-C(=O)-$, O (oxygen), NH, and $-(CH=CH)-$;

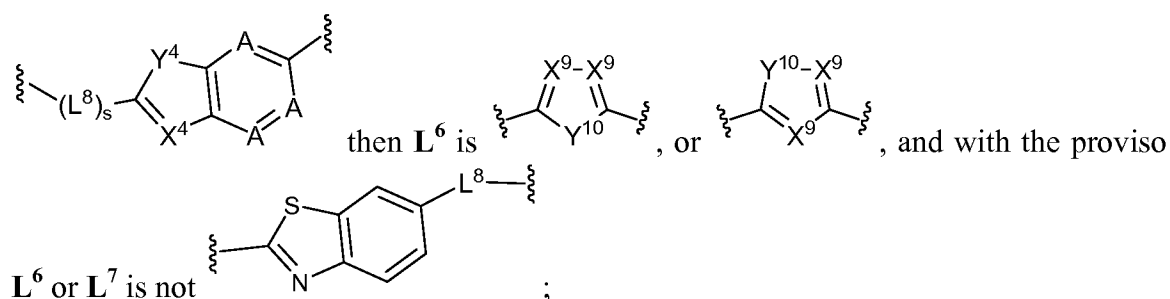
each A is separately selected from the group consisting of CR^3 and N (nitrogen);

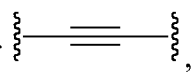
L^6 is selected from the group consisting of

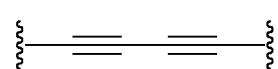
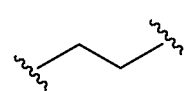
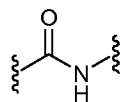


L^7 is selected from the group consisting of





each L^8 is separately selected from the group consisting of ,

, , , $-C(CF_3)_2NR^{2c}-$, $-C(R^2)_2-$, $-C(R^2)_2O-$, $-C(=O)-$, O (oxygen), NH, and $-(CH=CH)-$;

each X^4 is separately selected from the group consisting of CR^4 and N (nitrogen);

each Y^4 is separately selected from the group consisting of $C(R^4)_2$, NR^4 , O (oxygen), and S (sulfur);

each X^9 is separately selected from the group consisting of CH and N (nitrogen);

each Y^{10} is separately selected from the group consisting of $-CH_2-$ and $-NH-$;

each m separately is 1 or 2;

each n separately is 0, 1 or 2;

each p separately is 1, 2, 3 or 4;

each q separately is 1, 2, 3, 4 or 5;

each r separately is 0, 1, 2, 3, or 4;

each s separately is 0 or 1;

each R^3 is separately selected from the group consisting of hydrogen, C_{1-6} alkoxy, C_{1-6} alkylOC $_{1-6}$ alkyl, C_{1-6} alkylOC(=O)–, arylalkylOC(=O)–, $-COOH$, halo, hydroxy, R^aR^bN- , (R^aR^bN) alkyl, $(R^aR^bN)C(=O)-$, C_{1-6} alkyl optionally substituted with up to 9 halo and up to 5 hydroxy;

each R^4 is separately selected from the group consisting of H (hydrogen), C_{1-6} alkoxy, C_{1-6} alkylOC $_{1-6}$ alkyl, C_{1-6} alkylOC(=O)–, arylalkylOC(=O)–, $-COOH$, halo, C_{1-6} haloalkyl, hydroxy, R^aR^bN- , (R^aR^bN) alkyl, $(R^aR^bN)C(=O)-$, C_{1-6} alkyl optionally substituted with up to 9 halo and up to 5 hydroxy, or optionally two geminal R^4 are together oxo;

R^6 is C_{1-6} alkyl optionally substituted with up to 9 halo;

R^9 is selected from the group consisting of hydrogen and $-C(=O)R^{9a}$;

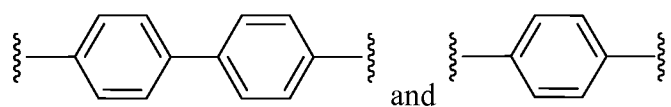
R^{9a} is selected from the group consisting of $-NR^{9b}R^{9c}$, $-OR^{9d}$, C_{1-6} alkyl optionally substituted with up to 9 halo, and optionally substituted aryl;

R^{9b} is selected from the group consisting of hydrogen, C_{1-6} alkyl optionally substituted with up to 9 halo, and optionally substituted aryl;

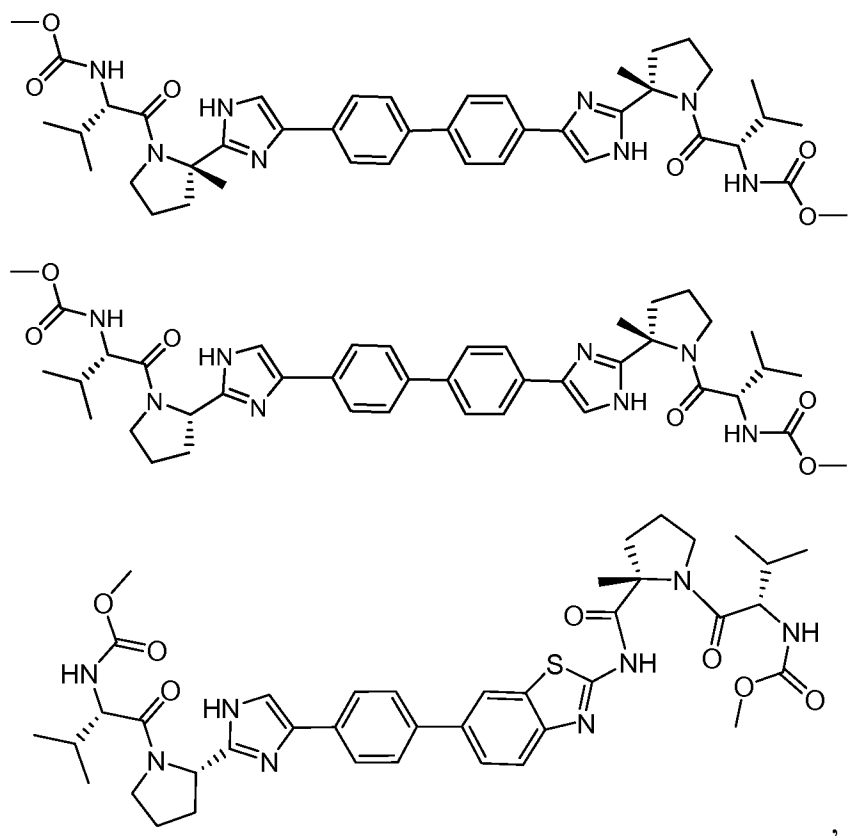
R^{9c} is selected from the group consisting of C_{1-6} alkyl optionally substituted with up to 9 halo, and optionally substituted aryl; and

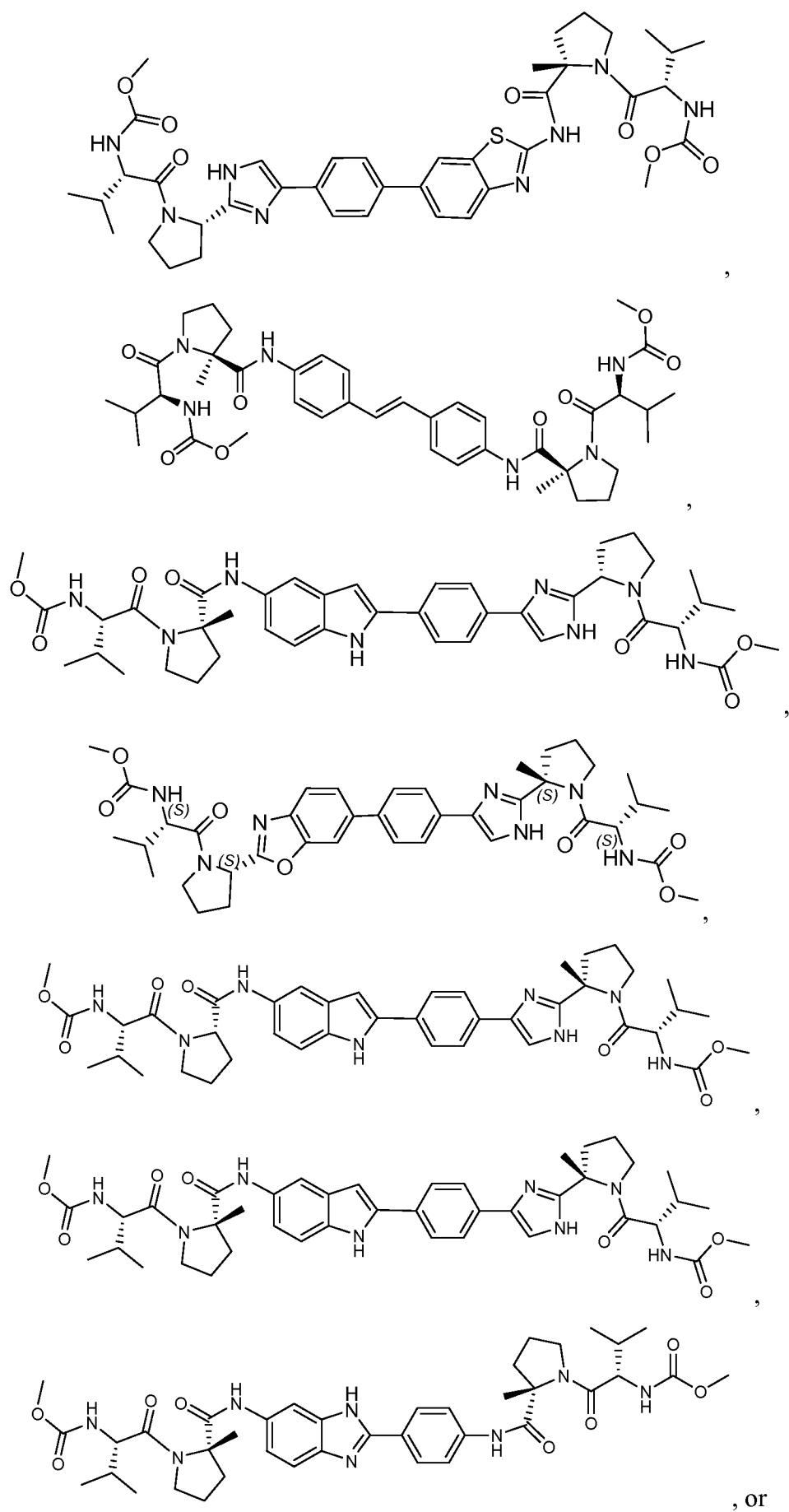
R^{9d} is selected from the group consisting of C_{1-6} alkyl optionally substituted with up to 9 halo, and optionally substituted aryl.

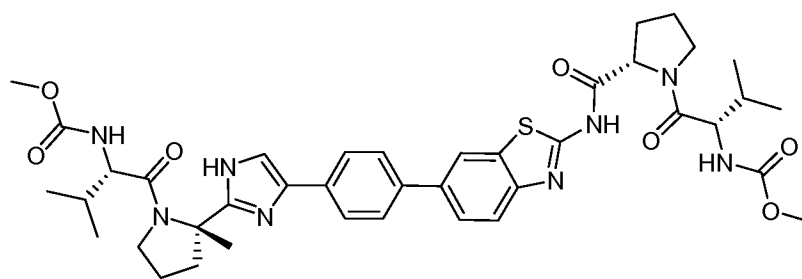
[0022] In some embodiments of Formula **XVII**, L^4 can be selected from the group consisting of



[0023] In some embodiments, the compound of Formula **XVI** has the structure:

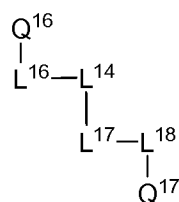






or a pharmaceutically acceptable salt thereof.

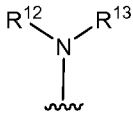
[0024] Some embodiments provide a compound having the structure of Formula XVIII:

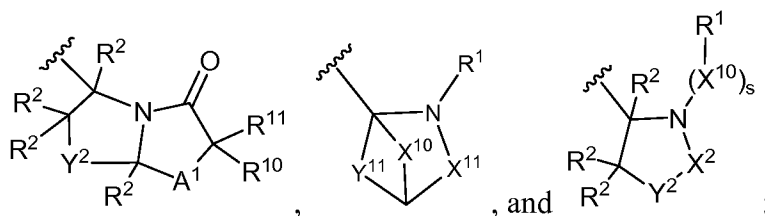


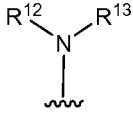
XVIII

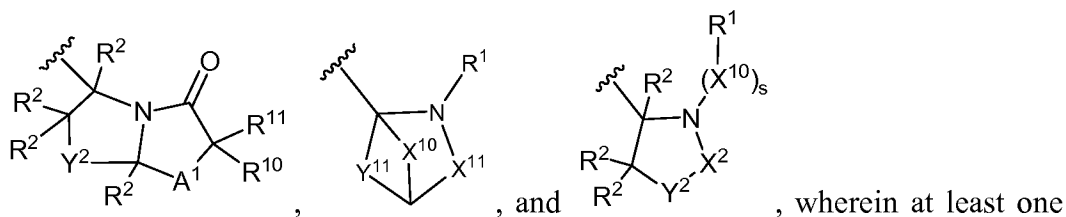
or a pharmaceutically acceptable salt thereof,

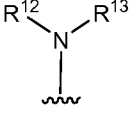
wherein:

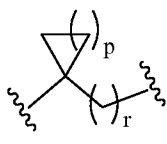
Q^{16} is selected from the group consisting of ,



Q^{17} is selected from the group consisting of ,



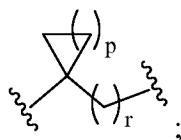
of Q^{16} and Q^{17} is not  ;

each $\mathbf{X}^2$ is $(\text{C}(\mathbf{R}^2)_2)_q$, , or $\mathbf{X}^2$ is null;

each $\mathbf{Y}^2$ is selected from O (oxygen), S (sulfur), S(O), SO₂, NR^2 , and $\text{C}(\mathbf{R}^2)_2$ with the proviso that when $\mathbf{X}^2$ is null $\mathbf{Y}^2$ is $\text{C}(\mathbf{R}^2)_2$;

each $\mathbf{X}^{10}$ is $(\text{C}(\mathbf{R}^2)_2)_q$;

each $\mathbf{X}^{11}$ is separately selected from the group consisting of $(\text{C}(\mathbf{R}^2)_2)_q$, and



each $\mathbf{Y}^{11}$ is separately selected from the group consisting of $-\text{O}(\text{C}(\mathbf{R}^2)_2)_n-$, $-\text{S}(\text{C}(\mathbf{R}^2)_2)_n-$, $-\text{S}(\text{O})(\text{C}(\mathbf{R}^2)_2)_n-$, $-\text{SO}_2(\text{C}(\mathbf{R}^2)_2)_n-$, $-\text{NR}^2(\text{C}(\mathbf{R}^2)_2)_n-$, and $(\text{C}(\mathbf{R}^2)_2)_q$;

each $\mathbf{R}^{12}\mathbf{R}^{13}\text{N}$ is separately selected, wherein $\mathbf{R}^{12}$ and $\mathbf{R}^{13}$ are each separately selected from hydrogen, $-(\mathbf{Y}^{14})(\text{C}(\mathbf{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\mathbf{R}^2)_2)_r]-[\mathbf{Y}^{14}(\text{C}(\mathbf{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\mathbf{R}^2)_2)_r]_s-(\mathbf{Y}^{14})_s-\mathbf{R}^{80}$, $-(\mathbf{Y}^{14})(\text{C}(\mathbf{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\mathbf{R}^2)_2)_r]-[\mathbf{Y}^{14}(\text{C}(\mathbf{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\mathbf{R}^2)_2)_r]_s-(\mathbf{Y}^{14})_s-\mathbf{R}^{80}$, alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, $(\mathbf{R}^e\mathbf{R}^f\text{N})$ alkyl, $(\mathbf{R}^e\mathbf{R}^f\text{N})$ alkylC(=O)-, and $(\mathbf{R}^e\mathbf{R}^f\text{N})\text{C}(=\text{O})-$,

said alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, and alkyl in $(\mathbf{R}^e\mathbf{R}^f\text{N})$ alkyl and $(\mathbf{R}^e\mathbf{R}^f\text{N})$ alkylC(=O)- are each optionally substituted with one or more $\mathbf{R}^{1ab}$,

or $\mathbf{R}^{12}\mathbf{R}^{13}\text{N}$ is a heterocyclyl linked through a ring nitrogen atom optionally substituted with one or more of oxo, $-(\mathbf{Y}^{14})(\text{C}(\mathbf{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\mathbf{R}^2)_2)_r]-[\mathbf{Y}^{14}(\text{C}(\mathbf{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\mathbf{R}^2)_2)_r]_s-(\mathbf{Y}^{14})_s-\mathbf{R}^{80}$, $-(\mathbf{Y}^{14})(\text{C}(\mathbf{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\mathbf{R}^2)_2)_r]-[\mathbf{Y}^{14}(\text{C}(\mathbf{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\mathbf{R}^2)_2)_r]_s-(\mathbf{Y}^{14})_s-\mathbf{R}^{80}$,

$Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, (R^eR^fN) alkyl, (R^eR^fN) alkylC(=O)–, and $(R^eR^fN)C(=O)–$,

said alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, and alkyl in (R^eR^fN) alkyl and (R^eR^fN) alkylC(=O)– are each optionally substituted with one or more R^{1ab} ;

each R^{1ab} is separately selected from the group consisting of $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, $-C(R^{2a})_2NR^{3a}R^{3b}$, alkoxyalkyl, C_{1-6} alkylOC(=O)–, C_{1-6} alkylOC(=O) C_{1-6} alkyl, C_{1-6} alkylC(=O) C_{1-6} alkyl, aryl, aryl(CH₂)_n–, aryl(CH₂)_nO–, aryl(CH=CH)_m–, arylalkylO–, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)(CH=CH)_m–, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclyl, heterocyclyl(CH=CH)_m–, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, R^cR^dN –, $R^cR^dN(CH_2)_n$ –, $(R^cR^dN)(CH=CH)_m$ –, (R^cR^dN) alkyl, $(R^cR^dN)C(=O)–$, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9 halo;

each R^{80} is separately selected from the group consisting of hydrogen, alkoxyalkyl, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and (R^eR^fN) alkyl, said alkoxyalkyl, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylalkyl,

heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and alkyl in $(R^e R^f N)$ alkyl are each optionally substituted with one or more R^{1ac} ;

each R^{1ac} is separately selected from the group consisting of $-C(R^{2a})_2NR^{3a}R^{3b}$, alkoxyalkyl, $C_{1-6}alkylOC(=O)-$, $C_{1-6}alkylOC(=O)C_{1-6}alkyl$, $C_{1-6}alkylC(=O)C_{1-6}alkyl$, aryl, $aryl(CH_2)_n-$, $aryl(CH_2)_nO-$, $aryl(CH=CH)_m-$, $arylalkylO-$, $arylalkyl$, $arylOalkyl$, cycloalkyl, $(cycloalkyl)(CH=CH)_m-$, $(cycloalkyl)alkyl$, $cycloalkylOalkyl$, heterocyclyl, $heterocyclyl(CH=CH)_m-$, $heterocyclylalkoxy$, $heterocyclylalkyl$, $heterocyclylOalkyl$, hydroxyalkyl, $R^c R^d N-$, $R^c R^d N(CH_2)_n-$, $(R^c R^d N)(CH=CH)_m-$, $(R^c R^d N)alkyl$, $(R^c R^d N)C(=O)-$, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo;

each Y^{14} is separately selected from the group consisting of $-C(=O)-$, $-S(=O)-$, $-C(=S)-$, $-S(=O)_2-$, $-C(=O)O-$, $-C(=O)NR^{2c}-$, $-S(=O)_2NR^{2c}-$, $-C(=O)NR^{2c}C(=O)-$, and $-C(CF_3)_2NR^{2c}-$,

each R^1 is separately selected from the group consisting of R^{1aa} , $R^{1a}C(=O)-$ and $R^{1a}C(=S)-$;

each R^{1a} is separately selected from the group consisting of $-C(R^{2a})_2NR^{3a}R^{3b}$, alkoxyalkyl, $C_{1-6}alkylOC(=O)-$, $C_{1-6}alkylOC(=O)C_{1-6}alkyl$, $C_{1-6}alkylC(=O)C_{1-6}alkyl$, aryl, $aryl(CH_2)_n-$, $aryl(CH_2)_nO-$, $aryl(CH=CH)_m-$, $arylalkylO-$, $arylalkyl$, $arylOalkyl$, cycloalkyl, $(cycloalkyl)(CH=CH)_m-$, $(cycloalkyl)alkyl$, $cycloalkylOalkyl$, heterocyclyl, $heterocyclyl(CH=CH)_m-$, $heterocyclylalkoxy$, $heterocyclylalkyl$, $heterocyclylOalkyl$, hydroxyalkyl, $R^c R^d N-$, $R^c R^d N(CH_2)_n-$, $(R^c R^d N)(CH=CH)_m-$, $(R^c R^d N)alkyl$, $(R^c R^d N)C(=O)-$, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo;

each R^{1aa} is separately selected from the group consisting of $-C(R^{2a})_2NR^{3a}R^{3b}$, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-$, $[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-$, $Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxyC(=O)-, $C_{1-6}alkyl$,

C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, (R^eR^fN)alkyl, (R^eR^fN)alkylC(=O)-, and (R^eR^fN)C(=O)-,

said alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, and alkyl in (R^eR^fN)alkyl and (R^eR^fN)alkylC(=O)- are each optionally substituted with one or more R^{1ab};

each R¹⁰ is R^cR^dN-;

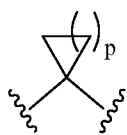
each R¹¹ is separately selected from the group consisting of H (hydrogen), alkoxyalkyl, C₁₋₆alkylOC(=O)C₁₋₆alkyl, C₁₋₆alkylC(=O)C₁₋₆alkyl, aryl(CH₂)_n-, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, R^cR^dN(CH₂)_n-, (R^cR^dN)alkyl, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each R^cR^dN is separately selected, wherein R^c and R^d are each separately selected from hydrogen, alkoxyC(=O)-, C₁₋₆alkyl, C₁₋₆alkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, (R^eR^fN)alkyl, (R^eR^fN)alkylC(=O)-, and (R^eR^fN)C(=O)-, wherein the alkyl part of arylalkyl, arylalkylC(=O)-, heterocyclylalkyl, and heterocyclylalkylC(=O)- are each optionally substituted with one R^eR^fN- group; and wherein the aryl part of arylalkyl, arylalkylC(=O)-, arylC(=O)-, and arylsulfonyl, and the heterocyclyl part of heterocyclylalkyl, heterocyclylalkylC(=O)-, and heterocyclylC(=O)- are each optionally substituted with up to three substituents each independently selected from the group consisting of cyano, halo, nitro, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each $\mathbf{R}^e\mathbf{R}^f\mathbf{N}$ is separately selected, wherein $\mathbf{R}^e$ and $\mathbf{R}^f$ are each separately selected from hydrogen, C_{1-6} alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, heterocyclalkyl, $(\mathbf{R}^x\mathbf{R}^y\mathbf{N})\text{alkyl}$, and $(\mathbf{R}^x\mathbf{R}^y\mathbf{N})\text{C(=O)-}$;

each $\mathbf{R}^x\mathbf{R}^y\mathbf{N}$ is separately selected, wherein $\mathbf{R}^x$ and $\mathbf{R}^y$ are each separately selected from hydrogen, $\text{C}_{1-6}\text{alkylOC(=O)-}$, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylC(=O)-}$, aryl, arylalkyl, cycloalkyl, and heterocyclyl;

each $\text{C}(\mathbf{R}^{2a})_2$ is separately selected, wherein each $\mathbf{R}^{2a}$ is separately selected from the group consisting of hydrogen, C_{1-6} alkyl optionally substituted with up to 9 halo, $\text{aryl}(\text{CH}_2)_n-$, and $\text{heteroaryl}(\text{CH}_2)_n-$, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9

halo, or optionally $\text{C}(\mathbf{R}^{2a})_2$ is  ;

each $\mathbf{R}^{3a}$ is separately selected from the group consisting of hydrogen, and optionally substituted C_{1-6} alkyl;

each $\mathbf{R}^{3b}$ is separately selected from the group consisting of optionally substituted C_{1-6} alkyl, heteroaryl, $-(\text{CH}_2)_n\text{C(=O)NR}^{4a}\mathbf{R}^{4b}$, $-(\text{CH}_2)_n\text{C(=O)OR}^{5a}$, and $-(\text{CH}_2)_n\text{C(=O)}\mathbf{R}^{6a}$ said heteroaryl optionally substituted with cyano, halo, nitro, hydroxyl, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9 halo;

each $\mathbf{R}^{4a}\mathbf{R}^{4b}\mathbf{N}$ is separately selected, wherein $\mathbf{R}^{4a}$ and $\mathbf{R}^{4b}$ are each separately selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, and $\text{aryl}(\text{CH}_2)_n-$;

each $\mathbf{R}^{5a}$ is separately selected from the group consisting of optionally substituted C_{1-6} alkyl, and $\text{aryl}(\text{CH}_2)_n-$;

each $\mathbf{R}^{6a}$ is separately selected from the group consisting of optionally substituted C_{1-6} alkyl, and $\text{aryl}(\text{CH}_2)_n-$;

each $\mathbf{A}^1$ is separately selected from the group consisting of C_{2-6} alkenyl, C_{1-6} alkyl, and $-(\text{CH}_2)_n\text{-O}-(\text{CH}_2)_m-$, each optionally substituted with one or more $\mathbf{R}^2$;

each $\mathbf{R}^2$ is separately selected, wherein $\mathbf{R}^2$ is selected from the group consisting of hydrogen, halo, hydroxy, C_{1-6} alkoxy, C_{1-6} alkyl, C_{2-6} alkenyl,

C₂₋₆alkynyl, alkoxyalkyl, C₃₋₇cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, (R^eR^fN)alkyl, R^aR^bN-, said C₁₋₆alkyl optionally substituted with one or more halo, -OR^{2b}, -C(=O)OR^{2b}, -C(=O)NHR^{2b}, -NHC(=NH)NHR^{2b}, -NHR^{2b}, SR^{2b}, imidazolyl, indolyl, -SCH₃, phenyl, and 4-hydroxyphenyl, said C₁₋₆alkoxy, alkoxyalkyl, aryl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and alkyl in (R^eR^fN)alkyl each optionally substituted with one or more R⁴, or optionally two vicinal R² and the carbons to which they are attached are together a fused three- to six-membered carbocyclic ring optionally substituted with up to two C₁₋₆alkyl groups;

R^{2b} is selected from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

each R^{2c} is selected from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, said alkyl optionally substituted with R^eR^fN-, alkoxy, or C₁₋₆alkylS-;

each R^aR^bN is separately selected, wherein R^a and R^b are each separately selected from the group consisting of hydrogen, C₂₋₆alkenyl, and C₁₋₆alkyl;

L¹⁴ is -J¹¹-J²-J¹²-;

J² is aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, or polycyclic hydrocarbon, each optionally substituted with one or more R¹⁵;

J¹¹ is C(R⁴)₂, NR⁴, O (oxygen), or S (sulfur);

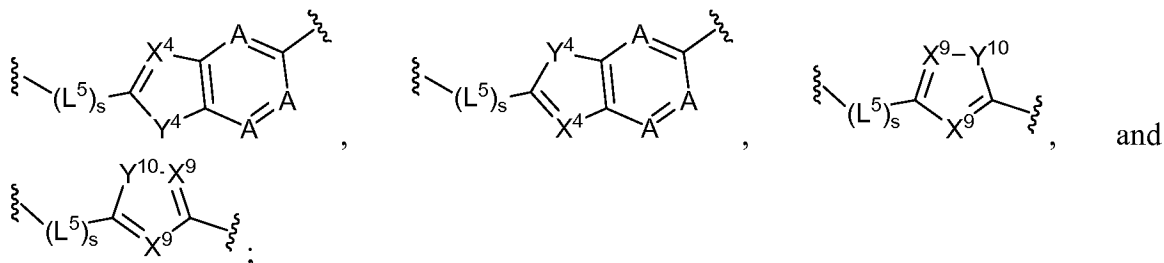
J¹² is -C(=O)-, S(O), SO₂, or -C(=NR⁴)-;

each R¹⁴ is separately selected from the group consisting of hydroxy, C₁₋₆alkoxy optionally substituted with up to 9 fluoro, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC(=O)-, arylalkylOC(=O)-, -COOH, halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each R¹⁵ is separately selected from the group consisting of halo, hydroxy, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC(=O)-, arylalkylOC(=O)-, -COOH, R⁹, R^xR^yN, R^xR^yNC(=O), R^xR^yNC₁₋₆alkyl, heteroaryl, aryl, C₁₋₆alkyl optionally substituted with up to 9 halo, C₁₋₆alkyl substituted with up to 5 hydroxy, C₁₋₆alkoxy optionally substituted with up to 9 halo, C₁₋₆haloalkyl, R^aR^bN-, (R^aR^bN)alkyl,

($R^a R^b N$)C(=O)–, C_{1-6} alkyl substituted with up to 5 hydroxy, said substituent aryl and heteroaryl are each optionally substituted with one or more R^{14} , or optionally two vicinal R^{15} and the carbons to which they are attached are together a fused three- to six-membered carbocyclic ring optionally substituted with up to two C_{1-6} alkyl groups, or optionally two geminal R^{15} and the carbon to which they are attached are together a three- to six-membered carbocyclic ring optionally substituted with up to two C_{1-6} alkyl groups, or optionally two geminal R^{15} are together oxo;

L^{16} is selected from the group consisting of



each L^5 is separately selected from the group consisting of

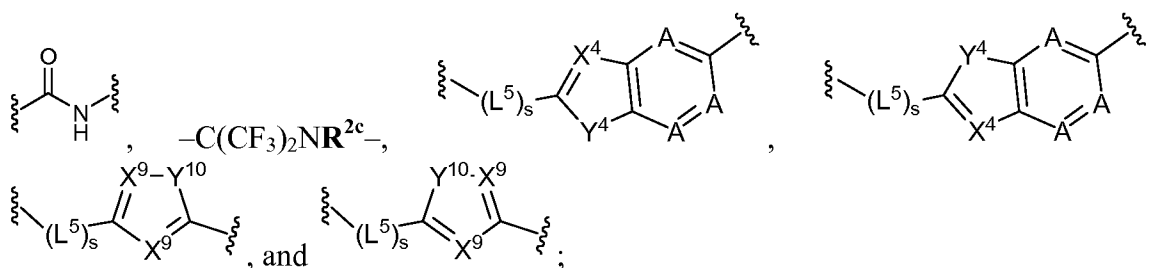
, , , $-C(CF_3)_2NR^{2c}-$, , $-C(R^2)_2$, $-C(R^2)_2O-$, $-C(=O)-$, O (oxygen), NH, and $-(CH=CH)-$;

each A is separately selected from the group consisting of CR^3 and N (nitrogen);

each R^3 is separately selected from the group consisting of hydrogen, C_{1-6} alkoxy, C_{1-6} alkylOC $_{1-6}$ alkyl, C_{1-6} alkylOC(=O)–, arylalkylOC(=O)–, $-COOH$, halo, hydroxy, $R^a R^b N$ –, ($R^a R^b N$)alkyl, ($R^a R^b N$)C(=O)–, C_{1-6} alkyl optionally substituted with up to 9 halo and up to 5 hydroxy;

L^{17} is selected from the group consisting of aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, or polycyclic hydrocarbon, each optionally substituted with one or more R^{15} ;

L^{18} is selected from the group consisting of



each X^4 is separately selected from the group consisting of CR^4 and N (nitrogen);

each Y^4 is separately selected from the group consisting of $C(R^4)_2$, NR^4 , O (oxygen), and S (sulfur);

each X^9 is separately selected from the group consisting of CH and N (nitrogen);

each Y^{10} is separately selected from the group consisting of $-CH_2-$ and $-NH-$;

each **m** separately is 1 or 2;

each **n** separately is 0, 1 or 2;

each **p** separately is 1, 2, 3 or 4;

each **q** separately is 1, 2, 3, 4 or 5;

each **r** separately is 0, 1, 2, 3, or 4;

each **s** separately is 0 or 1;

each R^4 is separately selected from the group consisting of H (hydrogen), C_{1-6} alkoxy, C_{1-6} alkylOC $_{1-6}$ alkyl, C_{1-6} alkylOC(=O)–, arylalkylOC(=O)–, $-COOH$, halo, C_{1-6} haloalkyl, hydroxy, R^aR^bN- , $(R^aR^bN)alkyl$, $(R^aR^bN)C(=O)-$, $C_{1-6}alkyl$ optionally substituted with up to 9 halo and up to 5 hydroxy, or optionally two geminal R^4 are together oxo;

R^9 is selected from the group consisting of hydrogen and $-C(=O)R^{9a}$;

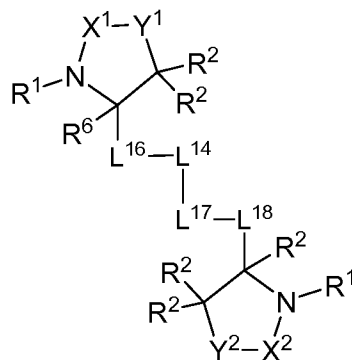
R^{9a} is selected from the group consisting of $-NR^{9b}R^{9c}$, $-OR^{9d}$, $C_{1-6}alkyl$ optionally substituted with up to 9 halo, and optionally substituted aryl;

R^{9b} is selected from the group consisting of hydrogen, $C_{1-6}alkyl$ optionally substituted with up to 9 halo, and optionally substituted aryl;

R^{9c} is selected from the group consisting of $C_{1-6}alkyl$ optionally substituted with up to 9 halo, and optionally substituted aryl; and

R^{9d} is selected from the group consisting of $C_{1-6}alkyl$ optionally substituted with up to 9 halo, and optionally substituted aryl.

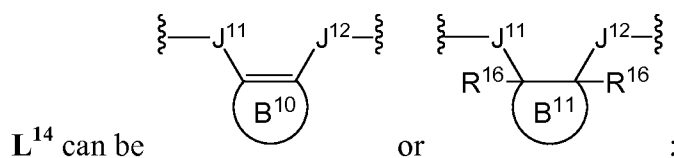
[0025] In some embodiments, the compound of Formula XVIII has the structure of Formula XVIIIa:



XVIIIa

or a pharmaceutically acceptable salt thereof,

wherein:

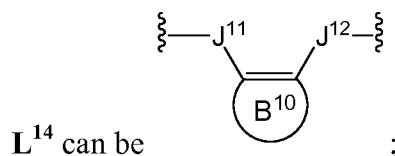


B^{10} can be aryl, heteroaryl, or cycloalkenyl, each optionally substituted with one or more R^{15} ;

B^{11} can be a heterocyclyl, cycloalkyl, or polycyclic hydrocarbon, each optionally substituted with one or more R^{15} ; and

each R^{16} can separately be hydrogen or R^{15} .

[0026] In some embodiments of Formula XVIIIa,

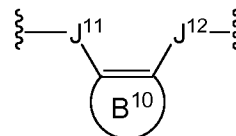


B^{10} can be aryl, or heteroaryl;

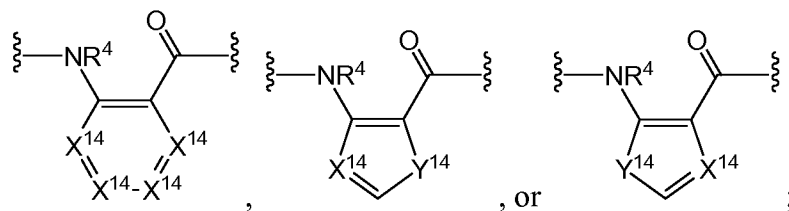
J^{11} can be NR^4 ; and

J^{12} can be $-C(=O)-$.

[0027] In some embodiments of Formula XVIIIa, B^{10} can be phenyl.



[0028] In some embodiments of Formula XVIIIa, can be

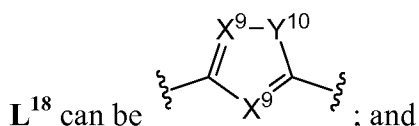
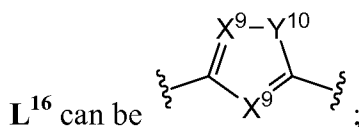


each X^{14} can separately be selected from the group consisting of CR^{17} and N (nitrogen);

Y^{14} can be selected from the group consisting of NR^{17} , O (oxygen), and S (sulfur);

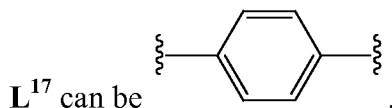
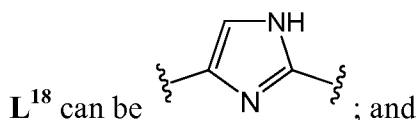
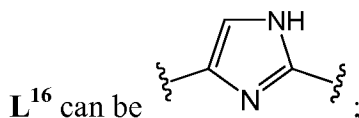
each R^{17} can be separately hydrogen or R^{15} .

[0029] In some embodiments of Formula **XVIIIa**,

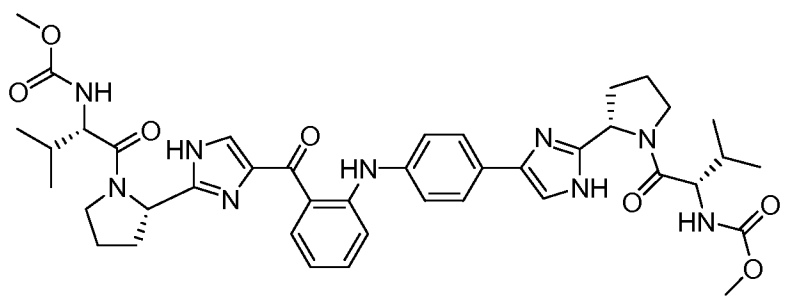


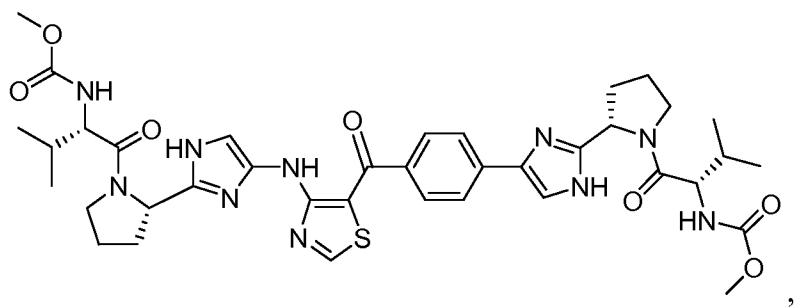
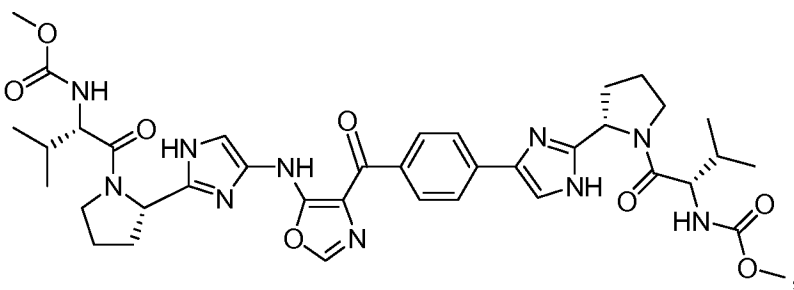
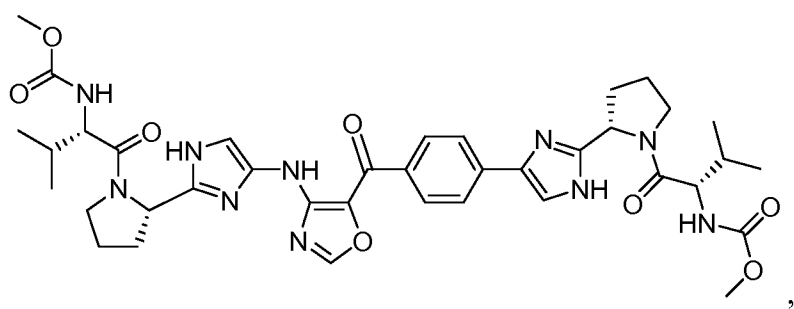
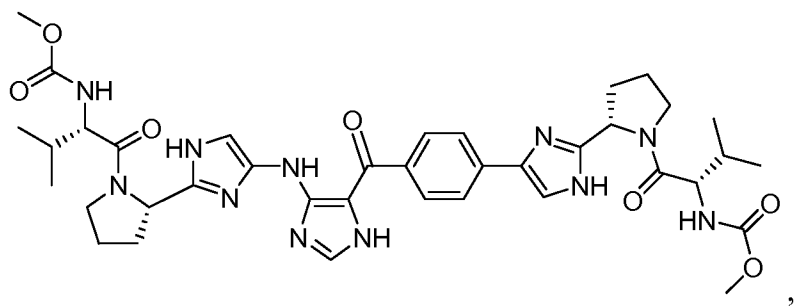
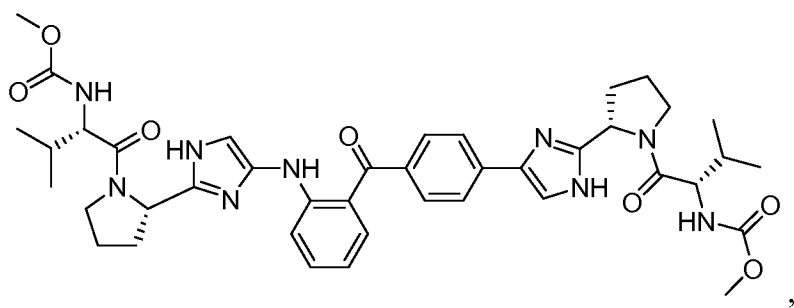
R^4 can be hydrogen.

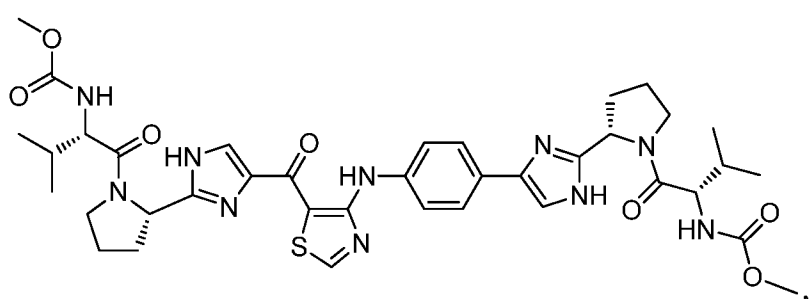
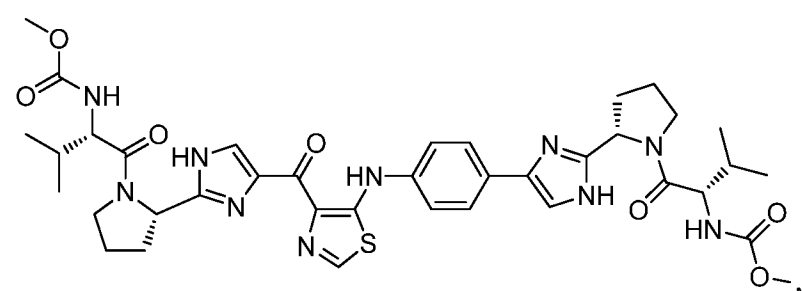
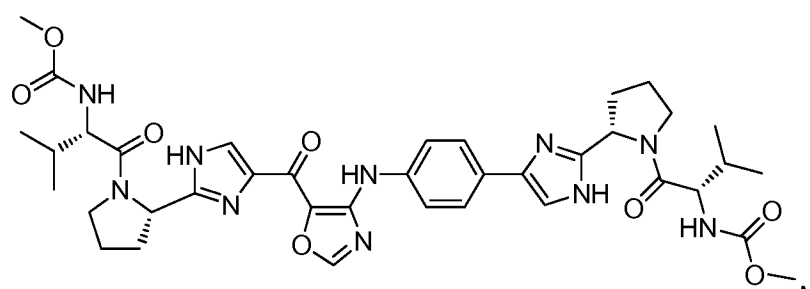
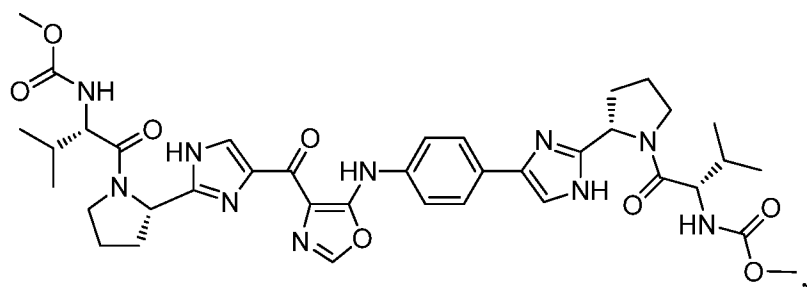
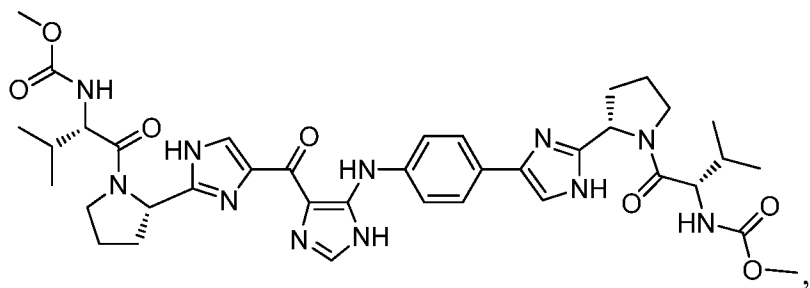
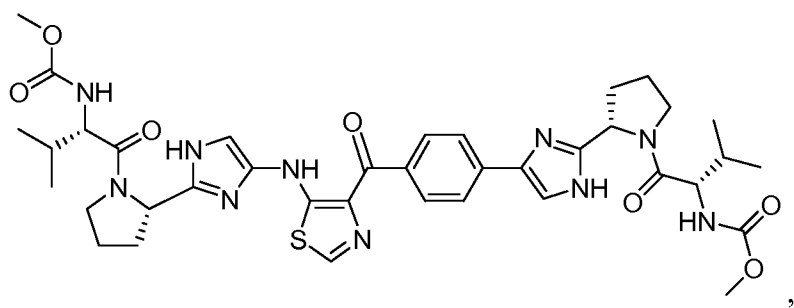
[0030] In some embodiments of Formula **XVIIIa**,

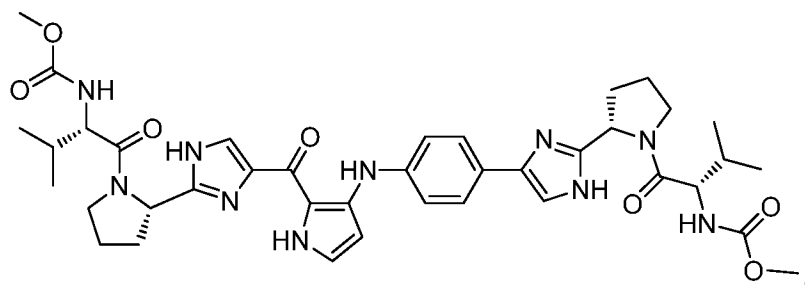
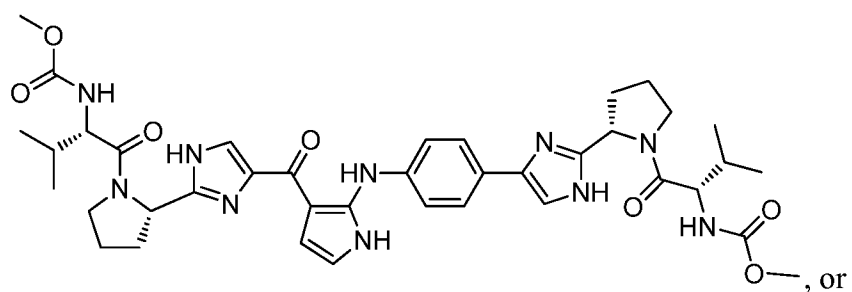
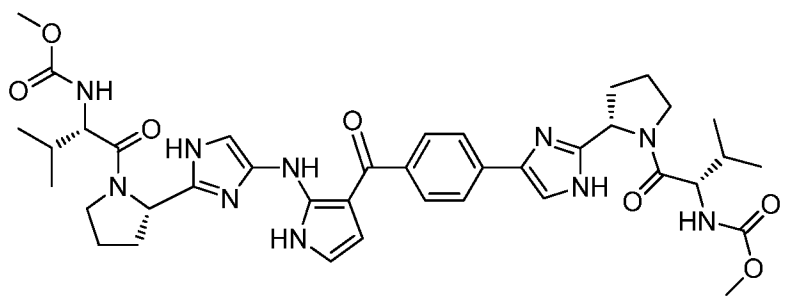
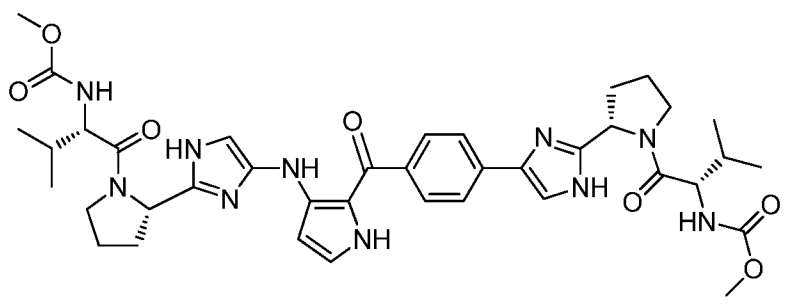


[0031] In some embodiments, the compound of Formula **XVIII** has the structure:



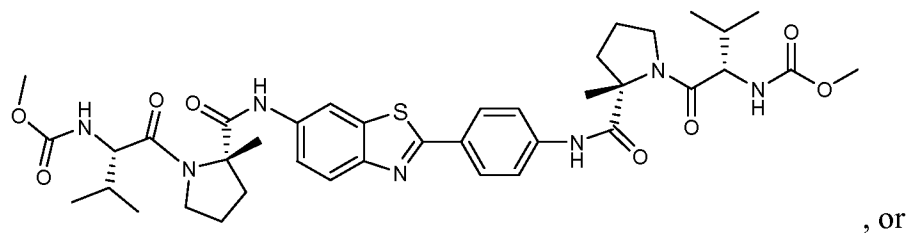


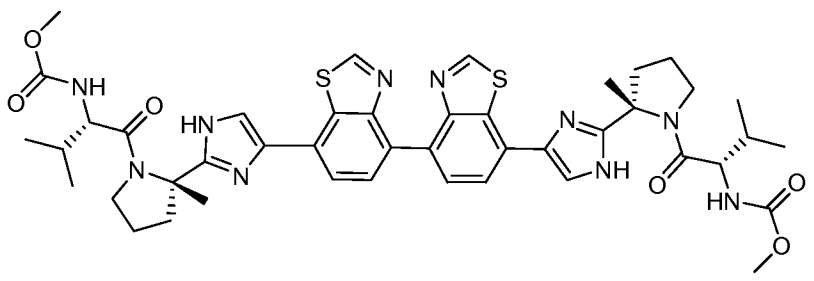




or a pharmaceutically acceptable salt thereof.

[0032] Some embodiments provide a compound having the structure:





or a pharmaceutically acceptable salt thereof.

[0033] Some embodiments provide a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formulas **XV**, **XVI**, **XVII** or **XVIII**.

[0034] Some embodiments provide a method of treating HCV infection in an individual, the method comprising administering to the individual an effective amount of a compound of Formulas **XV**, **XVI**, **XVII** or **XVIII** or a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formulas **XV**, **XVI**, **XVII** or **XVIII**.

[0035] Some embodiments provide a method of treating HCV infection in an individual, the method comprising administering to the individual an effective amount of a compound of Formulas **XV**, **XVI**, **XVII** or **XVIII** or a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formulas **XV**, **XVI**, **XVII** or **XVIII**. In some embodiments, the method further comprises identifying a subject suffering from a hepatitis C infection.

[0036] Some embodiments provide a method of treating liver fibrosis in an individual, the method comprising administering to the individual an effective amount of a compound of Formulas **XV**, **XVI**, **XVII** or **XVIII** or a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formulas **XV**, **XVI**, **XVII** or **XVIII**. In some embodiments, the method further comprises identifying a subject suffering from a hepatitis C infection.

[0037] Some embodiments provide a method of increasing liver function in an individual having a hepatitis C virus infection, the method comprising administering to the individual an effective amount of a compound of Formulas **XV**, **XVI**, **XVII** or **XVIII** or a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formulas **XV**, **XVI**, **XVII** or **XVIII**. In some embodiments, the method further comprises identifying a subject suffering from a hepatitis C infection.

DETAILED DESCRIPTION

Definitions

[0038] As used herein, common organic abbreviations are defined as follows:

Ac	Acetyl
Ac ₂ O	Acetic anhydride
aq.	Aqueous
Bn	Benzyl
Bz	Benzoyl
BOC or Boc	tert-Butoxycarbonyl
Bu	n-Butyl
cat.	Catalytic
Cbz	Carbobenzyloxy
CDI	1,1'-carbonyldiimidazole
Cy (c-C ₆ H ₁₁)	Cyclohexyl
°C	Temperature in degrees Centigrade
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	methylene chloride
DIEA	Diisopropylethylamine
DMA	Dimethylacetamide
DME	Dimethoxyethane
DMF	<i>N,N'</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
Et	Ethyl
EtOAc	Ethyl acetate
g	Gram(s)
h	Hour (hours)
HATU	2-(1 <i>H</i> -7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate
HOBT	N-Hydroxybenzotriazole
iPr	Isopropyl
LCMS	Liquid chromatography-mass spectrometry
LDA	Lithium diisopropylamide

mCPBA	meta-Chloroperoxybenzoic Acid
MeOH	Methanol
MeCN	Acetonitrile
mL	Milliliter(s)
MTBE	Methyl tertiary-butyl ether
NH ₄ OAc	Ammonium acetate
PG	Protecting group
Pd/C	Palladium on activated carbon
Ph	Phenyl
ppt	Precipitate
RCM	Ring closing metathesis
rt	Room temperature
sBuLi	sec-Butyllithium
TEA	Triethylamine
TCDI	1,1'-Thiocarbonyl diimidazole
Tert, t	tertiary
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMEDA	Tetramethylethylenediamine
μL	Microliter(s)

[0039] The terms “individual,” “host,” “subject,” and “patient” are used interchangeably herein, and refer to a mammal, including, but not limited to, primates, including simians and humans.

[0040] As used herein, the term “liver function” refers to a normal function of the liver, including, but not limited to, a synthetic function, including, but not limited to, synthesis of proteins such as serum proteins (e.g., albumin, clotting factors, alkaline phosphatase, aminotransferases (e.g., alanine transaminase, aspartate transaminase), 5'-nucleosidase, γ -glutamyltranspeptidase, etc.), synthesis of bilirubin, synthesis of cholesterol, and synthesis of bile acids; a liver metabolic function, including, but not limited to, carbohydrate metabolism, amino acid and ammonia metabolism, hormone metabolism, and lipid metabolism; detoxification of exogenous drugs; a hemodynamic function, including splanchnic and portal hemodynamics; and the like.

[0041] The term “sustained viral response” (SVR; also referred to as a “sustained response” or a “durable response”), as used herein, refers to the response of an individual to a treatment regimen for HCV infection, in terms of serum HCV titer. Generally, a “sustained viral response” refers to no detectable HCV RNA (e.g., less than about 500, less than about 200, or less than about 100 genome copies per milliliter serum) found in the patient’s serum for a period of at least about one month, at least about two months, at least about three months, at least about four months, at least about five months, or at least about six months following cessation of treatment.

[0042] “Treatment failure patients” as used herein generally refers to HCV-infected patients who failed to respond to previous therapy for HCV (referred to as “non-responders”) or who initially responded to previous therapy, but in whom the therapeutic response was not maintained (referred to as “relapsers”). The previous therapy generally can include treatment with IFN- α monotherapy or IFN- α combination therapy, where the combination therapy may include administration of IFN- α and an antiviral agent such as ribavirin.

[0043] As used herein, the terms “treatment,” “treating,” and the like, refer to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse affect attributable to the disease. “Treatment,” as used herein, covers any treatment of a disease in a mammal, particularly in a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression of the disease.

[0044] As used herein, the term “alkyl” refers to a branched or unbranched fully saturated acyclic aliphatic hydrocarbon group (i.e. composed of carbon and hydrogen containing no double or triple bonds). In some embodiments, alkyls may be substituted or unsubstituted. Alkyls include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, and the like, each of which may be optionally substituted in some embodiments.

[0045] As used herein, the term “heteroalkyl” refers to a branched or unbrached fully saturated acyclic aliphatic hydrocarbon group containing one or more heteroatoms in the carbon back bone (i.e., an alkyl group in which one or more carbon

atoms is replaced with a heteroatom). In some embodiments, heteroalkyls may be substituted or unsubstituted. Heteroalkyls include, but are not limited to, ethers, thioethers, and alkyl-amino-alkyls.

[0046] The term “halo” used herein refers to fluoro, chloro, bromo, or iodo.

[0047] The term “alkoxy” used herein refers to straight or branched chain alkyl radical covalently bonded to the parent molecule through an --O-- linkage. In some embodiments, alkoxy may be substituted or unsubstituted. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, n-butoxy, sec-butoxy, t-butoxy and the like.

[0048] The term “alkenyl” used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing at least one carbon-carbon double bond including, but not limited to, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like. In some embodiments, alkenyls may be substituted or unsubstituted.

[0049] The term “alkynyl” used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing at least one carbon-carbon triple bond including, but not limited to, 1-propynyl, 1-butyne, 2-butyne, and the like. In some embodiments, alkynyls may be substituted or unsubstituted.

[0050] The term “aryl” used herein refers to a homocyclic aromatic radical having one ring, two appended rings, or multiple fused rings. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, biphenyl, phenanthrenyl, naphthacenyl, and the like. In some embodiments, aryls may be substituted or unsubstituted.

[0051] The term “cycloalkyl” used herein refers to a saturated aliphatic ring system radical having three to twenty carbon atoms including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. In some embodiments, cycloalkyls may be substituted or unsubstituted.

[0052] The term “cycloalkenyl” used herein refers to an aliphatic ring system radical having three to twenty carbon atoms having at least one carbon-carbon double bond in the ring. Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. In some embodiments, cycloalkenyls may be substituted or unsubstituted.

[0053] The term “polycycloalkyl” used herein refers to saturated aliphatic ring system radical having at least two rings that are fused with or without bridgehead

carbons. Examples of polycycloalkyl groups include, but are not limited to, bicyclo[4.4.0]decanyl, bicyclo[2.2.1]heptanyl, adamantyl, norbornyl, and the like.

[0054] The term “polycycloalkenyl” used herein refers to aliphatic ring system radical having at least two rings that are fused with or without bridgehead carbons in which at least one of the rings has a carbon-carbon double bond. Examples of polycycloalkenyl groups include, but are not limited to, norbornylenyl, 1,1'-bicyclopentenyl, and the like.

[0055] The term “polycyclic hydrocarbon” used herein refers to a ring system radical in which all of the ring members are carbon atoms. Polycyclic hydrocarbons can be aromatic or can contain less than the maximum number of non-cumulative double bonds. Examples of polycyclic hydrocarbon include, but are not limited to, naphthyl, dihydronaphthyl, indenyl, fluorenyl, and the like.

[0056] The term “heterocyclic” or “heterocyclyl” or “heterocycloalkyl” used herein refers to a cyclic ring system radical having at least one non-aromatic ring in which one or more ring atoms are not carbon, namely heteroatom. Monocyclic “heterocyclic” or “heterocyclyl” moieties are non-aromatic. Bicyclic “heterocyclic” or “heterocyclyl” moieties include one non-aromatic ring wherein at least one heteroatom is present in a ring. Tricyclic “heterocyclic” or “heterocyclyl” moieties include at least one non-aromatic ring wherein at least one heteroatom is present in a ring. Examples of heterocyclic groups include, but are not limited to, morpholinyl, tetrahydrofuranyl, dioxolanyl, pyrrolidinyl, oxazolyl, pyranlyl, pyrrolyl, isoindoline and the like.

[0057] The term “heteroaryl” used herein refers to an aromatic ring system radical in which one or more ring atoms are not carbon, namely heteroatom, having one ring or multiple fused rings. In fused ring systems, the one or more heteroatoms may be present in only one of the rings. Examples of heteroaryl groups include, but are not limited to, benzothiazyl, benzoxazolyl, quinazolinyl, quinolinyl, isoquinolinyl, quinoxalinyl, pyridinyl, pyrrolyl, oxazolyl, indolyl, and the like. In some embodiments, heteroaryls may be substituted or unsubstituted.

[0058] The term “heteroatom” used herein refers to, for example, oxygen, sulfur and nitrogen.

[0059] The term “arylalkyl” used herein refers to one or more aryl groups appended to an alkyl radical. Examples of arylalkyl groups include, but are not limited to, benzyl, phenethyl, phenpropyl, phenbutyl, and the like. In some embodiments,

arylalkyls may be substituted or unsubstituted, and can be substituted on either the aryl or alkyl portion or on both.

[0060] The term “cycloalkylalkyl” used herein refers to one or more cycloalkyl groups appended to an alkyl radical. Examples of cycloalkylalkyl include, but are not limited to, cyclohexylmethyl, cyclohexylethyl, cyclopentylmethyl, cyclopentylethyl, and the like. In some embodiments, cycloalkylalkyls may be substituted or unsubstituted.

[0061] The term “heteroarylalkyl” used herein refers to one or more heteroaryl groups appended to an alkyl radical. Examples of heteroarylalkyl include, but are not limited to, pyridylmethyl, furanylmethyl, thiophenylethyl, and the like. In some embodiments, heteroarylalkyls may be substituted or unsubstituted, and can be substituted on either the heteroaryl or alkyl portion or on both.

[0062] The term “heterocyclalkyl” used herein refers to one or more heterocycl groups appended to an alkyl radical. Examples of heterocyclalkyl include, but are not limited to, morpholinylmethyl, morpholinylethyl, morpholinylpropyl, tetrahydrofuranylmethyl, pyrrolidinylpropyl, and the like.

[0063] The term “aryloxy” used herein refers to an aryl radical covalently bonded to the parent molecule through an --O-- linkage.

[0064] The term “alkylthio” used herein refers to straight or branched chain alkyl radical covalently bonded to the parent molecule through an --S-- linkage. Examples of alkylthio groups include, but are not limited to, methanesulfide, ethanesulfide, propanesulfide, isopropanesulfide, butanesulfide, n-buthanesulfide, sec-buthanesulfide, *tert*-butanesulfide and the like.

[0065] The term “arylthio” used herein refers to an aryl radical covalently bonded to the parent molecule through an --S-- linkage.

[0066] The term “alkylamino” used herein refers to nitrogen radical with one or more alkyl groups attached thereto. Thus, monoalkylamino refers to nitrogen radical with one alkyl group attached thereto and dialkylamino refers to nitrogen radical with two alkyl groups attached thereto.

[0067] The term “cyanoamino” used herein refers to nitrogen radical with nitrile group attached thereto.

[0068] The term “carbamyl” used herein refers to RNHCOO-.

[0069] The term “keto” and “carbonyl” used herein refers to C=O.

- [0070] The term “carboxy” used herein refers to $-\text{COOH}$.
- [0071] The term “sulfamyl” used herein refers to $-\text{SO}_2\text{NH}_2$.
- [0072] The term “sulfonyl” used herein refers to $-\text{SO}_2-$.
- [0073] The term “sulfinyl” used herein refers to $-\text{SO}-$.
- [0074] The term “thiocarbonyl” used herein refers to $\text{C}=\text{S}$.
- [0075] The term “thiocarboxy” used herein refers to CSOH .
- [0076] The term “sulfonamide” used herein refers to $-\text{SO}_2\text{NR}'_2$ where each R' is individually selected from H (hydrogen), $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, arylalkyl and aryl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl.
- [0077] The term “ester” used herein refers to $-\text{COOR}'$ where R' is selected from $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, arylalkyl and aryl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl.
- [0078] The term “C-amide” used herein refers to $-\text{C}(=\text{O})\text{NR}'_2$ where each R' is individually selected from H (hydrogen), $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, arylalkyl and aryl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl.
- [0079] The term “N-amide” used herein refers to $-\text{NR}'\text{C}(=\text{O})\text{R}'$ where each R' is individually selected from H (hydrogen), $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, arylalkyl and aryl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl.
- [0080] The term “N-carbamate” used herein refers to $-\text{NR}'\text{C}(=\text{O})\text{OR}'$ where each R' is individually selected from H (hydrogen), $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, arylalkyl and aryl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl.
- [0081] The term “O-carbamate” used herein refers to $-\text{OC}(=\text{O})\text{NR}'_2$ where each R' is individually selected from H (hydrogen), $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, arylalkyl and aryl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl.
- [0082] The term “urea” used herein refers to $-\text{NR}'\text{C}(=\text{O})\text{NR}'_2$ where each R' is individually selected from H (hydrogen), $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, arylalkyl and aryl optionally substituted with $\text{C}_1\text{-C}_6$ alkyl.
- [0083] As used herein, a radical indicates a species with one or more, unpaired electron such that the species containing the radical can be covalently bonded to one or more other species. Hence, in this context, a radical is not necessarily a free radical. Rather, a radical indicates a specific portion of a larger molecule. The term “radical” can be used interchangeably with the term “moiety” or “group.”

[0084] As used herein, a substituted group is derived from the unsubstituted parent structure in which there has been an exchange of one or more hydrogen atoms for another atom or group. When substituted, the substituent group(s) is (are) one or more group(s) individually and independently selected from C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, C₃-C₇ cycloalkyl (optionally substituted with halo, alkyl, alkoxy, carboxyl, haloalkyl, CN, -SO₂-alkyl, -CF₃, and -OCF₃), cycloalkyl geminally attached, C₁-C₆ heteroalkyl, C₃-C₁₀ heterocycloalkyl (e.g., tetrahydrofuryl) (optionally substituted with halo, alkyl, alkoxy, carboxyl, CN, -SO₂-alkyl, -CF₃, and -OCF₃), aryl (optionally substituted with halo, alkyl, aryl optionally substituted with C₁-C₆ alkyl, arylalkyl, alkoxy, carboxyl, CN, -SO₂-alkyl, -CF₃, and -OCF₃), arylalkyl (optionally substituted with halo, alkyl, alkoxy, aryl, carboxyl, CN, -SO₂-alkyl, -CF₃, and -OCF₃), heteroaryl (optionally substituted with halo, alkyl, alkoxy, aryl, aralkyl, carboxyl, CN, -SO₂-alkyl, -CF₃, and -OCF₃), halo (e.g., chloro, bromo, iodo and fluoro), cyano, hydroxy, -CF₃, C₁-C₆ alkoxy, aryloxy, sulfhydryl (mercapto), halo(C₁-C₆)alkyl, C₁-C₆ alkylthio, arylthio, mono- and di-(C₁-C₆)alkyl amino, quaternary ammonium salts, amino(C₁-C₆)alkoxy, hydroxy(C₁-C₆)alkylamino, amino(C₁-C₆)alkylthio, cyanoamino, nitro, carbamyl, keto (oxy), carbonyl, carboxy, glycolyl, glycyl, hydrazino, guanyl, sulfamyl, sulfonyl, sulfinyl, thiocarbonyl, thiocarboxy, sulfonamide, ester, C-amide, N-amide, N-carbamate, O-carbamate, and urea. The protecting groups that can form the protective derivatives of the above substituents are known to those of skill in the art and can be found in references such as Greene and Wuts *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1999. Wherever a substituent is described as "optionally substituted" that substituent can be substituted with the above substituents.

[0085] Asymmetric carbon atoms may be present in the compounds described. All such isomers, including diastereomers and enantiomers, as well as the mixtures thereof are intended to be included in the scope of the recited compound. In certain cases, compounds can exist in tautomeric forms. All tautomeric forms are intended to be included in the scope. Likewise, when compounds contain an alkenyl or alkenylene group, there exists the possibility of cis- and trans- isomeric forms of the compounds. Both cis- and trans- isomers, as well as the mixtures of cis- and trans- isomers, are contemplated. Thus, reference herein to a compound includes all of the aforementioned isomeric forms unless the context clearly dictates otherwise.

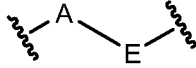
[0086] Various forms are included in the embodiments, including polymorphs, solvates, hydrates, conformers, salts, and prodrug derivatives. A polymorph is a composition having the same chemical formula, but a different structure. A solvate is a composition formed by solvation (the combination of solvent molecules with molecules or ions of the solute). A hydrate is a compound formed by an incorporation of water. A conformer is a structure that is a conformational isomer. Conformational isomerism is the phenomenon of molecules with the same structural formula but different conformations (conformers) of atoms about a rotating bond. Salts of compounds can be prepared by methods known to those skilled in the art. For example, salts of compounds can be prepared by reacting the appropriate base or acid with a stoichiometric equivalent of the compound. A prodrug is a compound that undergoes biotransformation (chemical conversion) before exhibiting its pharmacological effects. For example, a prodrug can thus be viewed as a drug containing specialized protective groups used in a transient manner to alter or to eliminate undesirable properties in the parent molecule. Thus, reference herein to a compound includes all of the aforementioned forms unless the context clearly dictates otherwise.

[0087] The term “pharmaceutically acceptable salt,” as used herein, and particularly when referring to a pharmaceutically acceptable salt of a compound, including a compound of Formulas XV, XVI, XVII or XVIII, as produced and synthesized by the methods disclosed herein, refers to any pharmaceutically acceptable salts of a compound, and preferably refers to an acid addition salt of a compound. With respect to compounds synthesized by the method of this embodiment that contain a basic nitrogen, the preferred examples of pharmaceutically acceptable salts are acid addition salts of pharmaceutically acceptable inorganic or organic acids, including, but not limited to, hydrohalic, sulfuric, phosphoric, aliphatic or aromatic carboxylic, or sulfonic acid. Examples of pharmaceutically acceptable inorganic or organic acids as a component of an addition salt, include but are not limited to, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid acetic acid, succinic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, nicotinic acid, methanesulfonic acid, p-toluenesulfonic acid or naphthalenesulfonic acid. With respect to compounds synthesized by the methods of this embodiment that contain an acidic functional group, the preferred examples of pharmaceutically acceptable salts include, but are not limited to, alkali metal salts (sodium or potassium), alkaline earth metal salts (calcium or magnesium), or ammonium

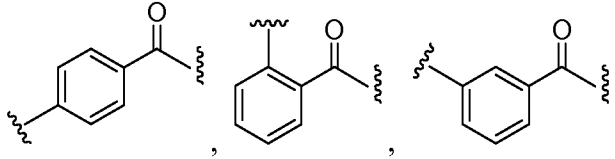
salts derived from ammonia or from pharmaceutically acceptable organic amines, for example C₁-C₇ alkylamine, cyclohexylamine, triethanolamine, ethylenediamine or tris-(hydroxymethyl)-aminomethane.

[0088] Isotopes may be present in the compounds described. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0089] Wherever a substituent as depicted as a di-radical (i.e., has two points of attachment to the rest of the molecule), it is to be understood that the substituent can be attached in any directional configuration unless otherwise indicated. Thus, for example, a

substituent depicted as $-AE-$ or  includes the substituent being oriented such that the **A** is attached at the leftmost attachment point of the molecule as well as the case in which **A** is attached at the rightmost attachment point of the molecule.

[0090] It is to be understood that certain radical naming conventions can include either a mono-radical or a di-radical, depending on the context. For example, where a substituent requires two points of attachment to the rest of the molecule, it is understood that the substituent is a di-radical. A substituent identified as alkyl, that requires two points of attachment, includes di-radicals such as $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, and the like; a substituent depicted as alkoxy that requires two points of attachment, includes di-radicals such as $-OCH_2-$, $-OCH_2CH_2-$, $-OCH_2CH(CH_3)CH_2-$, and the like; and a substituent depicted as arylC(=O)- that requires two points of

attachment, includes di-radicals such as , and the like.

[0091] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

[0092] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the embodiments belong. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the embodiments, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[0093] It must be noted that as used herein and in the appended claims, the singular forms “a,” “and,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a method” includes a plurality of such methods and reference to “a dose” includes reference to one or more doses and equivalents thereof known to those skilled in the art, and so forth.

Compounds

[0094] The present embodiments provide compounds of Formulas XV, XVI, XVII or XVIII, as defined above, as well as pharmaceutical compositions and formulations comprising any compound of Formulas XV, XVI, XVII or XVIII. A subject compound is useful for treating HCV infection and other disorders, as discussed below.

[0095] In many embodiments, a subject compound inhibits HCV viral replication. For example, a subject compound inhibits HCV viral replication by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%, or more, compared to HCV viral replication in the absence of the compound. Whether a subject compound inhibits HCV viral replication can be determined using methods known in the art, including an in vitro viral replication assay.

Compositions

[0096] The present embodiments further provide compositions, including pharmaceutical compositions, comprising compounds of the general Formulas XV, XVI, XVII or XVIII.

[0097] A subject pharmaceutical composition comprises a subject compound; and a pharmaceutically acceptable excipient. A wide variety of pharmaceutically acceptable excipients is known in the art and need not be discussed in detail herein. Pharmaceutically acceptable excipients have been amply described in a variety of

publications, including, for example, A. Gennaro (2000) "Remington: The Science and Practice of Pharmacy," 20th edition, Lippincott, Williams, & Wilkins; Pharmaceutical Dosage Forms and Drug Delivery Systems (1999) H.C. Ansel et al., eds., 7th ed., Lippincott, Williams, & Wilkins; and Handbook of Pharmaceutical Excipients (2000) A.H. Kibbe et al., eds., 3rd ed. Amer. Pharmaceutical Assoc.

[0098] The pharmaceutically acceptable excipients, such as vehicles, adjuvants, carriers or diluents, are known in the art. Moreover, pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the like, are known in the art.

[0099] In some embodiments, a compound as described herein is formulated in an aqueous buffer. Suitable aqueous buffers include, but are not limited to, acetate, succinate, citrate, and phosphate buffers varying in strengths from about 5mM to about 100mM. In some embodiments, the aqueous buffer includes reagents that provide for an isotonic solution. Such reagents include, but are not limited to, sodium chloride; and sugars e.g., mannitol, dextrose, sucrose, and the like. In some embodiments, the aqueous buffer further includes a non-ionic surfactant such as polysorbate 20 or 80. Optionally the formulations may further include a preservative. Suitable preservatives include, but are not limited to, a benzyl alcohol, phenol, chlorobutanol, benzalkonium chloride, and the like. In many cases, the formulation is stored at about 4°C. Formulations may also be lyophilized, in which case they generally include cryoprotectants such as sucrose, trehalose, lactose, maltose, mannitol, and the like. Lyophilized formulations can be stored over extended periods of time, even at ambient temperatures.

[0100] As such, administration of the compounds as described herein can be achieved in various ways, including oral, buccal, rectal, parenteral, intraperitoneal, intradermal, subcutaneous, intramuscular, transdermal, intratracheal, etc., administration. In some embodiments, administration is by bolus injection, e.g., subcutaneous bolus injection, intramuscular bolus injection, and the like.

[0101] The pharmaceutical compositions of the embodiments can be administered orally, parenterally or via an implanted reservoir. Oral administration or administration by injection is preferred.

[0102] Subcutaneous administration of a pharmaceutical composition of the embodiments is accomplished using standard methods and devices, e.g., needle and syringe, a subcutaneous injection port delivery system, and the like. See, e.g., U.S. Patent

Nos. 3,547,119; 4,755,173; 4,531,937; 4,311,137; and 6,017,328. A combination of a subcutaneous injection port and a device for administration of a pharmaceutical composition of the embodiments to a patient through the port is referred to herein as “a subcutaneous injection port delivery system.” In many embodiments, subcutaneous administration is achieved by bolus delivery by needle and syringe.

[0103] In pharmaceutical dosage forms, the compounds as described herein may be administered in the form of their pharmaceutically acceptable salts, or they may also be used alone or in appropriate association, as well as in combination, with other pharmaceutically active compounds. The following methods and excipients are merely exemplary and are in no way limiting.

[0104] For oral preparations, the compounds as described herein can be used alone or in combination with appropriate additives to make tablets, powders, granules or capsules, for example, with conventional additives, such as lactose, mannitol, corn starch or potato starch; with binders, such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators, such as corn starch, potato starch or sodium carboxymethylcellulose; with lubricants, such as talc or magnesium stearate; and if desired, with diluents, buffering agents, moistening agents, preservatives and flavoring agents.

[0105] The compounds as described herein can be formulated into preparations for injection by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

[0106] Furthermore, the compounds as described herein can be made into suppositories by mixing with a variety of bases such as emulsifying bases or water-soluble bases. The compounds of the embodiments can be administered rectally via a suppository. The suppository can include vehicles such as cocoa butter, carbowaxes and polyethylene glycols, which melt at body temperature, yet are solidified at room temperature.

[0107] Unit dosage forms for oral or rectal administration such as syrups, elixirs, and suspensions may be provided wherein each dosage unit, for example, teaspoonful, tablespoonful, tablet or suppository, contains a predetermined amount of the

composition containing one or more compounds as described herein. Similarly, unit dosage forms for injection or intravenous administration may comprise the compounds as described herein in a composition as a solution in sterile water, normal saline or another pharmaceutically acceptable carrier.

[0108] The term “unit dosage form,” as used herein, refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of compounds of the embodiments calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier or vehicle. The specifications for the novel unit dosage forms of the embodiments depend on the particular compound employed and the effect to be achieved, and the pharmacodynamics associated with each compound in the host.

[0109] The pharmaceutically acceptable excipients, such as vehicles, adjuvants, carriers or diluents, are readily known in the art. Moreover, pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the like, are readily known in the art.

Treating a hepatitis virus infection

[0110] The methods and compositions described herein are generally useful in treatment of an of HCV infection.

[0111] Preferred embodiments provide a method of treating a hepatitis C virus infection in an individual, the method comprising administering to the individual an effective amount of a composition comprising a subject compound.

[0112] Preferred embodiments provide a method of treating liver fibrosis in an individual, the method comprising administering to the individual an effective amount of a composition comprising a subject compound.

[0113] Preferred embodiments provide a method of increasing liver function in an individual having a hepatitis C virus infection, the method comprising administering to the individual an effective amount of a composition comprising a subject compound.

[0114] Whether a subject method is effective in treating an HCV infection can be determined by a reduction in viral load, a reduction in time to seroconversion (virus undetectable in patient serum), an increase in the rate of sustained viral response to therapy, a reduction of morbidity or mortality in clinical outcomes, or other indicator of disease response.

[0115] In general, an effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is an amount that is effective to reduce viral load or achieve a sustained viral response to therapy.

[0116] Whether a subject method is effective in treating an HCV infection can be determined by measuring viral load, or by measuring a parameter associated with HCV infection, including, but not limited to, liver fibrosis, elevations in serum transaminase levels, and necroinflammatory activity in the liver. Indicators of liver fibrosis are discussed in detail below.

[0117] In some embodiments, the methods involve administering an effective amount of a compound of Formulas XV, XVI, XVII or XVIII, optionally in combination with an effective amount of one or more additional antiviral agents. In some embodiments, an effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is an amount that is effective to reduce viral titers to undetectable levels, e.g., to about 1000 to about 5000, to about 500 to about 1000, or to about 100 to about 500 genome copies/mL serum. In some embodiments, an effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is an amount that is effective to reduce viral load to lower than 100 genome copies/mL serum.

[0118] In some embodiments, an effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is an amount that is effective to achieve a 1.5-log, a 2-log, a 2.5-log, a 3-log, a 3.5-log, a 4-log, a 4.5-log, or a 5-log reduction in viral titer in the serum of the individual.

[0119] In many embodiments, an effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is an amount that is effective to achieve a sustained viral response, e.g., non-detectable or substantially non-detectable HCV RNA (e.g., less than about 500, less than about 400, less than about 200, or less than about 100 genome copies per milliliter serum) is found in the patient's serum for a period of at least about one month, at least about two months, at least about three months, at least about four months, at least about five months, or at least about six months following cessation of therapy.

[0120] As noted above, whether a subject method is effective in treating an HCV infection can be determined by measuring a parameter associated with HCV infection, such as liver fibrosis. Methods of determining the extent of liver fibrosis are

discussed in detail below. In some embodiments, the level of a serum marker of liver fibrosis indicates the degree of liver fibrosis.

[0121] As one non-limiting example, levels of serum alanine aminotransferase (ALT) are measured, using standard assays. In general, an ALT level of less than about 45 international units is considered normal. In some embodiments, an effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is an amount effective to reduce ALT levels to less than about 45 IU/mL serum.

[0122] A therapeutically effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is an amount that is effective to reduce a serum level of a marker of liver fibrosis by at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, or at least about 80%, or more, compared to the level of the marker in an untreated individual, or to a placebo-treated individual. Methods of measuring serum markers include immunological-based methods, e.g., enzyme-linked immunosorbent assays (ELISA), radioimmunoassays, and the like, using antibody specific for a given serum marker.

[0123] In many embodiments, an effective amount of a compound of Formulas XV, XVI, XVII or XVIII and an additional antiviral agent is a synergistic amount. As used herein, a “synergistic combination” or a “synergistic amount” of a compound of Formulas XV, XVI, XVII or XVIII and an additional antiviral agent is a combined dosage that is more effective in the therapeutic or prophylactic treatment of an HCV infection than the incremental improvement in treatment outcome that could be predicted or expected from a merely additive combination of (i) the therapeutic or prophylactic benefit of the compound of Formulas XV, XVI, XVII or XVIII when administered at that same dosage as a monotherapy and (ii) the therapeutic or prophylactic benefit of the additional antiviral agent when administered at the same dosage as a monotherapy.

[0124] In some embodiments, a selected amount of a compound of Formulas XV, XVI, XVII or XVIII and a selected amount of an additional antiviral agent are effective when used in combination therapy for a disease, but the selected amount of the compound of Formulas XV, XVI, XVII or XVIII and/or the selected amount of the

additional antiviral agent is less effective when used in monotherapy for the disease. Thus, the embodiments encompass (1) regimens in which a selected amount of the additional antiviral agent enhances the therapeutic benefit of a selected amount of the compound of Formulas XV, XVI, XVII or XVIII when used in combination therapy for a disease, where the selected amount of the additional antiviral agent provides negligible therapeutic benefit when used in monotherapy for the disease (2) regimens in which a selected amount of the compound of Formulas XV, XVI, XVII or XVIII enhances the therapeutic benefit of a selected amount of the additional antiviral agent when used in combination therapy for a disease, where the selected amount of the compound of Formulas XV, XVI, XVII or XVIII provides negligible therapeutic benefit when used in monotherapy for the disease and (3) regimens in which a selected amount of the compound of Formulas XV, XVI, XVII or XVIII and a selected amount of the additional antiviral agent provide a therapeutic benefit when used in combination therapy for a disease, where each of the selected amounts of the compound of Formulas XV, XVI, XVII or XVIII and the additional antiviral agent, respectively, provides negligible therapeutic benefit when used in monotherapy for the disease. As used herein, a “synergistically effective amount” of a compound of Formulas XV, XVI, XVII or XVIII and an additional antiviral agent, and its grammatical equivalents, shall be understood to include any regimen encompassed by any of (1)-(3) above.

Fibrosis

[0125] The embodiments provides methods for treating liver fibrosis (including forms of liver fibrosis resulting from, or associated with, HCV infection), generally involving administering a therapeutic amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents. Effective amounts of compounds of Formulas XV, XVI, XVII or XVIII, with and without one or more additional antiviral agents, as well as dosing regimens, are as discussed below.

[0126] Whether treatment with a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is effective in reducing liver fibrosis can be determined by any of a number of well-established techniques for measuring liver fibrosis and liver function. Liver fibrosis reduction is determined by analyzing a liver biopsy sample. An analysis of a liver biopsy comprises assessments of two major components: necroinflammation assessed by “grade” as a measure of the

severity and ongoing disease activity, and the lesions of fibrosis and parenchymal or vascular remodeling as assessed by “stage” as being reflective of long-term disease progression. See, e.g., Brunt (2000) *Hepatology* 31:241-246; and METAVIR (1994) *Hepatology* 20:15-20. Based on analysis of the liver biopsy, a score is assigned. A number of standardized scoring systems exist which provide a quantitative assessment of the degree and severity of fibrosis. These include the METAVIR, Knodell, Scheuer, Ludwig, and Ishak scoring systems.

[0127] The METAVIR scoring system is based on an analysis of various features of a liver biopsy, including fibrosis (portal fibrosis, centrilobular fibrosis, and cirrhosis); necrosis (piecemeal and lobular necrosis, acidophilic retraction, and ballooning degeneration); inflammation (portal tract inflammation, portal lymphoid aggregates, and distribution of portal inflammation); bile duct changes; and the Knodell index (scores of periportal necrosis, lobular necrosis, portal inflammation, fibrosis, and overall disease activity). The definitions of each stage in the METAVIR system are as follows: score: 0, no fibrosis; score: 1, stellate enlargement of portal tract but without septa formation; score: 2, enlargement of portal tract with rare septa formation; score: 3, numerous septa without cirrhosis; and score: 4, cirrhosis.

[0128] Knodell's scoring system, also called the Hepatitis Activity Index, classifies specimens based on scores in four categories of histologic features: I. Periportal and/or bridging necrosis; II. Intralobular degeneration and focal necrosis; III. Portal inflammation; and IV. Fibrosis. In the Knodell staging system, scores are as follows: score: 0, no fibrosis; score: 1, mild fibrosis (fibrous portal expansion); score: 2, moderate fibrosis; score: 3, severe fibrosis (bridging fibrosis); and score: 4, cirrhosis. The higher the score, the more severe the liver tissue damage. Knodell (1981) *Hepatology* 1:431.

[0129] The Scheuer scoring system scores are as follows: score: 0, no fibrosis; score: 1, enlarged, fibrotic portal tracts; score: 2, periportal or portal-portal septa, but intact architecture; score: 3, fibrosis with architectural distortion, but no obvious cirrhosis; score: 4, probable or definite cirrhosis. Scheuer (1991) *J. Hepatology* 13:372.

[0130] The Ishak scoring system is described in Ishak (1995) *J. Hepatology* 22:696-699. Stage 0, No fibrosis; Stage 1, Fibrous expansion of some portal areas, with or without short fibrous septa; stage 2, Fibrous expansion of most portal areas, with or without short fibrous septa; stage 3, Fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging; stage 4, Fibrous expansion of portal areas with

marked bridging (P-P) as well as portal-central (P-C); stage 5, Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis); stage 6, Cirrhosis, probable or definite.

[0131] The benefit of anti-fibrotic therapy can also be measured and assessed by using the Child-Pugh scoring system which comprises a multicomponent point system based upon abnormalities in serum bilirubin level, serum albumin level, prothrombin time, the presence and severity of ascites, and the presence and severity of encephalopathy. Based upon the presence and severity of abnormality of these parameters, patients may be placed in one of three categories of increasing severity of clinical disease: A, B, or C.

[0132] In some embodiments, a therapeutically effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is an amount that effects a change of one unit or more in the fibrosis stage based on pre- and post-therapy liver biopsies. In particular embodiments, a therapeutically effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, reduces liver fibrosis by at least one unit in the METAVIR, the Knodell, the Scheuer, the Ludwig, or the Ishak scoring system.

[0133] Secondary, or indirect, indices of liver function can also be used to evaluate the efficacy of treatment with a compound of Formulas XV, XVI, XVII or XVIII. Morphometric computerized semi- automated assessment of the quantitative degree of liver fibrosis based upon specific staining of collagen and/or serum markers of liver fibrosis can also be measured as an indication of the efficacy of a subject treatment method. Secondary indices of liver function include, but are not limited to, serum transaminase levels, prothrombin time, bilirubin, platelet count, portal pressure, albumin level, and assessment of the Child-Pugh score.

[0134] An effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is an amount that is effective to increase an index of liver function by at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, or at least about 80%, or more, compared to the index of liver function in an untreated individual, or to a placebo-treated individual.

Those skilled in the art can readily measure such indices of liver function, using standard assay methods, many of which are commercially available, and are used routinely in clinical settings.

[0135] Serum markers of liver fibrosis can also be measured as an indication of the efficacy of a subject treatment method. Serum markers of liver fibrosis include, but are not limited to, hyaluronate, N-terminal procollagen III peptide, 7S domain of type IV collagen, C-terminal procollagen I peptide, and laminin. Additional biochemical markers of liver fibrosis include α -2-macroglobulin, haptoglobin, gamma globulin, apolipoprotein A, and gamma glutamyl transpeptidase.

[0136] A therapeutically effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is an amount that is effective to reduce a serum level of a marker of liver fibrosis by at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, or at least about 80%, or more, compared to the level of the marker in an untreated individual, or to a placebo-treated individual. Those skilled in the art can readily measure such serum markers of liver fibrosis, using standard assay methods, many of which are commercially available, and are used routinely in clinical settings. Methods of measuring serum markers include immunological-based methods, e.g., enzyme-linked immunosorbent assays (ELISA), radioimmunoassays, and the like, using antibody specific for a given serum marker.

[0137] As used herein, a “complication associated with cirrhosis of the liver” refers to a disorder that is a sequellae of decompensated liver disease, i.e., or occurs subsequently to and as a result of development of liver fibrosis, and includes, but it not limited to, development of ascites, variceal bleeding, portal hypertension, jaundice, progressive liver insufficiency, encephalopathy, hepatocellular carcinoma, liver failure requiring liver transplantation, and liver-related mortality.

[0138] A therapeutically effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is an amount that is effective in reducing the incidence (e.g., the likelihood that an individual will develop) of a disorder associated with cirrhosis of the liver by at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least

about 65%, at least about 70%, at least about 75%, or at least about 80%, or more, compared to an untreated individual, or to a placebo-treated individual.

[0139] Whether treatment with a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is effective in reducing the incidence of a disorder associated with cirrhosis of the liver can readily be determined by those skilled in the art.

[0140] Reduction in liver fibrosis can increase liver function. Thus, the embodiments provide methods for increasing liver function, generally involving administering a therapeutically effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents. Liver functions include, but are not limited to, synthesis of proteins such as serum proteins (e.g., albumin, clotting factors, alkaline phosphatase, aminotransferases (e.g., alanine transaminase, aspartate transaminase), 5'-nucleosidase, γ -glutamyltranspeptidase, etc.), synthesis of bilirubin, synthesis of cholesterol, and synthesis of bile acids; a liver metabolic function, including, but not limited to, carbohydrate metabolism, amino acid and ammonia metabolism, hormone metabolism, and lipid metabolism; detoxification of exogenous drugs; a hemodynamic function, including splanchnic and portal hemodynamics; and the like.

[0141] Whether a liver function is increased is readily ascertainable by those skilled in the art, using well-established tests of liver function. Thus, synthesis of markers of liver function such as albumin, alkaline phosphatase, alanine transaminase, aspartate transaminase, bilirubin, and the like, can be assessed by measuring the level of these markers in the serum, using standard immunological and enzymatic assays. Splanchnic circulation and portal hemodynamics can be measured by portal wedge pressure and/or resistance using standard methods. Metabolic functions can be measured by measuring the level of ammonia in the serum.

[0142] Whether serum proteins normally secreted by the liver are in the normal range can be determined by measuring the levels of such proteins, using standard immunological and enzymatic assays. Those skilled in the art know the normal ranges for such serum proteins. The following are non-limiting examples. The normal level of alanine transaminase is about 45 IU per milliliter of serum. The normal range of aspartate transaminase is from about 5 to about 40 units per liter of serum. Bilirubin is measured using standard assays. Normal bilirubin levels are usually less than about 1.2

mg/dL. Serum albumin levels are measured using standard assays. Normal levels of serum albumin are in the range of from about 35 to about 55 g/L. Prolongation of prothrombin time is measured using standard assays. Normal prothrombin time is less than about 4 seconds longer than control.

[0143] A therapeutically effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is one that is effective to increase liver function by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or more. For example, a therapeutically effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is an amount effective to reduce an elevated level of a serum marker of liver function by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or more, or to reduce the level of the serum marker of liver function to within a normal range. A therapeutically effective amount of a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents, is also an amount effective to increase a reduced level of a serum marker of liver function by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or more, or to increase the level of the serum marker of liver function to within a normal range.

Dosages, Formulations, and Routes of Administration

[0144] In the subject methods, the active agent(s) (e.g., compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agents) may be administered to the host using any convenient means capable of resulting in the desired therapeutic effect. Thus, the agent can be incorporated into a variety of formulations for therapeutic administration. More particularly, the agents of the embodiments can be formulated into pharmaceutical compositions by combination with appropriate, pharmaceutically acceptable carriers or diluents, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants and aerosols.

Other antiviral or antifibrotic agents

[0145] As discussed above, a subject method will in some embodiments be carried out by administering a compound of Formulas XV, XVI, XVII or XVIII, and optionally one or more additional antiviral agent(s).

[0146] In some embodiments, the method further includes administration of one or more interferon receptor agonist(s)

[0147] In other embodiments, the method further includes administration of pirfenidone or a pirfenidone analog.

[0148] Additional antiviral agents that are suitable for use in combination therapy include, but are not limited to, nucleotide and nucleoside analogs. Non-limiting examples include azidothymidine (AZT) (zidovudine), and analogs and derivatives thereof; 2',3'-dideoxyinosine (DDI) (didanosine), and analogs and derivatives thereof; 2',3'-dideoxycytidine (DDC) (dideoxycytidine), and analogs and derivatives thereof; 2',3'-dideoxy-2',3'-dideoxythymidine (D4T) (stavudine), and analogs and derivatives thereof; combivir; abacavir; adefovir dipoxil; cidofovir; ribavirin; ribavirin analogs; and the like.

[0149] In some embodiments, the method further includes administration of ribavirin. Ribavirin, 1- β -D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide, available from ICN Pharmaceuticals, Inc., Costa Mesa, Calif., is described in the Merck Index, compound No. 8199, Eleventh Edition. Its manufacture and formulation is described in U.S. Pat. No. 4,211,771. Some embodiments also involve use of derivatives of ribavirin (see, *e.g.*, U.S. Pat. No. 6,277,830). The ribavirin may be administered orally in capsule or tablet form, or in the same or different administration form and in the same or different route as the subject compound. Of course, other types of administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, intravenously, by suppository, by sustained release dosage form, etc. Any form of administration will work so long as the proper dosages are delivered without destroying the active ingredient.

[0150] In some embodiments, the method further includes administration of ritonavir. Ritonavir, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester [5*S*-(5*R**,8*R**,10*R**,11*R**)], available from Abbott Laboratories, is an inhibitor of the protease of the human immunodeficiency virus and also of the

cytochrome P450 3A and P450 2D6 liver enzymes frequently involved in hepatic metabolism of therapeutic molecules in man.

[0151] In some embodiments, the method further includes administration of a protease inhibitor. In some embodiments, the method further includes administration of an NS5A inhibitor. In some embodiments, the method further includes administration of a helicase inhibitor. In some embodiments, the method further includes administration of a polymerase inhibitor.

[0152] In some embodiments, an additional antiviral agent is administered during the entire course of the subject compound treatment. In other embodiments, an additional antiviral agent is administered for a period of time that is overlapping with that of the subject compound treatment, e.g., the additional antiviral agent treatment can begin before the subject compound treatment begins and end before the subject compound treatment ends; the additional antiviral agent treatment can begin after the subject compound treatment begins and end after the subject compound treatment ends; the additional antiviral agent treatment can begin after the subject compound treatment begins and end before the subject compound treatment ends; or the additional antiviral agent treatment can begin before the subject compound treatment begins and end after the subject compound treatment ends.

Methods of Treatment

Monotherapies

[0153] The compounds as described herein may be used in acute or chronic therapy for HCV disease. In many embodiments, the compounds as described herein can be administered for a period of about 1 day to about 7 days, or about 1 week to about 2 weeks, or about 2 weeks to about 3 weeks, or about 3 weeks to about 4 weeks, or about 1 month to about 2 months, or about 3 months to about 4 months, or about 4 months to about 6 months, or about 6 months to about 8 months, or about 8 months to about 12 months, or at least one year, and may be administered over longer periods of time. The compounds as described herein can be administered 5 times per day, 4 times per day, tid, bid, qd, qod, biw, tiw, qw, qow, three times per month, or once monthly. In other embodiments, the NS5A inhibitor compound is administered as a continuous infusion.

[0154] In many embodiments, an compounds as described herein of the embodiments can be administered orally.

[0155] In connection with the above-described methods for the treatment of HCV disease in a patient, a compound as described herein may be administered to the patient at a dosage from about 0.01 mg to about 100 mg/kg patient bodyweight per day, in 1 to 5 divided doses per day. In some embodiments, the compounds as described herein can be administered at a dosage of about 0.5 mg to about 75 mg/kg patient bodyweight per day, in 1 to 5 divided doses per day.

[0156] The amount of active ingredient that may be combined with carrier materials to produce a dosage form can vary depending on the host to be treated and the particular mode of administration. A typical pharmaceutical preparation can contain from about 5% to about 95% active ingredient (w/w). In other embodiments, the pharmaceutical preparation can contain from about 20% to about 80% active ingredient.

[0157] Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms and the susceptibility of the subject to side effects. Preferred dosages for a given compound as described herein can be readily determinable by those of skill in the art by a variety of means. A preferred means can be to measure the physiological potency of a given interferon receptor agonist.

[0158] In many embodiments, multiple doses of NS5A inhibitor compound are administered. For example, an NS5A inhibitor compound is administered once per month, twice per month, three times per month, every other week (qow), once per week (qw), twice per week (biw), three times per week (tiw), four times per week, five times per week, six times per week, every other day (qod), daily (qd), twice a day (qid), or three times a day (tid), over a period of time ranging from about one day to about one week, from about two weeks to about four weeks, from about one month to about two months, from about two months to about four months, from about four months to about six months, from about six months to about eight months, from about eight months to about 1 year, from about 1 year to about 2 years, or from about 2 years to about 4 years, or more.

Combination therapies with a TNF- α antagonist and an interferon

[0159] Some embodiments provide a method of treating an HCV infection in an individual having an HCV infection, the method comprising administering an effective amount of one of the compounds as described herein, and effective amount of a TNF- α antagonist, and an effective amount of one or more interferons.

Subjects Suitable for Treatment

[0160] In certain embodiments, the specific regimen of drug therapy used in treatment of the HCV patient is selected according to certain disease parameters exhibited by the patient, such as the initial viral load, genotype of the HCV infection in the patient, liver histology and/or stage of liver fibrosis in the patient.

[0161] Any of the above treatment regimens can be administered to individuals who have been diagnosed with an HCV infection. Any of the above treatment regimens can be administered to individuals having advanced or severe stage liver fibrosis as measured by a Knodell score of 3 or 4 or no or early stage liver fibrosis as measured by a Knodell score of 0, 1, or 2. Any of the above treatment regimens can be administered to individuals who have failed previous treatment for HCV infection (“treatment failure patients,” including non-responders and relapsers).

[0162] Individuals who have been clinically diagnosed as infected with HCV are of particular interest in many embodiments. Individuals who are infected with HCV are identified as having HCV RNA in their blood, and/or having anti-HCV antibody in their serum. Such individuals include anti-HCV ELISA-positive individuals, and individuals with a positive recombinant immunoblot assay (RIBA). Such individuals may also, but need not, have elevated serum ALT levels.

[0163] Individuals who are clinically diagnosed as infected with HCV include naïve individuals (e.g., individuals not previously treated for HCV, particularly those who have not previously received IFN- α -based and/or ribavirin-based therapy) and individuals who have failed prior treatment for HCV (“treatment failure” patients). Treatment failure patients include non-responders (i.e., individuals in whom the HCV titer was not significantly or sufficiently reduced by a previous treatment for HCV, e.g., a previous IFN- α monotherapy, a previous IFN- α and ribavirin combination therapy, or a previous pegylated IFN- α and ribavirin combination therapy); and relapsers (i.e., individuals who were previously treated for HCV, e.g., who received a previous IFN- α monotherapy, a previous IFN- α and ribavirin combination therapy, or a previous pegylated IFN- α and ribavirin combination therapy, whose HCV titer decreased, and subsequently increased).

[0164] In particular embodiments of interest, individuals have an HCV titer of at least about 10^5 , at least about 5×10^5 , or at least about 10^6 , or at least about 2×10^6 , genome copies of HCV per milliliter of serum. The patient may be infected with any HCV genotype (genotype 1, including 1a and 1b, 2, 3, 4, 6, etc. and subtypes (e.g., 2a, 2b,

3a, etc.)), particularly a difficult to treat genotype such as HCV genotype 1 and particular HCV subtypes and quasispecies.

[0165] Also of interest are HCV-positive individuals (as described above) who exhibit severe fibrosis or early cirrhosis (non-decompensated, Child's-Pugh class A or less), or more advanced cirrhosis (decompensated, Child's-Pugh class B or C) due to chronic HCV infection and who are viremic despite prior anti-viral treatment with IFN- α -based therapies or who cannot tolerate IFN- α -based therapies, or who have a contraindication to such therapies. In particular embodiments of interest, HCV-positive individuals with stage 3 or 4 liver fibrosis according to the METAVIR scoring system are suitable for treatment with the methods described herein. In other embodiments, individuals suitable for treatment with the methods of the embodiments are patients with decompensated cirrhosis with clinical manifestations, including patients with far-advanced liver cirrhosis, including those awaiting liver transplantation. In still other embodiments, individuals suitable for treatment with the methods described herein include patients with milder degrees of fibrosis including those with early fibrosis (stages 1 and 2 in the METAVIR, Ludwig, and Scheuer scoring systems; or stages 1, 2, or 3 in the Ishak scoring system.).

Synthesis

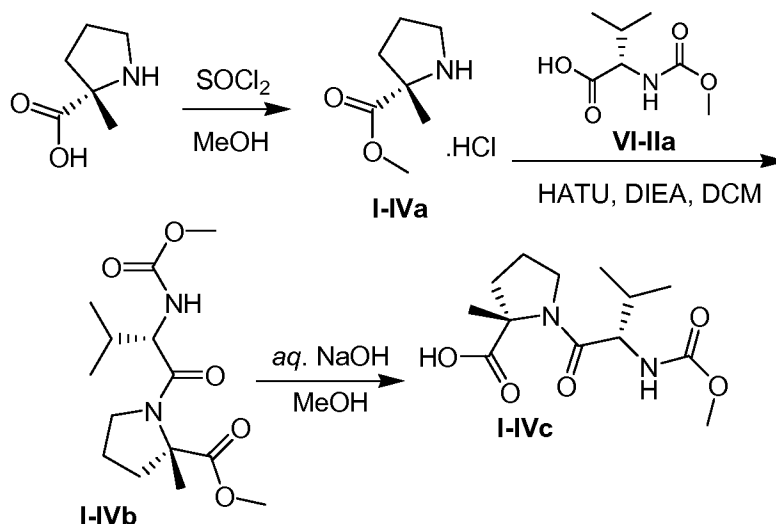
[0166] The compounds and processes of the present disclosure will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the present disclosure may be prepared. Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art. The variables are as defined above unless otherwise noted below.

SECTION I

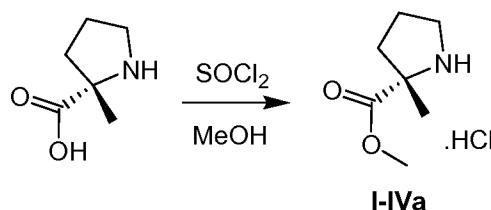
PREPARATION OF SYNTHETIC INTERMEDIATE: SECTION I

Example X-IV: Preparation of Intermediate I-IVc

Scheme X-IV



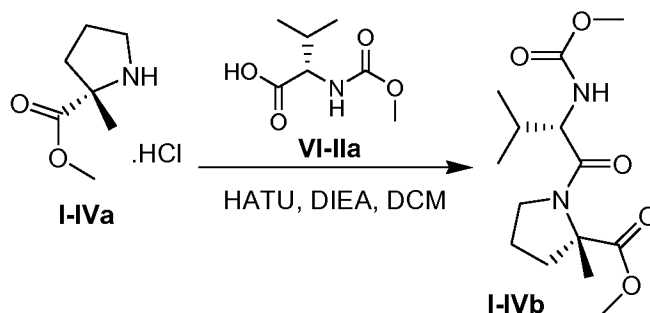
Scheme X-IVa



General Procedure X-W

[0167] To a mixture of 2-methyl-L-proline (1.0 g, 7.8 mmol) in 20 mL of dry methanol was added SOCl_2 (2.8 g, 23.3 mmol) dropwise at 0°C under nitrogen protection. The resulting mixture was stirred at room temperature overnight, and then the solvent was removed under reduced pressure to afford compound I-IVa as an HCl salt (1.4 g, yield 100%). ^1H NMR (300 MHz, CD_3OD): δ 3.86 (s, 3H), 3.42-3.46 (m, 2H), 2.36-2.45 (m, 1H), 2.00-2.19 (m, 3H), 1.68 (s, 3H).

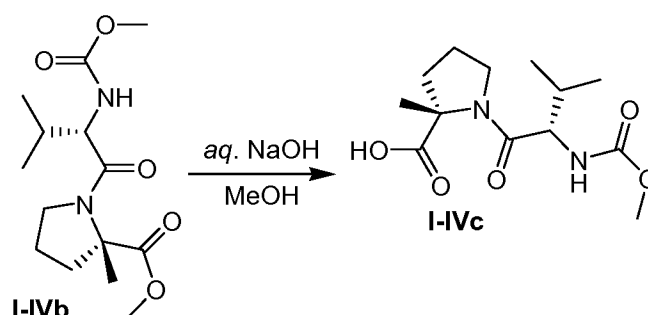
Scheme X-IVb



General Procedure X-X

[0168] To a solution of compound **I-IVa** (1.35 g, 7.7 mmol) in 30 mL of DCM was added compound **VI-IIa** (1.5 g, 8.5 mmol), HATU (4.4 g, 11.6 mmol) and DIEA (3 g, 23 mmol). The resulting mixture was stirred at room temperature overnight. Subsequently, the mixture was diluted with DCM and washed with brine. The organic layers were dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography (PE/EA=3/1) to afford compound **I-IVb** (1.5 g, yield 65%). **MS (ESI)** m/z (M+H)⁺ 301.

Scheme X-IVc



General Procedure X-Y

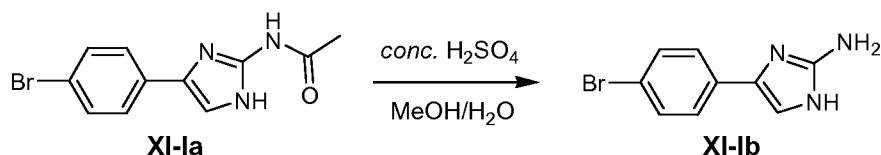
[0169] A mixture of compound **I-IVb** (1.5 g, 5 mmol) and NaOH (0.6 g, 15 mmol) in MeOH (30 mL) and H₂O (5 mL) was stirred at 70°C for 2 hours. The methanol under reduce pressure and the residue was dissolved with 20 mL of H₂O, then the solution was acidified to pH 2~3 with 2N HCl and extracted with DCM (50 mL×2). The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated to afford compound **I-IVc** (0.8 g, yield 57%), which was used in next step without further purification. ¹H NMR (300 MHz, DMSO-*d*₆): δ 12.20 (s, 1H), 7.24 (d, *J*=8.4 Hz, 1 H), 3.54-3.98 (m, 3H), 3.50 (s, 3H), 1.78-2.05 (m, 5H), 1.34 (s, 3H), 0.84-0.88 (m, 6H).

SECTION II

PREPARATION OF COMPOUNDS: SECTION II

Example XI-I: General synthetic protocol for the preparation of compounds 701-705

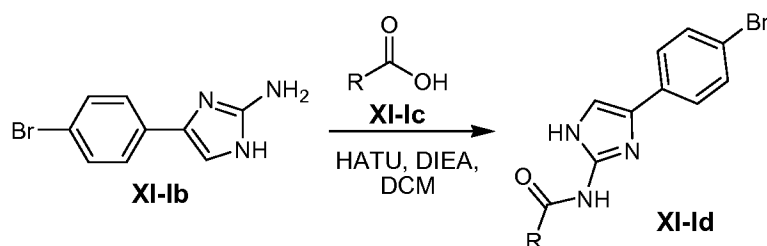
Scheme XI-Ib



General Procedure XI-B

[0171] *Conc.* H₂SO₄ (3 mL) was added to a solution of compound **XI-1a** (2.5 g, 8.9 mmol) in MeOH (10 mL) and H₂O (10 mL). The reaction mixture was stirred at reflux for 5 hrs. After being cooled to r.t., the mixture was basified with Na₂CO₃ to pH~9, and extracted with DCM. The organic layer was separated, dried over MgSO₄, filtered and concentrated to afford compound **XI-1b** (1.4 g, yield 65%). **MS (ESI)** *m/z* (M+H)⁺ 239.

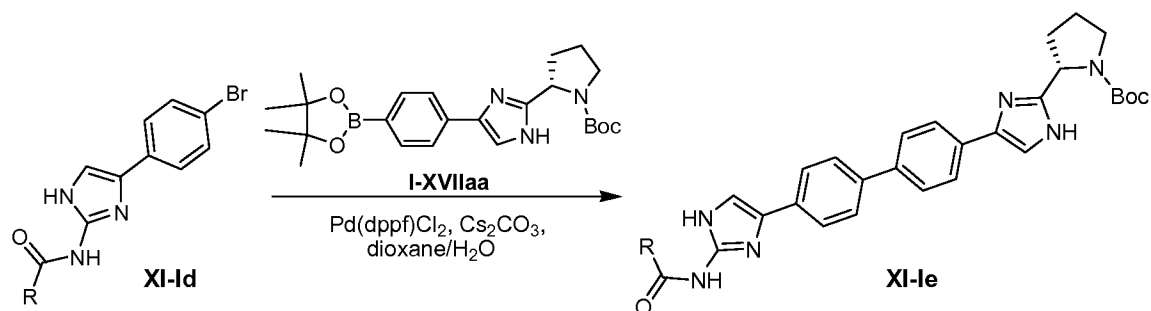
Scheme XI-Ic



General Procedure XI-C

[0172] Compound **XI-Ib** (1 eq.) was added to a mixture of acid **XI-Ic** (1.2 eq.), HATU (1.2 eq.) and DIEA (3 eq.) in DCM. The reaction mixture was stirred at r.t. for 1 h, and then diluted with DCM, washed with water and brine. The organic layer was separated, dried, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC to afford a compound of general structure **XI-Id**.

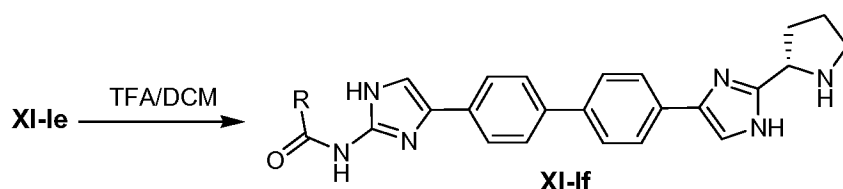
Scheme XI-Id



General Procedure XI-D

[0173] To a stirred mixture of a compound of general structure **XI-Id** (1 eq.), compound **I-XVIIaa** (1.1 eq.), and Cs_2CO_3 (2.2 eq.) in 1,4-dioxane and H_2O (v/v=7/1) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (10 mol%) under N_2 protection. The reaction mixture was stirred at 90 °C for 12hrs. After being cooled to r.t., the mixture was diluted with EtOAc, washed with water and brine. The organic layer was separated, dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (PE:EA=1:2) to afford a compound of general structure **XI-Ie**.

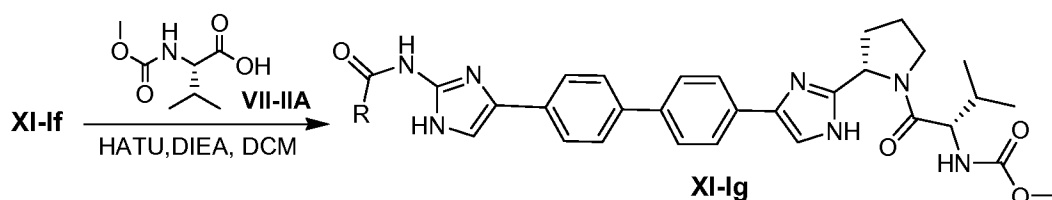
Scheme XI-Ie



General Procedure XI-E

[0174] A compound of general structure **XI-Ie** (1 eq.) was dissolved in a solution of TFA in DCM (v%=30%, 2 mL). The reaction mixture was stirred at r.t. for 1 h. After concentrated under reduced pressure, the residue was neutralized with aq. NaOH (1 M), and extracted with DCM. The organic layer was dried over MgSO_4 , filtered and concentrated to afford a compound of general structure **XI-If**, which was used directly in the next reaction without further purification.

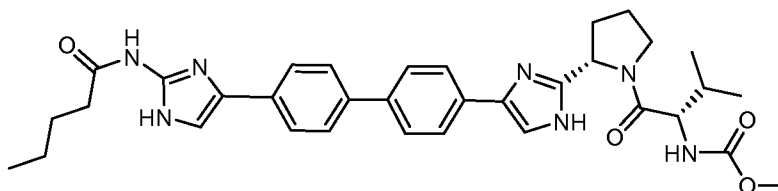
Scheme XI-If



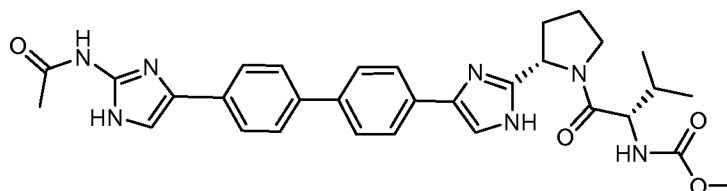
General Procedure XI-F

[0175] To a stirred mixture of compound **VII-IIA** (1.5 eq.), HATU (1.5 eq.) and DIEA (3 eq.) in DCM was added a compound of general structure **XI-If** (1 eq.). The reaction mixture was stirred at r.t. for 3 hrs. After diluted with DCM, the organic layer was washed with water and brine, filtered and concentrated under reduced pressure. The residue was purified by Prep-HPLC to afford a compound of general structure **XI-Ig**.

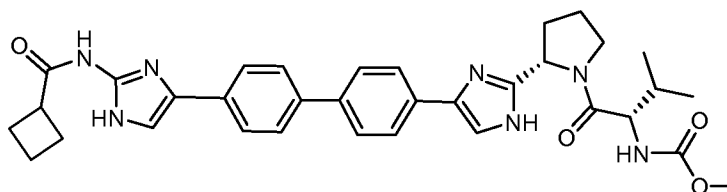
[0176] The above synthetic approach was adopted for preparation of the following compounds:

Example XI-Ia: Synthesis of Compound 701**701**

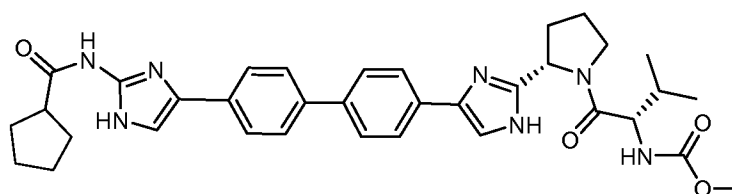
[0177] Compound **701** was prepared according to General Procedure XI-A-F, 15 mg, yield 63%; $^1\text{H NMR}$ (CD_3OD , 400MHz) δ 7.80-7.64 (m, 8H), 7.32 (s, 1H), 7.24 (s, 1H), 5.19-5.21 (m, 1H), 4.25 (d, $J=7.6\text{Hz}$, 1H), 3.88-4.03 (m, 2H), 3.67 (s, 3 H), 2.46 (t, $J=7.6\text{Hz}$, 2H), 2.18-2.40 (m, 3H), 1.98-2.13 (m, 2H), 1.68-1.76 (m, 2H), 1.42-1.48 (m, 2H), 0.91-1.02 (m, 9H). **MS (ESI)** m/z ($\text{M}+\text{H}$) $^+$ 612.4.

Example XI-Ib: Synthesis of Compound 702**702**

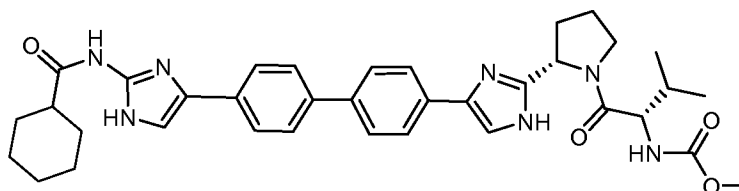
[0178] Compound **702** was prepared according to General Procedure XI-A-F, 10 mg, yield 18%; $^1\text{H NMR}$ (MeOD , 400MHz) δ 7.85-7.64 (m, 8H), 7.35 (brs, 1H), 7.26 (s, 1H), 5.17-5.25 (m, 1H), 4.20-4.30 (m, 1H), 3.85-4.09 (m, 2H), 3.70 (s, 3 H), 2.46-2.48 (m, 2H), 2.24 (s, 3H), 1.98-2.14 (m, 3H), 0.94-1.02 (m, 6H). **MS (ESI)** m/z ($\text{M}+\text{H}$) $^+$ 570.2.

Example XI-Ic: Synthesis of Compound 703**703**

[0179] Compound **703** was prepared according to General Procedure XI-A-F, 10 mg, yield 19%; $^1\text{H NMR}$ (MeOD , 400MHz) δ 7.66-7.78 (m, 8H), 7.33 (s, 1H), 7.25 (s, 1H), 5.18-5.21 (m, 1H), 4.25 (d, $J=7.6\text{ Hz}$, 1H), 3.87-4.02 (m, 2H), 3.67 (s, 3 H), 1.94-2.44 (m, 12H), 0.91-0.98 (m, 6H). **MS (ESI)** m/z ($\text{M}+\text{H}$) $^+$ 610.3.

Example XI-Id: Synthesis of Compound 704**704**

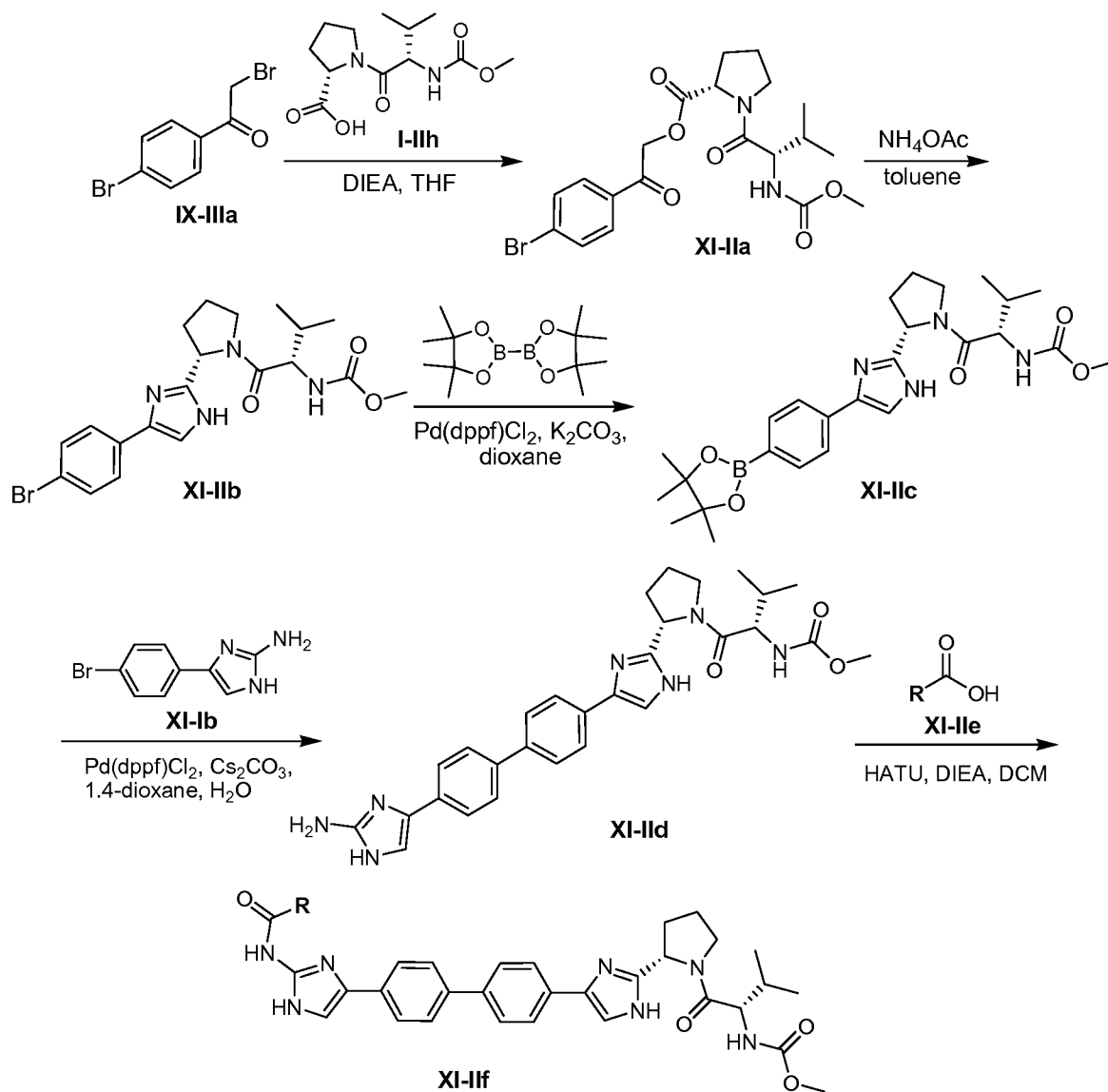
[0180] Compound **704** was prepared according to General Procedure XI-A-F, 9.4 mg, yield 18%; $^1\text{H NMR}$ (CD_3OD , 400MHz) δ 7.63-7.75 (m, 8H), 7.30 (s, 1H), 7.22 (s, 1H), 5.13-5.20 (m, 1H), 4.22 (d, $J=7.5$ Hz, 1H), 3.86-4.01 (m, 2H), 3.65 (s, 3 H), 2.85-2.91 (m, 1H), 2.17-2.37 (m, 3H), 1.76-2.07 (m, 8H), 1.66-1.68 (m, 2H), 0.89-0.95 (m, 6H). **MS (ESI)** m/z ($\text{M}+\text{H}$) $^+$ 624.4.

Example XI-Id: Synthesis of Compound 705**705**

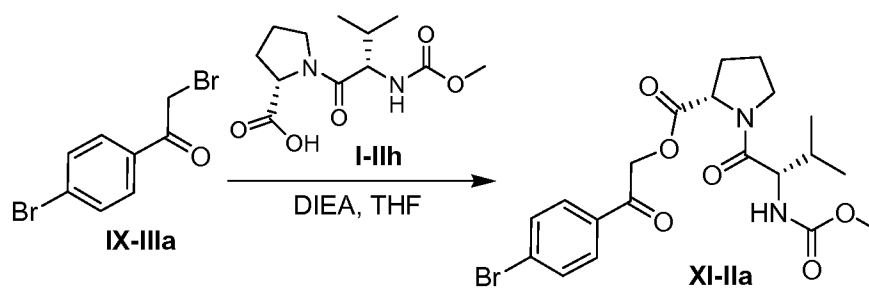
[0181] Compound **705** was prepared according to General Procedure XI-A-F, 10.5 mg, yield 15%; $^1\text{H NMR}$ (CD_3OD 400MHz) δ 7.61-7.80 (m, 8H), 7.32 (brs, 1H), 7.23 (s, 1H), 5.15-5.22 (m, 1H), 4.23 (d, $J=7.6$ Hz, 1H), 3.84-4.09 (m, 2H), 3.65 (s, 3 H), 2.18-2.48 (m, 4H), 2.05-2.09 (m, 2H), 1.83-1.93 (m, 4H), 1.72-1.75 (m, 1H), 1.51-1.57 (m, 2H), 1.30-1.40 (m, 3H), 0.99-0.89 (m, 6H). **MS (ESI)** m/z ($\text{M}+\text{H}$) $^+$ 638.4.

Example XI-II: General synthetic protocol for the preparation of compounds 706-707

Scheme XI-II



Scheme XI-IIa

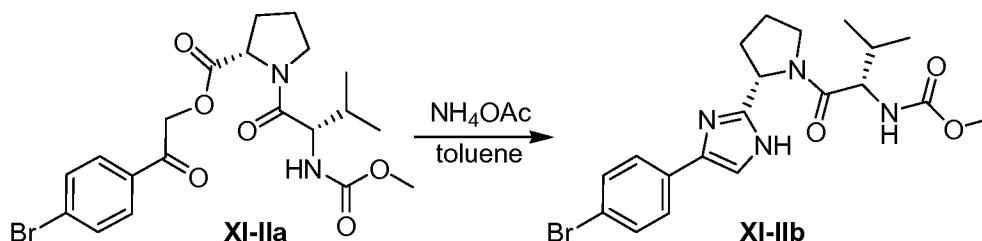


General Procedure XI-G

[0182] A mixture of 2-bromo-1-(4-bromophenyl)ethanone (**IX-IIIa**) (20 g, 72.2 mmol), compound **I-IIh** (23 g, 84.5 mmol) and DIEA (24 g, 200 mmol) in THF (250

mL) was stirred at r.t. for 12 hrs. The mixture was concentrated *in vacuo* to remove THF and then the residue was re-dissolved in EtOAc. The mixture was washed with water and brine, dried over MgSO₄ and concentrated. The residue was purified by column chromatography (PE:EA=5:1~1:1) to afford compound **XI-IIa** (25 g, yield 74%). **MS (ESI)** *m/z* (M+H)⁺ 470.

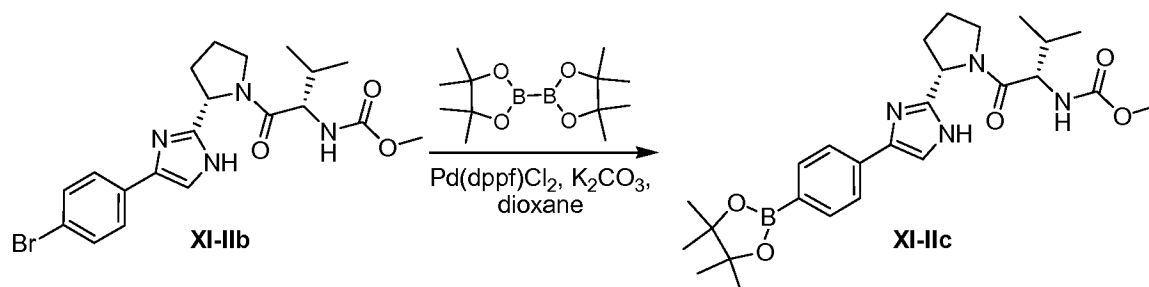
Scheme XI-IIb



General Procedure XI-H

[0183] A mixture of compound **XI-IIa** (25 g, 53.1 mmol) and NH_4OAc (40 g, 530 mmol) in toluene (250 mL) was stirred at reflux for 10 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography (PE:EA=5:1~1:2) to afford compound **XI-IIb** (15.2 g, yield: 64%). **MS (ESI)** *m/z* (M+H)⁺ 450.

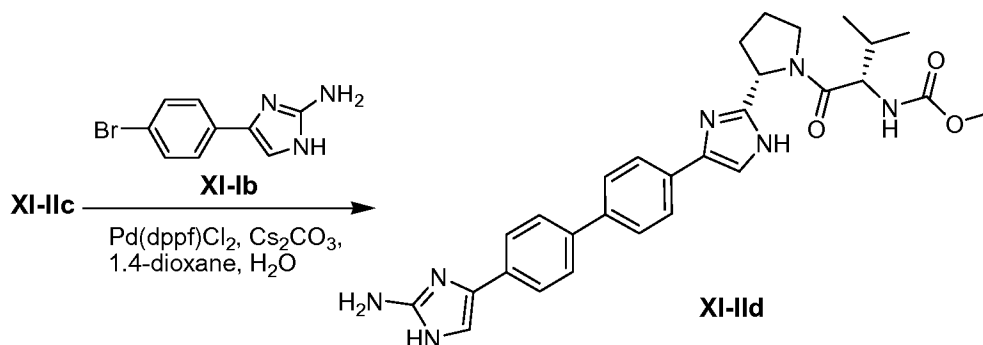
Scheme XI-IIc



General Procedure XI-I

[0184] To a stirred mixture of compound **XI-IIb** (15.2 g, 33.9 mmol), Bis(pinacolato)diboron (12.9 g, 50.8 mmol), and K_2CO_3 (9.5 g, 67.7 mmol) in 1,4-dioxane (150 mL) was added Pd(dppf)Cl_2 (1.5 g) under N_2 protection. The resulting mixture was stirred at 90 °C for 12 hrs. After cooling r.t., the mixture was diluted with EtOAc, washed with water and brine, dried over MgSO₄ and concentrated. The residue was purified by column chromatography (PE:EA=1:4~1:10) to afford compound **XI-IIc** (7.2 mg, yield 43%). **MS (ESI)** *m/z* 497 (M+H)⁺.

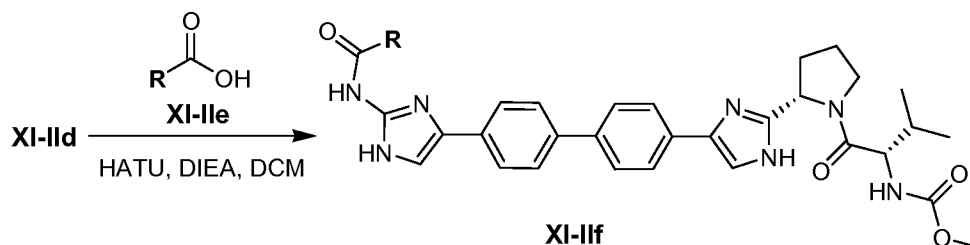
Scheme XI-IIId



General Procedure XI-J

[0185] To a stirred mixture of compound **XI-IIc** (2.2 g, 4.4 mmol), compound **XI-Ib** (1.0 g, 4.2 mmol) and Cs₂CO₃ (2.96 g, 8.4 mmol) in 1,4-dioxane (30 mL) and H₂O (3 mL) was added Pd(dppf)Cl₂ (200 mg) under N₂ protection. The reaction mixture was stirred at 90 °C overnight. The mixture was then diluted with EtOAc, washed with water and brine, dried over MgSO₄ and concentrated. The residue was purified by column chromatography (EA~EA:MeOH=20:1) to afford compound **XI-IId** (500 mg, yield 23%).
MS (ESI) *m/z* (M+H)⁺ 528.

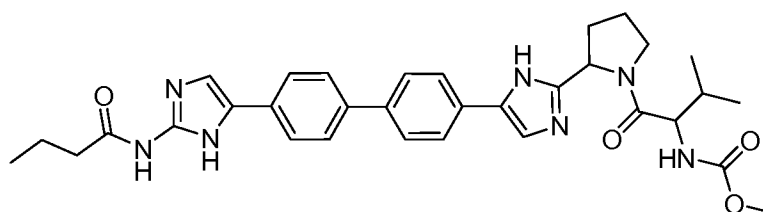
Scheme XI-IIe



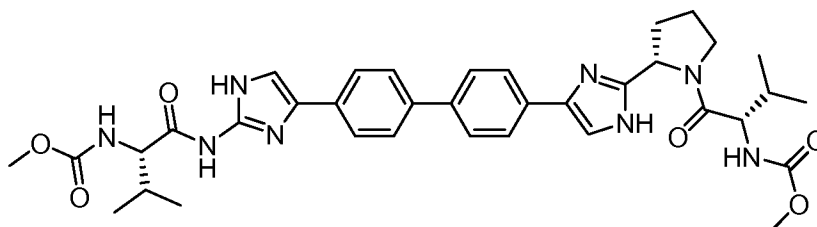
General Procedure XI-K

[0186] A mixture of compound **XI-II d** (1 eq.), HATU (1.2 eq.), DIEA (2 eq.) and general compound **XI-II e** (1.2 eq.) in DCM was stirred at r.t. for 12 hrs. The mixture was diluted with DCM, washed with water and brine, separated the organic layer, dried over Na₂SO₄ and concentrated. The residue was purified by Prep-HPLC to afford general compound **XI-II f**.

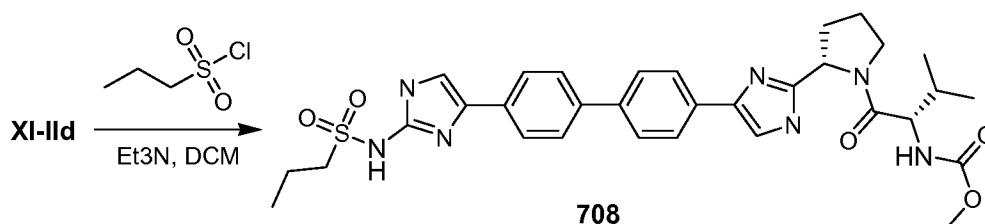
[0187] The above synthetic approach was adopted for preparation of the following compounds:

Example XI-IIa: Synthesis of Compound 706**706**

[0188] Compound **706** was prepared according to General Procedures XI-G to XI-K, 10.2 mg, yield 17.3%; $^1\text{H NMR}$ (CD_3OD , 400MHz) δ 7.66-7.79 (m, 8H), 7.34 (s, 1H), 7.25 (s, 1H), 5.17-5.21 (m, 1H), 4.25 (d, $J=7.6$ Hz, 1H), 3.87-4.06 (m, 2H), 3.67 (s, 3 H), 2.44 (t, $J=7.6$ Hz, 2H), 2.17-2.39 (m, 3H), 1.95-2.13 (m, 2H), 1.73-1.82 (m, 2H), 0.91-1.07 (m, 9H). **MS (ESI)** m/z ($\text{M}+\text{H}$) 598.2.

Example XI-IIb: Synthesis of Compound 707**707**

[0189] Compound **707** was prepared according to General Procedures XI-G to XI-K, 20 mg, yield 12.8%; $^1\text{H NMR}$ (CD_3OD , 400MHz) δ 7.66-7.78 (m, 8H), 7.34 (s, 1H), 7.26 (s, 1H), 5.18-5.21 (m, 1H), 4.13-4.29 (m, 2H), 3.85-4.05 (m, 2H), 3.70 (s, 3H), 3.67 (s, 3 H), 1.96-2.44 (m, 6H), 0.96-1.07 (m, 12H). **MS (ESI)** m/z ($\text{M}+\text{H}$) $^+$ 685.4.

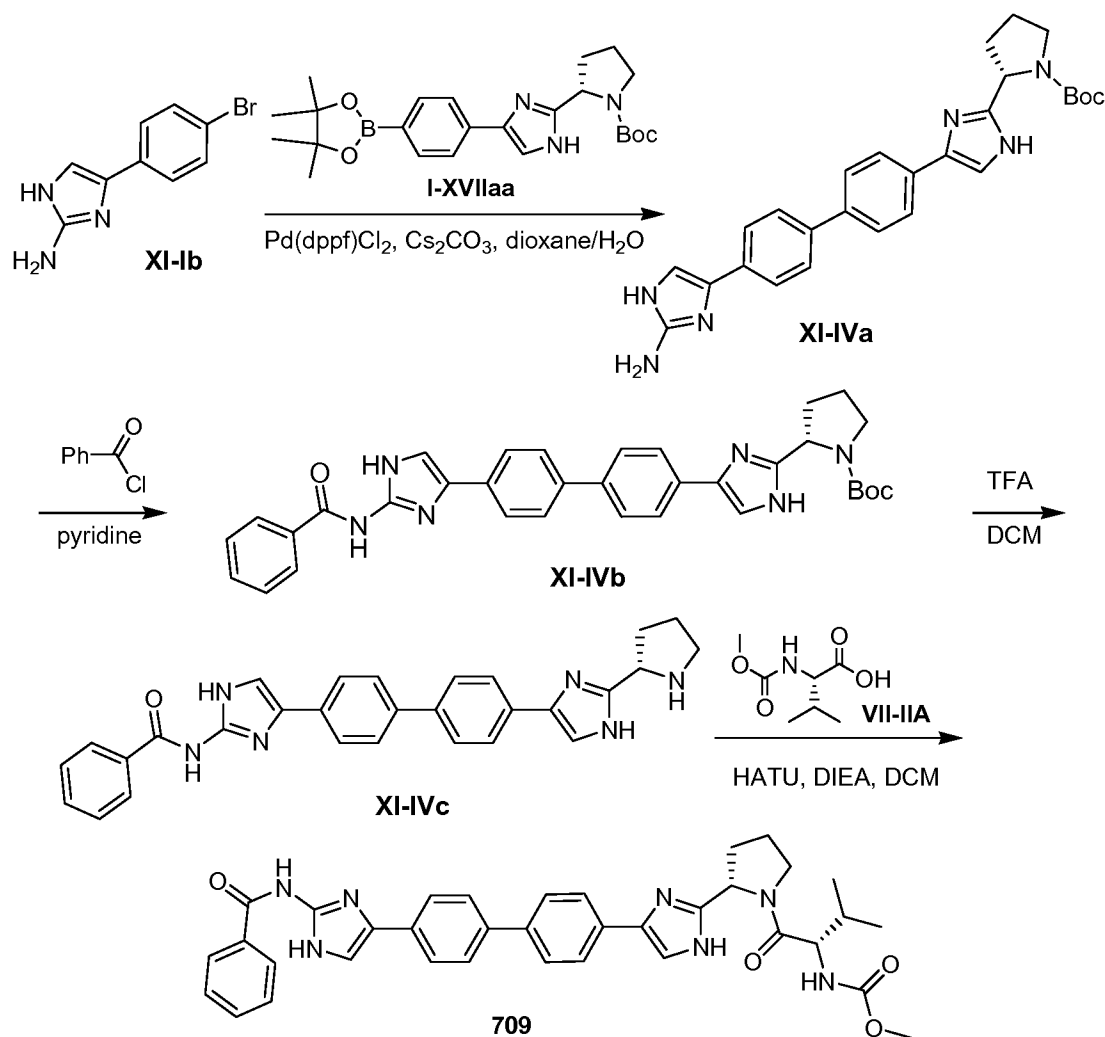
Example XI-III: Preparation of Compound 708**Scheme XI-III****708****General Procedure XI-L**

[0190] To a stirred solution of compound **XI-IIId** (100 mg, 0.19 mmol) and Et_3N (30 mg, 0.3 mmol) in DCM (2 mL) was added propane-1-sulfonyl chloride (42 mg, 0.3 mmol), and the resulting mixture was stirred at r.t. for 1 h. The mixture was diluted with DCM, washed with water and brine, and the organic layer was separated, dried and

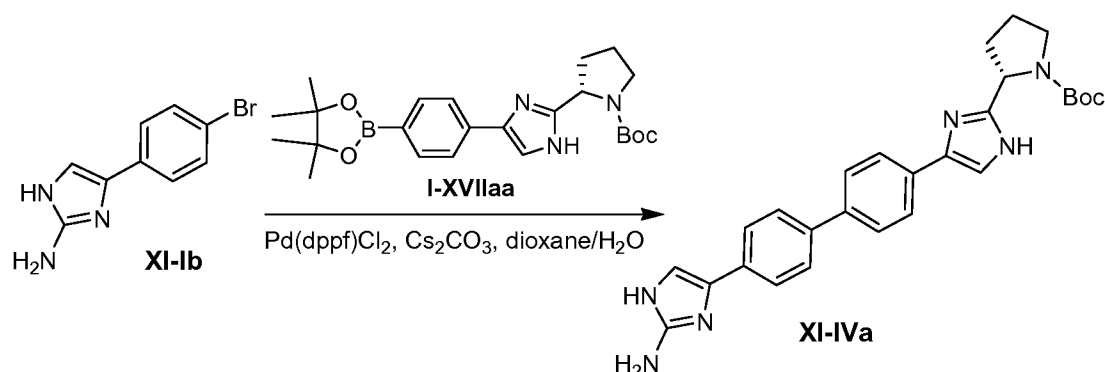
concentrated. The residue was purified by Prep-HPLC to afford compound **708** (20 mg, yield 16.7%). ¹H NMR (CD₃OD, 400MHz) δ 7.64-7.80 (m, 8H), 7.33 (s, 2H), 5.17-5.21 (m, 1H), 4.25 (d, J =7.2 Hz, 1H), 3.84-4.05 (m, 2H), 3.67 (s, 3 H), 3.54-3.58 (m, 2H), 2.19-2.39 (m, 3H), 1.96-2.12 (m, 2H), 1.81-1.91 (m, 2H), 1.07 (t, J =7.6 Hz, 3H), 0.91-0.97 (m, 6H). MS (ESI) m/z (M+H)⁺ 634.4.

Example XI-IV: Preparation of Compound **709**

Scheme XI-IV



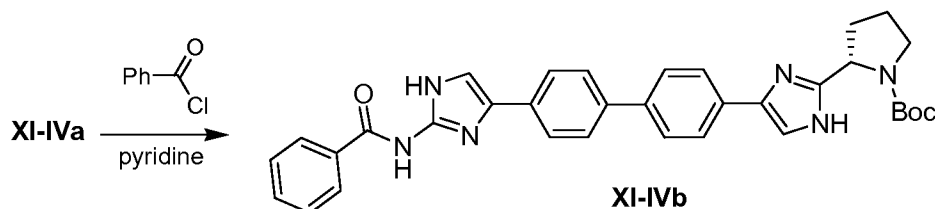
Scheme XI-IVa



General Procedure XI-M

[0191] To a stirred mixture of compound **XI-Ib** (2 g, 8.4 mmol), compound **I-XVIIaa** (3.86 g, 8.8 mmol), and Cs₂CO₃ (5.93 g, 16.8 mmol) in 1,4-dioxane (30 mL) and H₂O (2 mL) was added Pd(dppf)Cl₂ (300 mg) under N₂ protection. The resulting mixture was stirred at 100 °C for 16 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over MgSO₄ and concentrated. The residue was purified by column chromatography (PE:EA=2:1-EA:MeOH=15:1) to afford compound **XI-IVa** (900 mg, yield 23%). **MS (ESI)** *m/z* (M+H)⁺ 471.

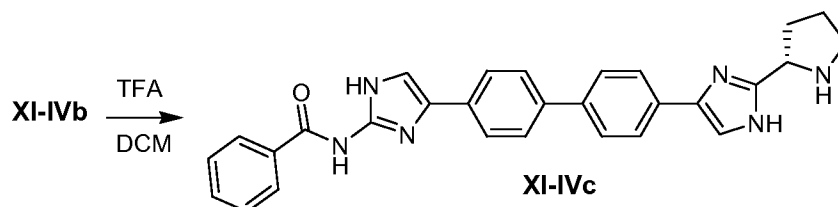
Scheme XI-IVb



General Procedure XI-N

[0192] To a stirred solution of compound **XI-IVa** (100 mg, 0.21 mmol) in pyridine was added benzoyl chloride (42 mg, 0.3 mmol), the reaction mixture was stirred at r.t. for 2 hrs. The solvent was concentrated under vacuum, re-dissolved in EtOAc, washed with water and brine, dried over MgSO₄ and concentrated to afford compound **XI-IVb** (60 mg, yield 49 %), which was used directly in the next reaction without further purification. **MS (ESI) *m/z* (M+H)⁺** 575.

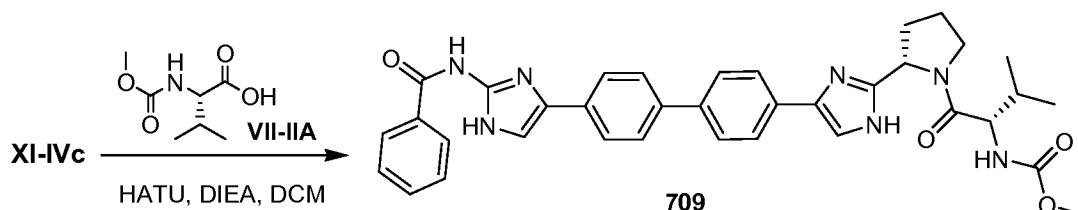
Scheme XI-IVc



General Procedure XI-O

[0193] To compound **XI-IVb** (60 mg, 0.1 mmol) in DCM was added TFA (0.5 mL). The reaction mixture was stirred at r.t. for 1 h. The solvent was concentrated under vacuum to afford compound **XI-IVc** (40 mg, yield: 80.8 %), which was used directly in the next reaction without further purification. **MS (ESI) m/z (M+H)⁺ 475.**

Scheme XI-IVd

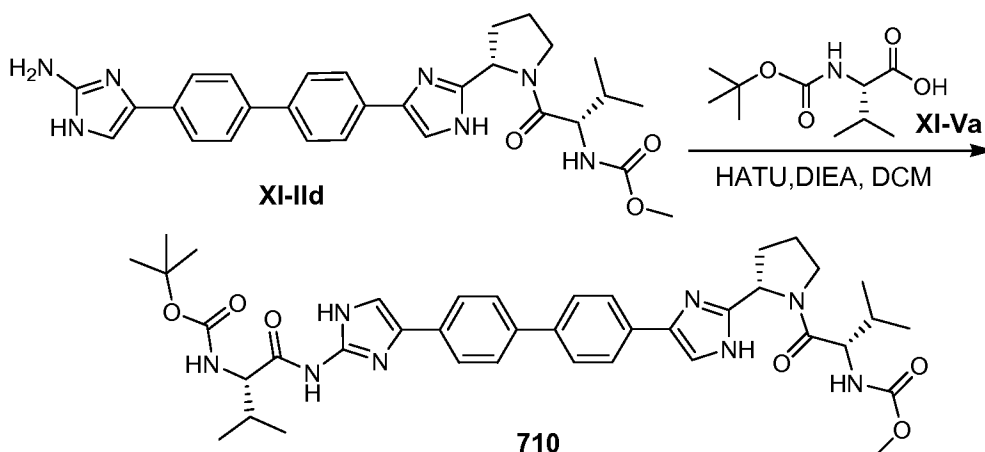


General Procedure XI-P

[0194] To a stirred mixture of compound **XI-IVc** (40 mg, 0.08 mmol), HATU (46 mg, 0.12 mmol) and DIEA (21 mg, 0.16 mmol) in DCM was added compound **VII-IIA** (21 mg, 0.12 mmol). The resulting mixture was stirred at r.t. for 1 h and then diluted with DCM, washed with water and brine. The organic layer was separated, dried and concentrated. The residue was purified by prep-HPLC to afford compound **709** (11 mg, yield 21%). **¹H NMR** (CD₃OD, 400MHz) δ 7.64-7.83 (m, 9H), 7.14-7.53 (m, 6H), 5.31-5.37 (m, 1H), 4.17 (d, $J=6.8$ Hz, 1H), 3.88-3.92 (m, 1H), 3.70 (s, 3H), 3.61-3.67 (m, 3 H), 1.95-2.49 (m, 5H), 1.02-1.07 (m, 6H). **MS (ESI) m/z (M+H)⁺ 632.4.**

Example XI-V: Preparation of Compound **710**

Scheme XI-V



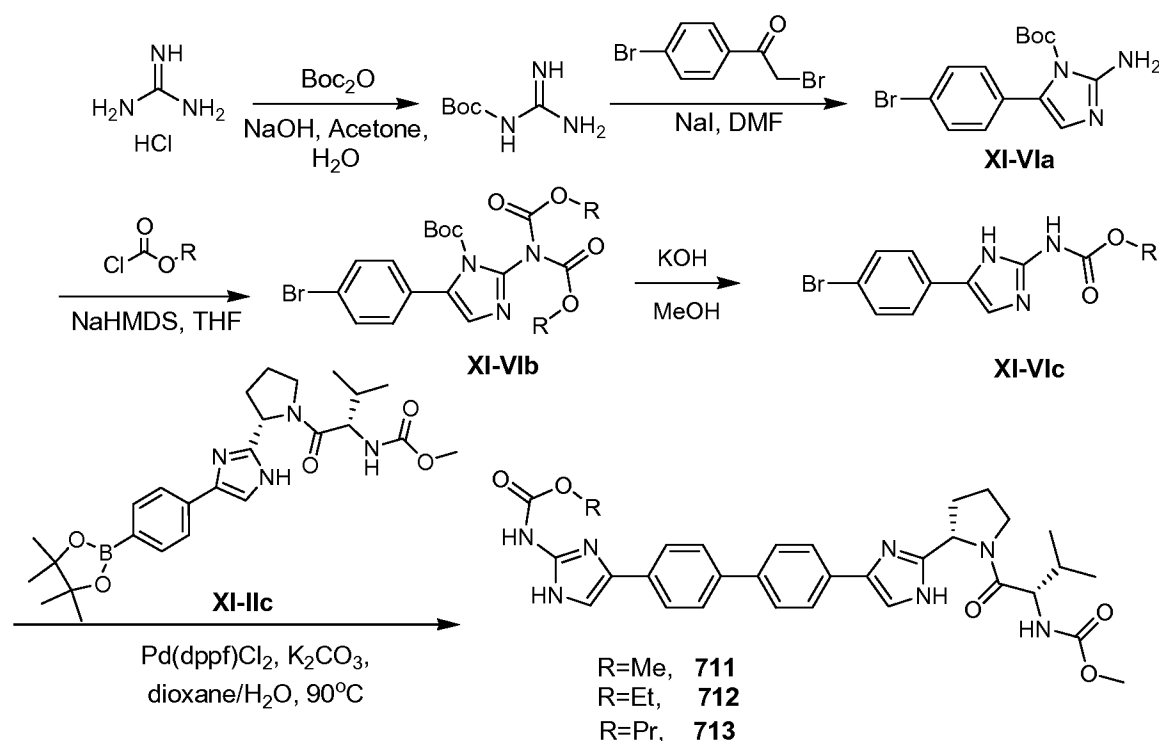
General Procedure XI-Q

[0195] Compound **XI-Va** (65 mg, 0.3 mmol) was dissolved in DCM (2 mL), followed by addition of Compound **XI-IIa** (100 mg, 0.19 mmol), HATU (114 mg, 0.3 mmol) and DIEA (52 mg, 0.4 mmol). The resulting mixture was stirred at r.t. for 12 hrs.

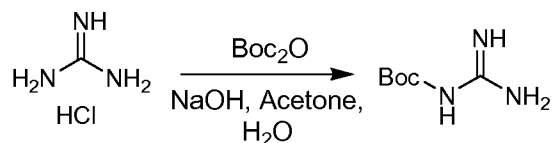
The mixture was then diluted with DCM (40 mL), ad washed with water and brine. The organic layer was separated, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by Prep-HPLC to afford Compound **710** (15 mg, yield 11%). ¹H NMR (400MHz, CD₃OD) δ 7.66-7.81 (m, 8H), 7.34 (s, 1H), 7.27 (s, 1H), 5.18-5.23 (m, 1H), 4.25 (d, *J*=7.6 Hz, 1H), 4.10-4.15 (m, 1H), 3.98-4.06 (m, 1H), 3.86-3.94 (m, 1H), 3.67 (s, 3H), 2.02-2.41 (m, 6H), 1.49 (s, 9H), 1.07-0.91 (m, 12H). MS (ESI) *m/z* (M+H)⁺ 727.5.

Example XI-VI: Preparation of Compounds **711-713**

Scheme XI-VI



Scheme XI-VIa

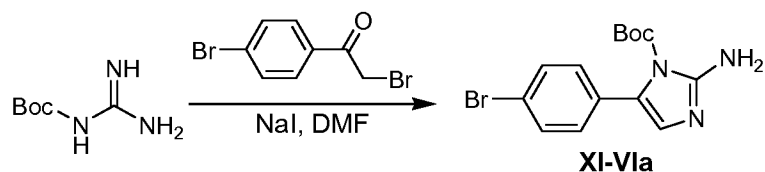


General Procedure XI-R

[0196] Guanidine hydrochloride (200 g, 2.1 mol) was dissolved in acetone (200 mL), followed by addition of a solution of *aq.* NaOH (10.5 M, 400 mL) and Di-tert-butyl dicarbonate (113 g, 0.52 mol). The reaction mixture was stirred at 0°C for 8 hrs. The mixture was concentrated *in vacuo* to remove acetone, and then it was poured into

water (200 mL), and extracted with EtOAc (300 mL $\times$ 3). The combined organic layers were washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The crude N-Boc-guanidine was used in next step directly without further purification (43 g, yield 52%).

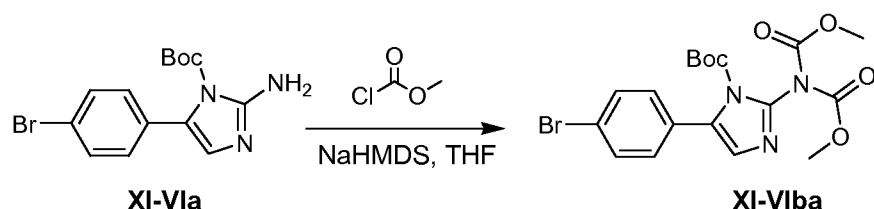
Scheme XI-VIb



General Procedure XI-R

[0197] A flask was charged with crude N-Boc-guanidine (23 g, 144 mmol) and DMF (50 mL) and then NaI (5 g, 33.3 mmol) and 4-bromophenacyl bromide (10 g, 36.1 mmol) were added thereto at 0°C. The resulting mixture was slowly warmed to r.t. and stirred for an additional 12 hrs. The mixture was poured into water (100 mL), and extracted with EtOAc (100 mL $\times$ 3). The combined organic layers were washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Petroleum ether: EtOAc =10:1) to afford compound **XI-VIa** (4.1 g, yield 33%). **MS (ESI) m/z (M+H)⁺ 339.**

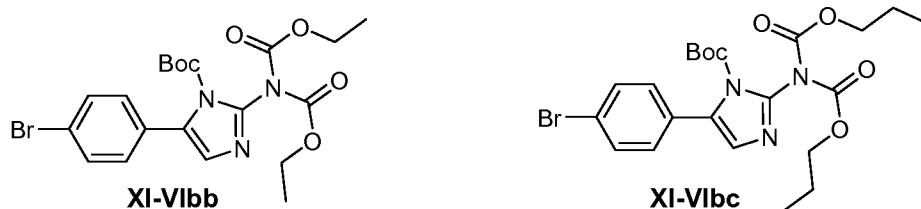
Scheme XI-VIc



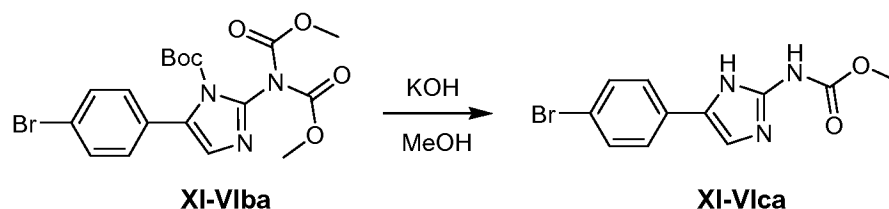
General Procedure XI-S

[0198] To a solution of compound **XI-VIa** (170 mg, 0.5 mmol) in anhydrous THF (3 mL) was added NaHMDS (1 mL, 1 mmol) at 0°C. The mixture was stirred at 0°C for 10 min, and then a solution of methyl chloroformate (94 mg, 1 mmol) in THF (1 mL) was added, the reaction mixture was stirred at 0°C for 30 min. After the starting material was consumed, the mixture was poured into water (20 mL), and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by prep-TLC (Petroleum ether: EtOAc =3:1) to afford compound **XI-VIbb** (100 mg, yield 44%). **MS (ESI) m/z (M+H)⁺ 455.**

[0199] The following compounds were prepared using General Procedure XI-S:



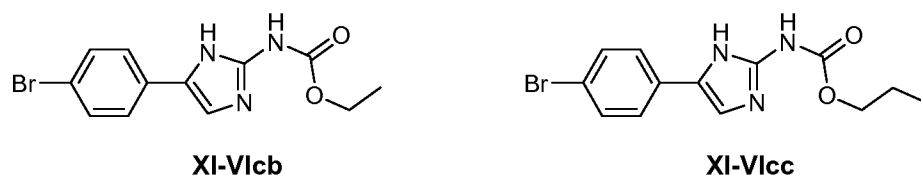
Scheme XI-VId



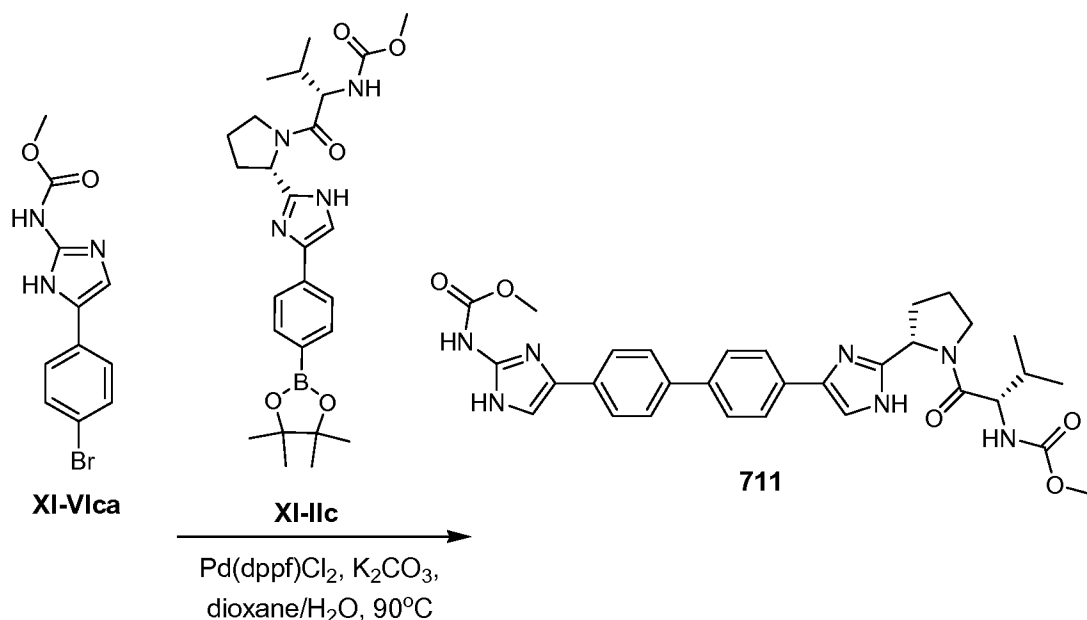
General Procedure XI-T

[0200] Compound **XI-VIba** (80 mg, 0.18 mmol) was taken up with MeOH (2 mL) and *aq.* KOH (1 M, 1 mL). The resulting mixture was stirred at r.t. for 5 hrs. Then the mixture was concentrated *in vacuo* to remove MeOH, and the residue was diluted with water (10 mL), and extracted with DCM (20 mL $\times$ 3). The organic layers were combined, washed with water and brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by prep-TLC (Petroleum ether: EtOAc =3:1) to afford compound **XI-VIca** (50 mg, yield 96%). **MS (ESI) m/z (M+H)⁺ 297.**

[0201] The following compounds were prepared using General Procedure XI-T:



Scheme XI-VIe

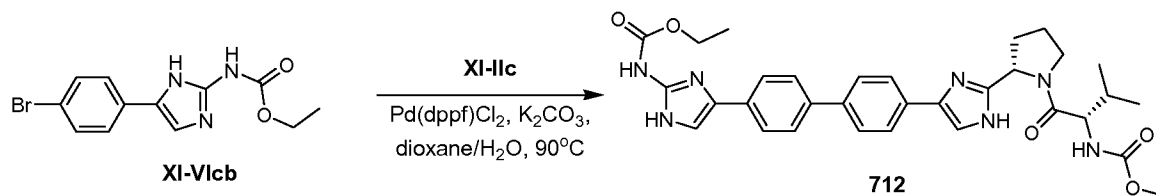


General Procedure XI-U

[0202] A flask was charged with compound **XI-VIca** (50 mg, 0.17 mmol), compound **XI-IIc** (85 mg, 0.17 mmol), K_2CO_3 (48 mg, 0.35 mmol), 1,4-dioxane (3.5 mL) and H_2O (0.5 mL), and then purged with nitrogen for three times. The nitrogen protected mixture was treated with Pd(dppf)Cl_2 (13 mg, 0.017 mmol). The reaction mixture under nitrogen protection was then stirred at 90°C for 12 hrs. After being cooled to r.t., the mixture was diluted with EtOAc (50 mL), and washed with water and brine. The organic layer was separated, dried over MgSO_4 and concentrated under reduced pressure. The residue was initially purified by Prep-TLC (EtOAc:MeOH=10:1) to get the crude product, which was purified by prep-HPLC to afford compound **711** (6.1 mg, yield 6.2%). $^1\text{H NMR}$ (400MHz, CD_3OD) δ 7.65-7.77 (m, 8H), 7.33 (s, 1H), 7.24 (s, 1H), 5.18-5.20 (m, 1H), 4.25 (d, $J=7.2$ Hz, 1H), 3.86-4.02 (m, 2H), 3.88 (s, 3H), 3.67 (s, 3H), 2.01-2.38 (m, 5H), 0.91-1.02 (m, 6H). **MS (ESI) m/z ($\text{M}+\text{H}$) $^+$** 586.1.

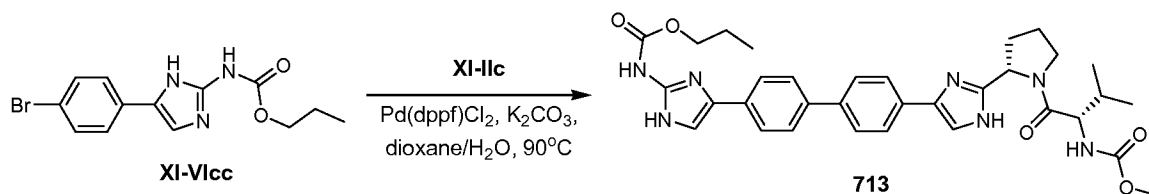
[0203] The following compounds were prepared using General Procedure XI-U:

Scheme XI-VIf



[0204] Compound **712**; 2.5 mg, yields 3.3%. ¹H NMR (300MHz, CD₃OD) δ 7.62-7.77 (m, 8H), 7.30 (s, 1H), 7.20 (s, 1H), 5.13-5.19 (m, 1H), 4.21-4.28 (m, 3H), 3.83-4.03 (m, 2H), 3.64 (s, 3H), 1.98-2.39 (m, 5H), 1.29-1.36 (m, 3H), 0.88-0.98 (m, 6H). MS (ESI) *m/z* (M+H)⁺ 600.3.

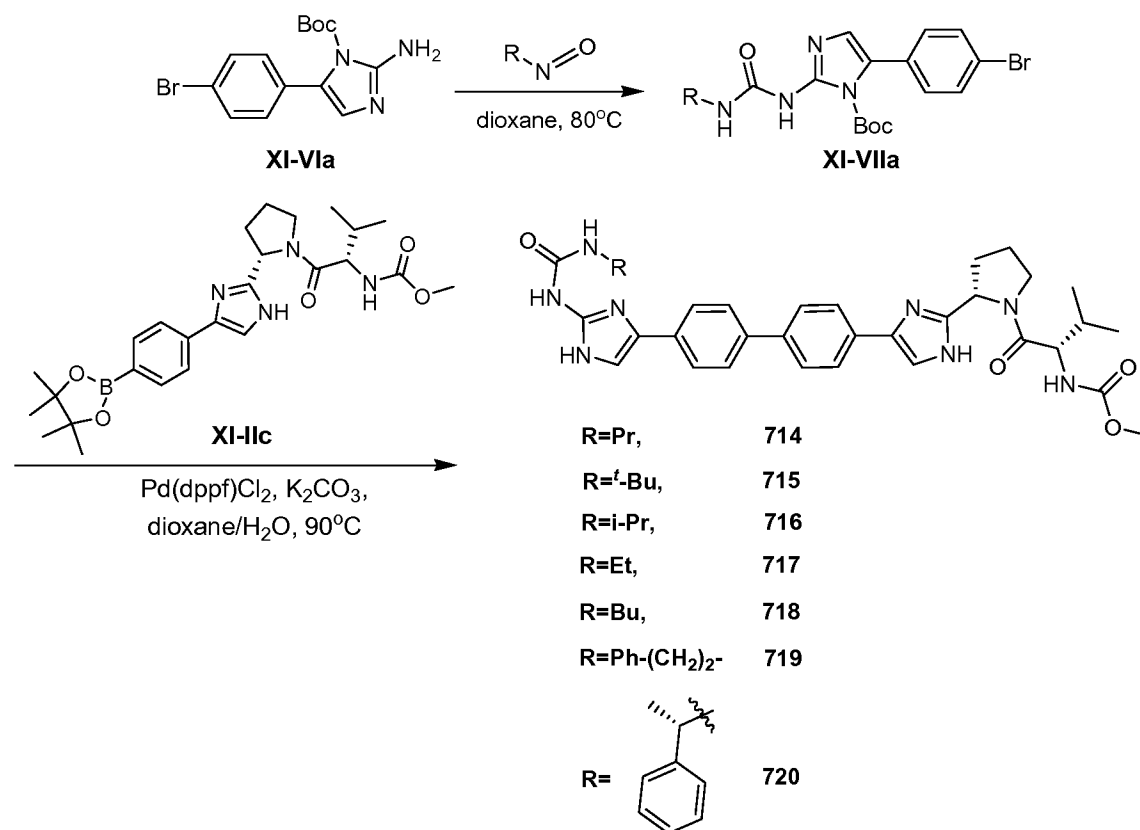
Scheme XI-VIg



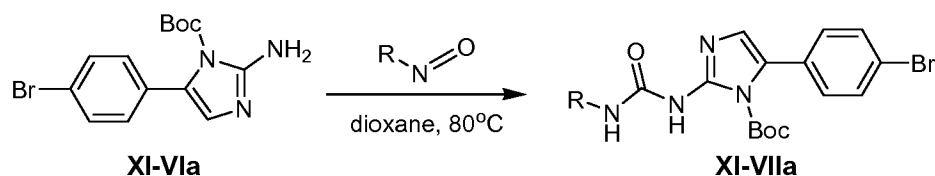
[0205] Compound **713**; 10 mg, yield 11%; ¹H NMR (400MHz, CD₃OD) δ 7.65-7.77 (m, 8H), 7.33 (s, 1H), 7.23 (s, 1H), 5.18-5.21 (m, 1H), 4.25 (d, *J*=7.2 Hz, 1H), 4.20 (t, *J*=7.2 Hz, 2H), 3.86-4.06 (m, 2H), 3.67 (s, 3H), 2.01-2.41 (m, 5H), 1.71-1.80 (m, 2H), 0.91-1.05 (m, 9H). **MS (ESI) *m/z* (M+H)⁺** 614.1.

Example XI-VII: Preparation of Compounds 714-720

Scheme XI-VII



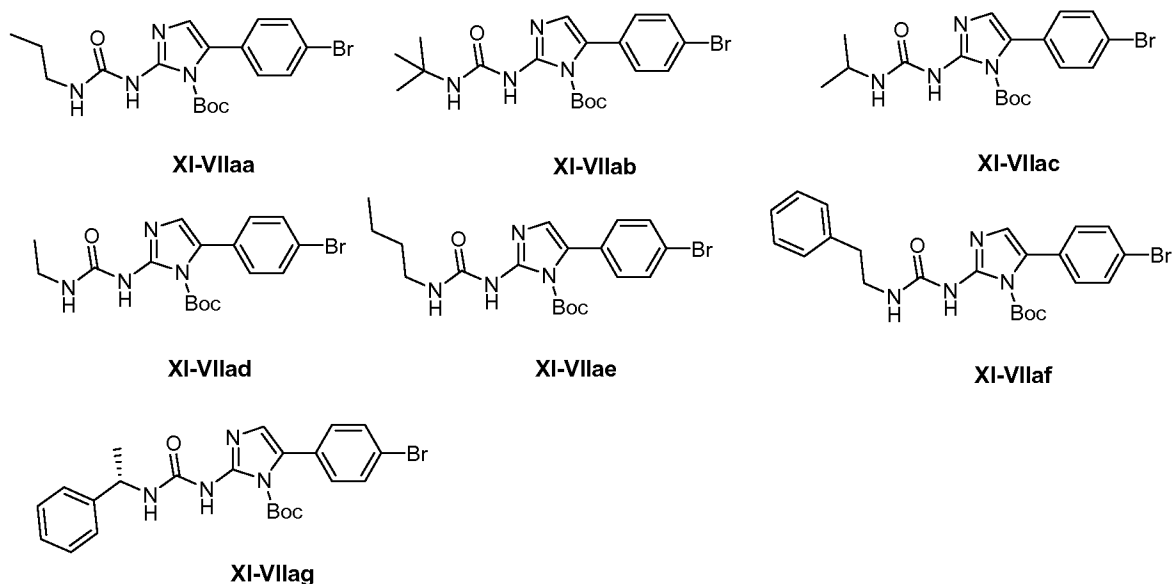
Scheme XI-VIIa



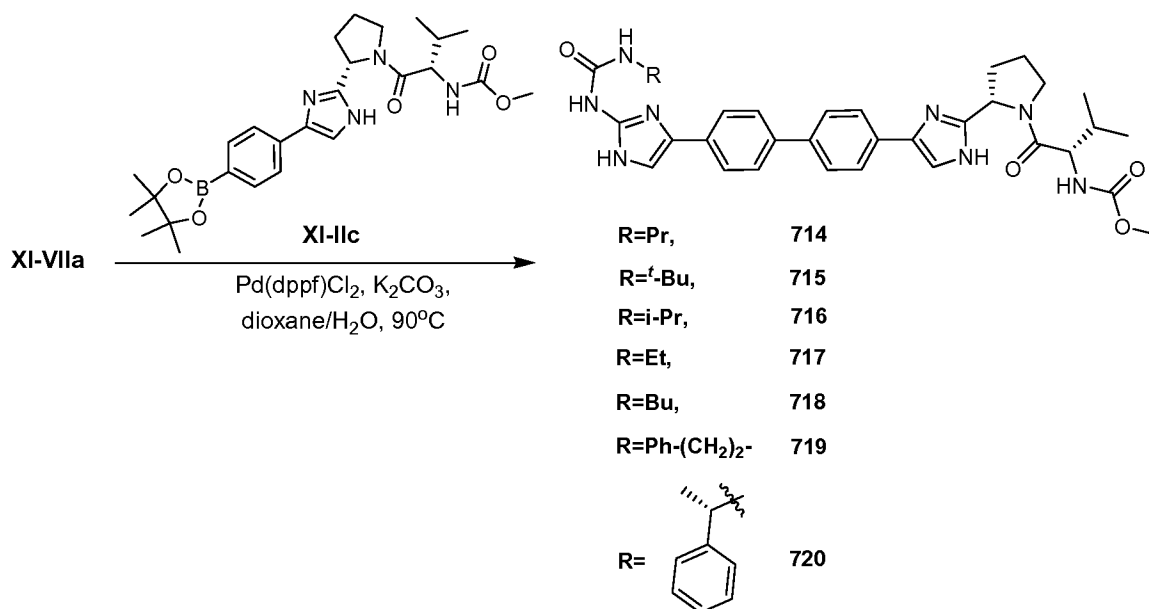
General Procedure XI-V

[0206] To a solution compound **XI-VIa** (200 mg, 0.59 mmol) in 1,4-dioxane (3 mL) was added isocyanate (1.3 mmol). The reaction mixture was heated to 80°C for 5 hrs. After being cooled to r.t., the mixture was diluted with EtOAc (40 mL), washed with water and brine. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (Petroleum ether: EtOAc =3:1) to afford general compound **XI-VIIa**.

[0207] The following compounds were prepared using General Procedure XI-V:



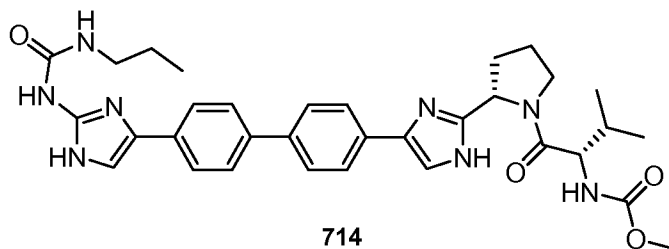
Scheme XI-VIIIb



General Procedure XI-W

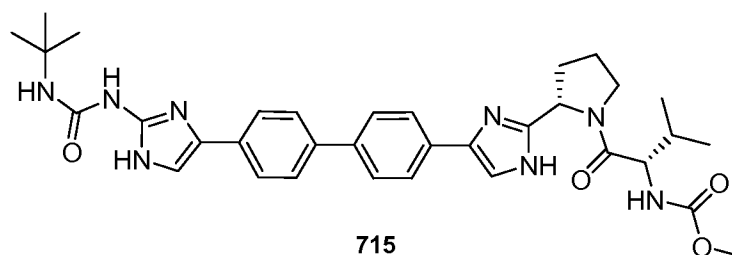
[0208] A flask was charged with general compound **XI-VIIa** (1 eq.), compound **XI-IIc** (1.05 eq.), Cs₂CO₃ (2.2 eq.), 1,4-dioxane and H₂O (0.05 mmol/mL, v/v=7/1), and then purged with nitrogen for three times. The nitrogen protected mixture was treated with Pd(dppf)Cl₂ (10 mol%). The reaction mixture was stirred at 90°C for 12 hrs under nitrogen protection. After being cooled to r.t., the mixture was diluted with EtOAc (50 mL), washed with water and brine. The organic layer was separated, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Each residue was separately purified by Prep-TLC (Petroleum ether: EtOAc =1:2) to afford each of the final compounds.

[0209] The following compounds were prepared using General Procedure XI-W:

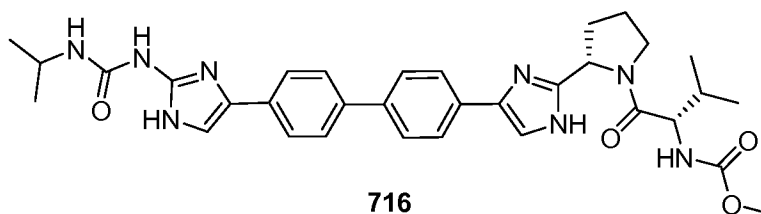


[0210] Compound **714**; 8 mg, yield 6%. ¹H NMR (400MHz, CD₃OD): δ 7.59-7.74 (m, 8H), 7.30 (s, 1H), 7.13 (s, 1H), 5.14-5.18 (m, 1H), 4.22 (d, *J*=7.5 Hz, 1H), 3.81-

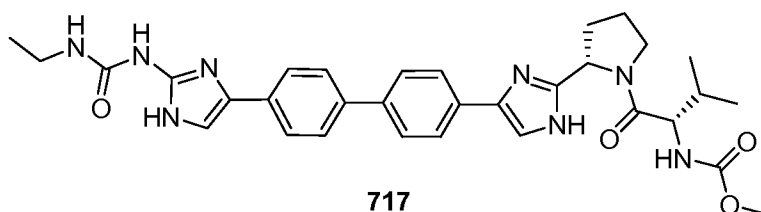
4.04 (m, 2H), 3.64 (s, 3H), 3.22 (t, $J=3.9$ Hz, 2H), 1.92-2.40 (m, 5H), 1.51-1.64 (m, 2H), 0.88-1.00 (m, 9H). **MS (ESI) m/z (M+H)⁺** 613.3.

**715**

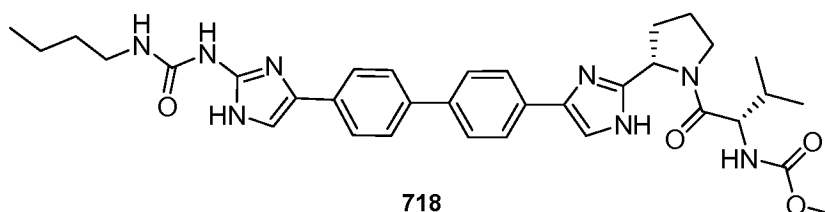
[0211] Compound **715**; 3.0 mg, yields 4%. **¹H NMR** (400MHz, CD₃OD): δ 7.63-7.73 (m, 8H), 7.31 (s, 1H), 7.15 (s, 1H), 5.16-5.19 (m, 1H), 4.22-4.24 (m, 1H), 3.87-4.03 (m, 2H), 3.65 (s, 3H), 2.02-2.37 (m, 5H), 1.41 (s, 9H), 0.89-0.95 (m, 6H). **MS (ESI) m/z (M+H)⁺** 627.0.

**716**

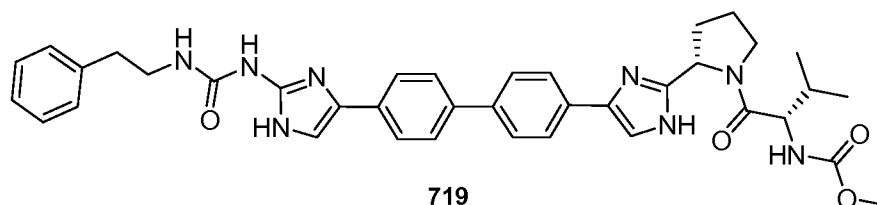
[0212] Compound **716**; 6.0 mg, yields 4%. **¹H NMR** (400MHz, CD₃OD): δ 7.63-7.73 (m, 8H), 7.31 (s, 1H), 7.16 (s, 1H), 5.16-5.19 (m, 1H), 4.22-4.24 (m, 1H), 3.86-4.01 (m, 3H), 3.65 (s, 3H), 2.02-2.37 (m, 5H), 1.23 (d, $J=6.4$ Hz, 6H), 0.89-0.95 (m, 6H). **MS (ESI) m/z (M+H)⁺** 613.0.

**717**

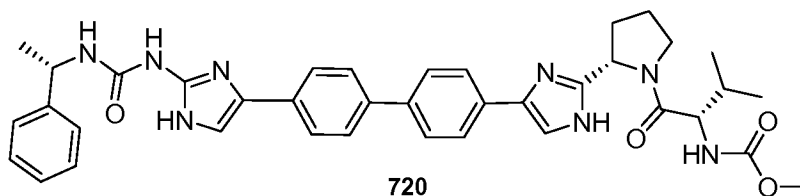
[0213] Compound **717**; 8.0 mg, yields 4%. **¹H NMR** (300MHz, CD₃OD): δ 7.64-7.74 (m, 8H), 7.42 (s, 1H), 7.20 (s, 1H), 5.15-5.20 (m, 1H), 4.20-4.23 (m, 1H), 3.82-4.05 (m, 2H), 3.64 (s, 3H), 1.99-2.41 (m, 7H), 1.17-1.22 (m, 3H), 0.88-0.94 (m, 6H). **MS (ESI) m/z (M+H)⁺** 599.2.

**718**

[0214] Compound **718**; 3.2 mg, yields 12%. ^1H NMR (300MHz, CD_3OD): δ 7.60-7.81 (m, 8H), 7.33 (brs, 1H), 7.17 (s, 1H), 5.13-5.26 (m, 1H), 4.23 (d, $J=6.8\text{Hz}$, 1H), 3.87-4.08 (m, 2H), 3.65 (s, 3H), 3.23-3.29 (m, 2H), 1.96-2.39 (m, 5H), 1.51-1.63 (m, 2H), 1.37-1.50 (m, 2H), 0.88-1.03 (m, 9H). MS (ESI) m/z ($\text{M}+\text{H}$) $^+$ 627.0.



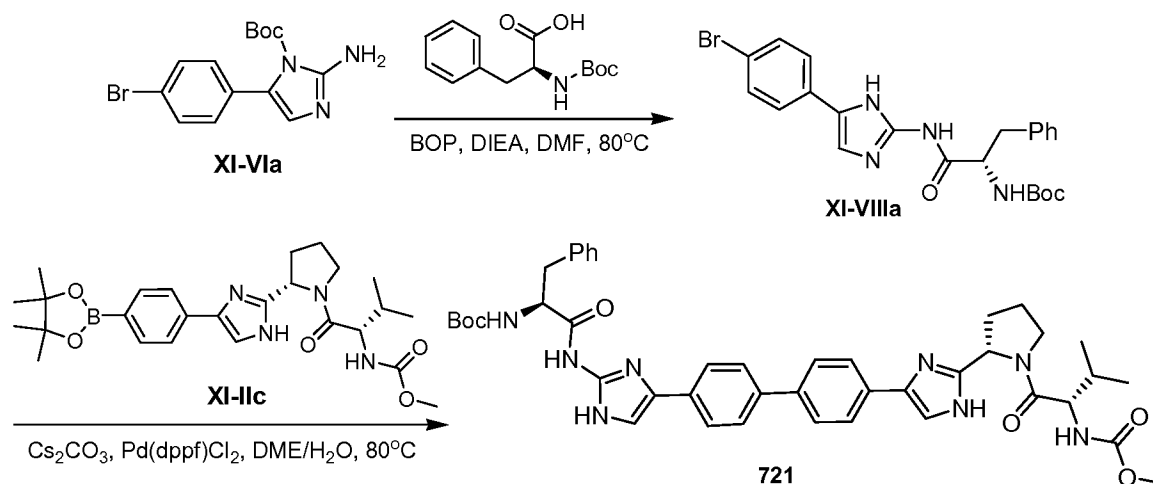
[0215] Compound **719**; 3.2 mg, yield 18%; ^1H NMR (400MHz, CD_3OD): δ 7.62-7.72 (m, 8H), 7.26-7.33 (m, 5H), 7.14-7.24 (m, 2H), 5.14-5.20 (m, 1H), 4.23 (d, $J=7.2\text{ Hz}$, 1H), 3.84-4.05 (m, 2H), 3.65 (s, 3H), 3.45-3.57 (m, 2H), 2.84-2.90 (m, 2H), 1.97-2.41 (m, 5H), 0.89-1.00 (m, 6H). MS (ESI) m/z ($\text{M}+\text{H}$) $^+$ 675.3.



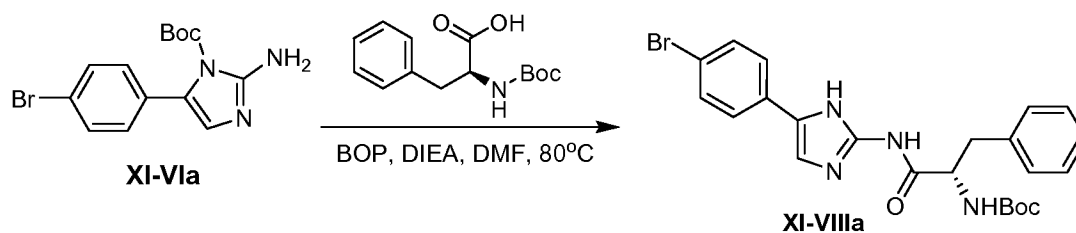
[0216] Compound **720**; 5 mg, yields 4%. ^1H NMR (400MHz, CD_3OD): δ 7.73-8.11 (m, 8H), 7.36-7.43 (m, 5H), 7.26-7.28 (m, 1H), 7.10-7.20 (m, 1H), 5.35-5.36 (m, 1H), 4.24-4.26 (m, 1H), 4.01-4.05 (m, 1H), 3.91-3.99 (m, 1H), 3.62 (s, 3H), 2.32-2.39 (m, 4H), 2.05-2.22 (m, 2H), 1.58-1.64 (m, 3H), 0.85-1.09 (m, 6H). MS (ESI) m/z ($\text{M}+\text{H}$) $^+$ 675.2.

Example XI-VIII: Preparation of Compounds **721**:

Scheme XI-VIII



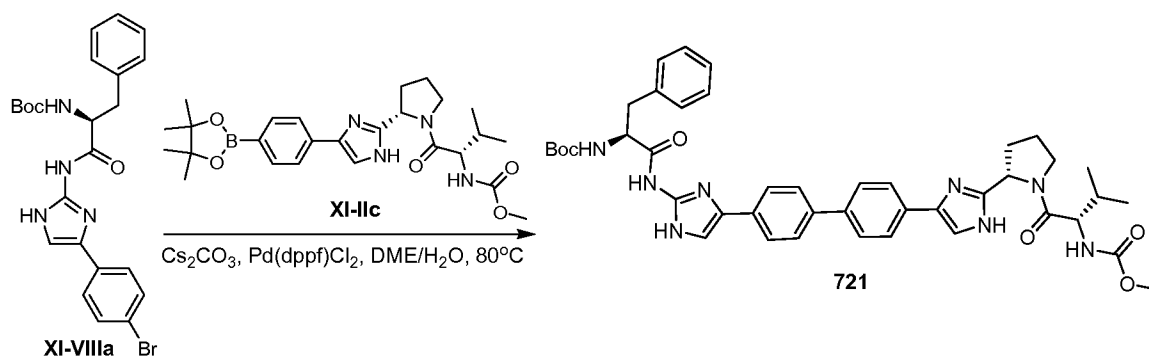
Scheme XI-VIIIa



General Procedure XI-X

[0217] A flask were charged with compound **XI-VIa** (255 mg, 0.75 mmol), N-Boc-L-phenylalanine (200 mg, 0.75 mmol), BOP (66 mg, 1.5 mmol), and DIEA (290 mg, 2.3 mmol) followed by addition of DMF (5 mL). The resulting mixture was stirred at 80°C overnight. After being cooled to r.t., the mixture was diluted with EtOAc (20 mL), washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by prep-TLC (DCM/MeOH=20/1) to afford compound **XI-VIIIa** (60 mg, yield 16%). **MS (ESI) m/z (M+H)⁺ 487.**

Scheme XI-VIIIb

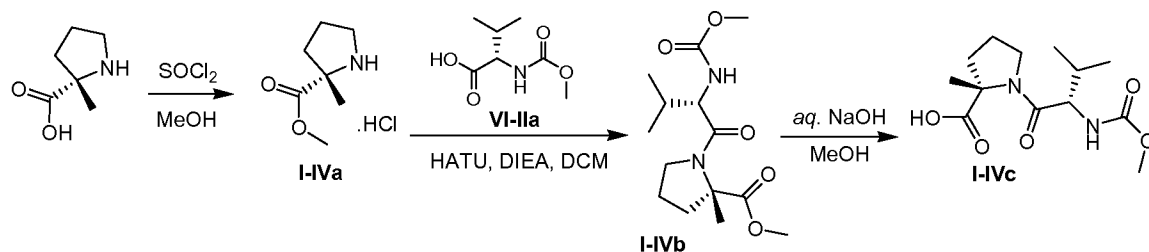


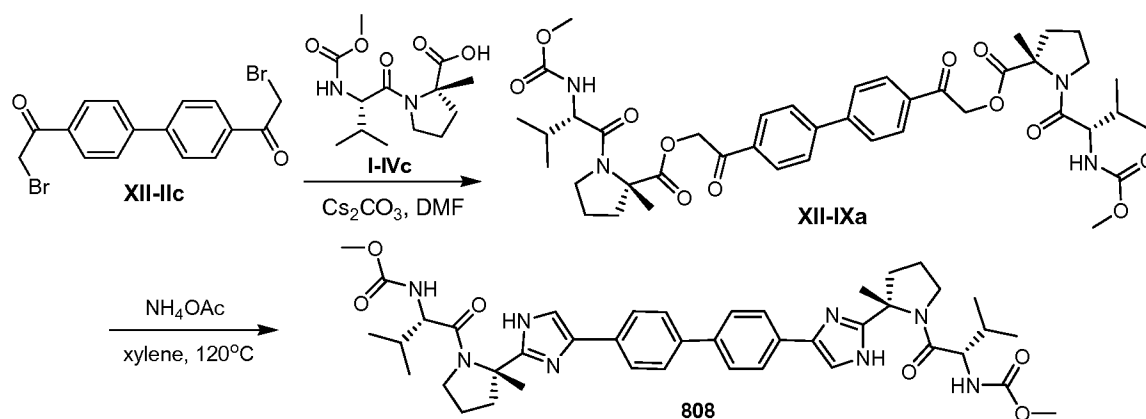
General Procedure XI-XI

[0218] A flask was charged with compound **XI-VIIIa** (40 mg, 0.08 mmol), compound **XI-IIc** (41 mg, 0.08 mmol), Cs₂CO₃ (52 mg, 0.16 mmol), DME (3 mL) and H₂O (0.5 mL), and then purged with nitrogen for three times. The nitrogen protected mixture was treated with Pd(dppf)Cl₂ (20 mg, 0.027 mmol). The resulting mixture was stirred at 80°C for 3 hrs under nitrogen protection. After being cooled to r.t., the mixture was diluted with EtOAc (50 mL), and washed with water and brine. The organic layer was separated, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by Prep-HPLC to afford compound **721** (4.5 mg, yield 7%). ¹H NMR (400MHz, CD₃OD): δ 7.82-7.90 (m, 9 H), 7.54 (s, 1H), 7.23-7.33 (m, 5 H), 5.23-5.27 (m, 1 H), 4.50-4.54 (m, 1 H), 4.22-4.24 (m, 1 H), 4.09-4.14 (m, 1 H), 3.84-3.91 (m, 1 H), 3.66 (s, 3 H), 3.20-3.25 (m, 1 H), 2.96-3.01 (m, 1 H), 2.55-2.60 (m, 1 H), 2.03-2.30 (m, 4 H), 1.39 (s, 9 H), 0.89-0.94 (m, 6 H). MS (ESI) *m/z* (M+H)⁺ 775.1.

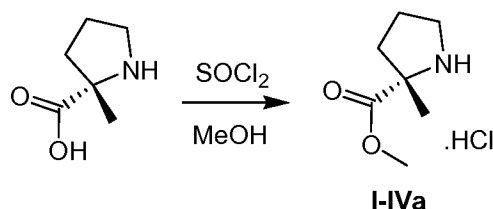
Example XII-IX: Preparation of Compound 808

Scheme XII-IX





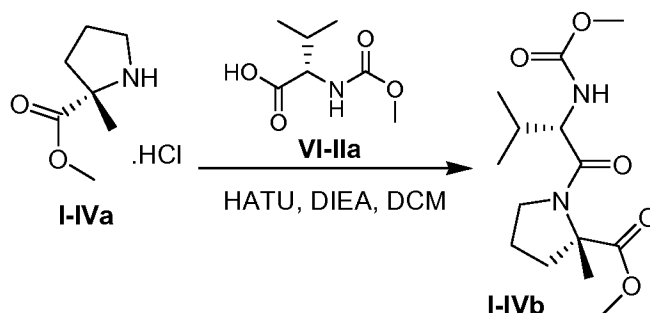
Scheme X-IVa



General Procedure X-W

[0219] To a mixture of 2-methyl-L-proline (1.0 g, 7.8 mmol) in 20 mL of dry methanol was added SOCl_2 (2.8 g, 23.3 mmol) dropwise at 0°C under nitrogen protection. The resulting mixture was stirred at room temperature overnight, and then the solvent was removed under reduced pressure to afford compound **I-IVa** as an HCl salt (1.4 g, yield 100%). $^1\text{H NMR}$ (300 MHz, CD_3OD): δ 3.86 (s, 3H), 3.42-3.46 (m, 2H), 2.36-2.45 (m, 1H), 2.00-2.19 (m, 3H), 1.68 (s, 3H).

Scheme X-IVb

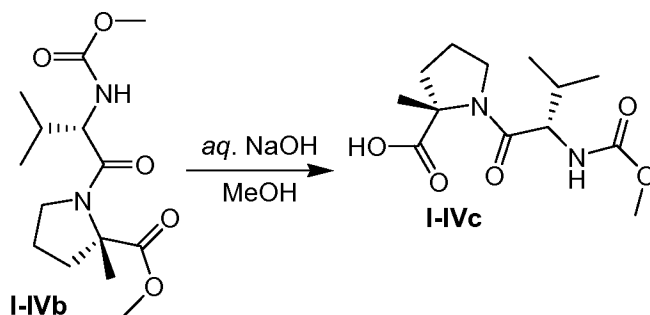


General Procedure X-X

[0220] To a solution of compound **I-IVa** (1.35 g, 7.7 mmol) in 30 mL of DCM was added compound **VI-IIa** (1.5 g, 8.5 mmol), HATU (4.4 g, 11.6 mmol) and DIEA (3 g, 23 mmol). The resulting mixture was stirred at room temperature overnight. Subsequently, the mixture was diluted with DCM and washed with brine. The organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by

column chromatography (PE/EA=3/1) to afford compound **I-IVb** (1.5 g, yield 65%). **MS (ESI)** m/z (M+H)⁺ 301.

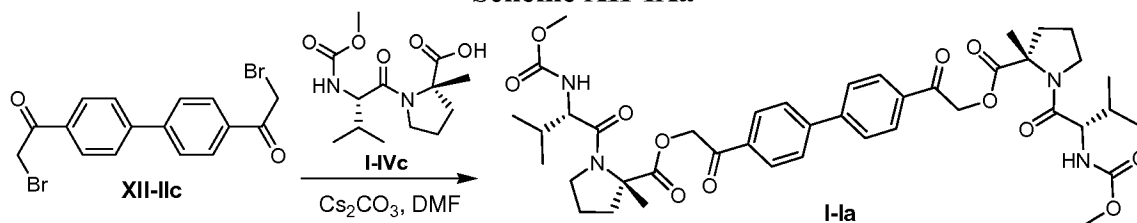
Scheme X-IVc



General Procedure X-Y

[0221] A mixture of compound **I-IVb** (1.5 g, 5 mmol) and NaOH (0.6 g, 15 mmol) in MeOH (30 mL) and H₂O (5 mL) was stirred at 70°C for 2 hours. The methanol under reduce pressure and the residue was dissolved with 20 mL of H₂O, then the solution was acidified to pH 2~3 with 2N HCl and extracted with DCM (50 mL×2). The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated to afford compound **I-IVc** (0.8 g, yield 57%), which was used in next step without further purification. ¹H NMR (300 MHz, DMSO-*d*₆): δ 12.20 (s, 1H), 7.24 (d, *J*=8.4 Hz, 1 H), 3.54-3.98 (m, 3H), 3.50 (s, 3H), 1.78-2.05 (m, 5H), 1.34 (s, 3H), 0.84-0.88 (m, 6H).

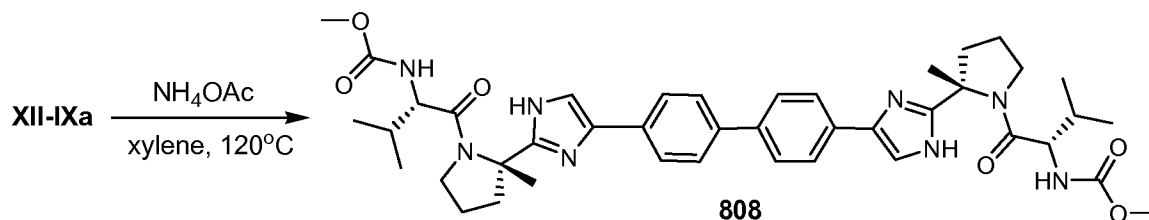
Scheme XII-IXa



General Procedure XII-AW

[0222] The mixture of compound **XII-IIc** (100 mg, 0.25 mmol), compound **I-IVc** (145 mg, 0.50 mmol), Cs₂CO₃ (244 mg, 0.75 mmol) in DMF (5 mL) was stirred at room temperature for 2 hrs. The mixture was diluted with EtOAc (50 mL), and washed with water and brine. The organic layer was separated, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give a crude residue. The residue was purified by prep-TLC (DCM/MeOH=20/1) to afford compound **XII-IXa** (100 mg, yield 50%). **MS (ESI)** m/z (M+H)⁺ 807.

Scheme XII-IXb

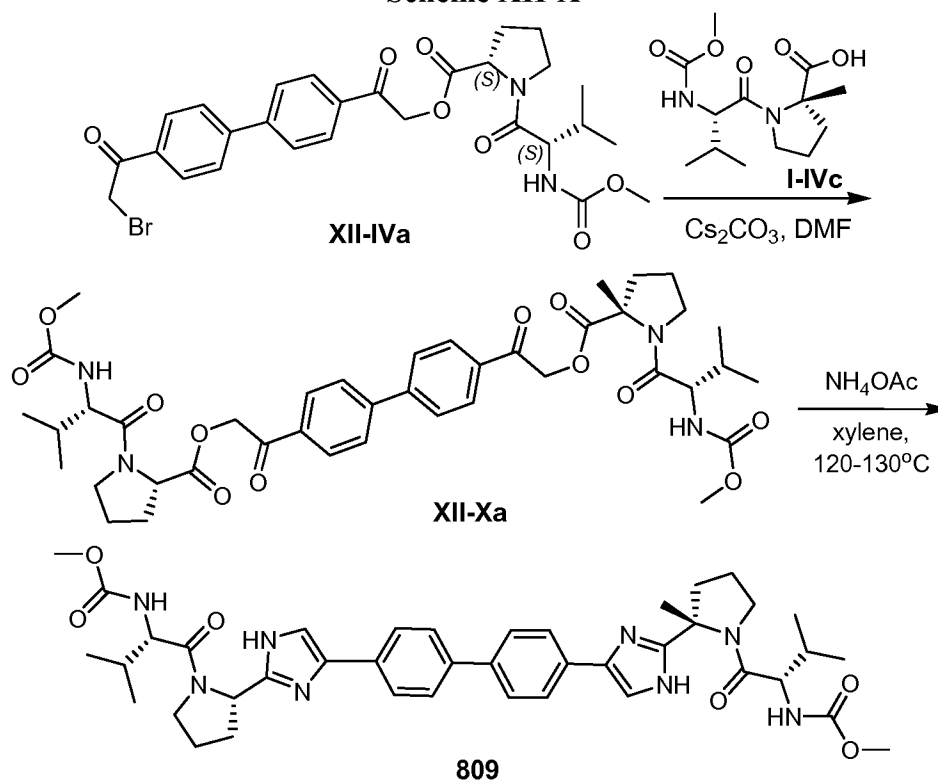


General Procedure XII-AX

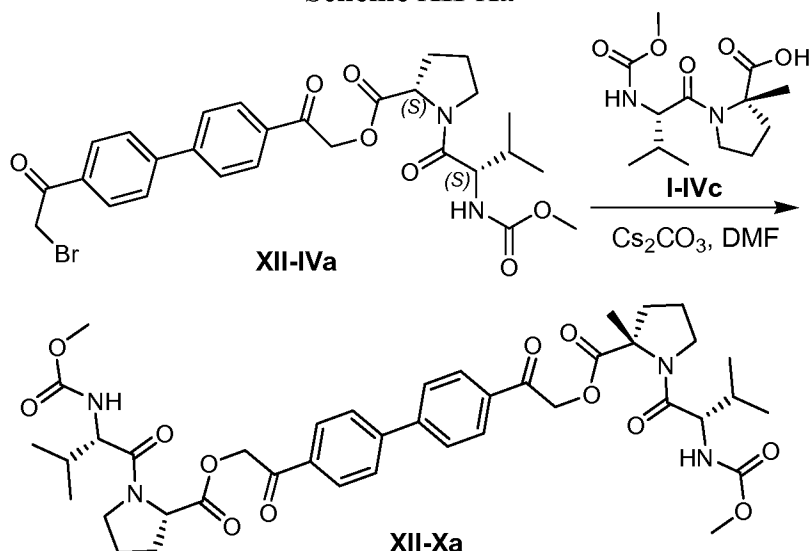
[0223] A mixture of compound **XII-IXa** (100 mg, 0.12 mmol) and NH_4OAc (185 mg, 2.4 mmol) in xylene (10 mL) was stirred at 120°C for 5 hours in a sealed tube. After being cooled to r.t., the solvent was removed under reduce pressure and the resulting residue was diluted with EtOAc (30 mL), and washed with water and brine. The organic layer was separated, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by Prep-HPLC to afford compound **808** (12 mg, yield 14%). $^1\text{H NMR}$ (400 MHz, CD_3OD): δ 7.64-7.75 (m, 8H), 7.30 (s, 2H), 4.18-4.20 (m, 2H), 3.88-4.08 (m, 4H), 3.65 (s, 6H), 2.50-2.57 (m, 2H), 2.01-2.16 (m, 8H), 1.86 (s, 6H), 0.87-0.98 (m, 12H). **MS (ESI)** m/z ($\text{M}+\text{H}$) $^+$ 767.4.

EXAMPLE XII-X: Preparation of Compound **809**

Scheme XII-X



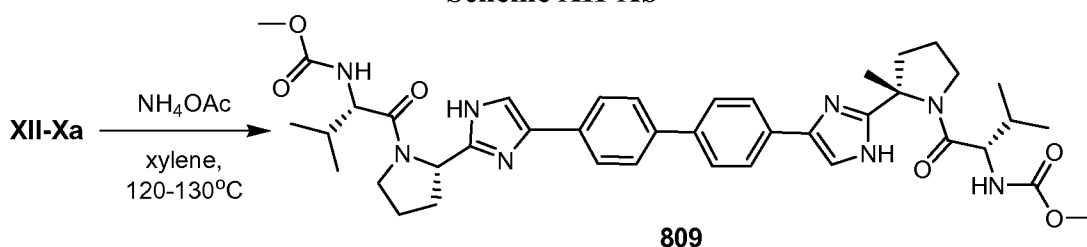
Scheme XII-Xa



General Procedure XII-AY

[0224] A flask was charged with compound **XII-IVa** (100 mg, 0.17 mmol), compound **I-IVc** (50 mg, 0.17 mmol), Cs_2CO_3 (222 mg 0.68 mmol) and DMF (10 mL). The resulting mixture was stirred at room temperature for 3 hours. Subsequently, water (30 mL) was added, and the mixture was extracted with EtOAc (30 mL $\times$ 2). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated to afford compound **XII-Xa** (90 mg, yield 67%), which was used in next step without further purification.

Scheme XII-Xb



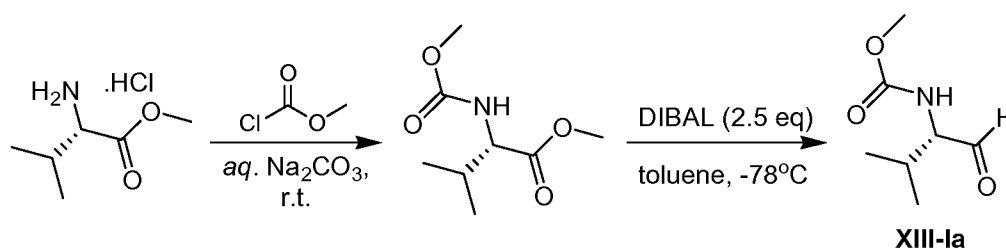
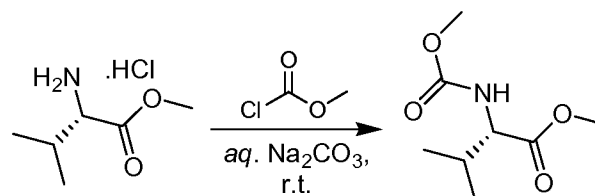
General Procedure XII-AZ

[0225] A mixture of compound **XII-Xa** (0.09 g, 0.11 mmol) and NH_4OAc (0.175 g, 2.27 mmol) in xylene (10 mL) was stirred at 120-130°C for 4 hrs in a sealed tube. After cooling to room temperature, water (30 mL) was added, and the mixture was extracted with EtOAc (30 mL $\times$ 2). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to dryness to give a residue. The residue was purified by Prep-HPLC to afford compound **809** (6 mg, yield 10%). ^1H NMR (400MHz, CD_3OD): δ 7.60-7.86 (m, 8 H), 7.20-7.25 (m, 2H), 5.14-5.20 (m, 1H), 4.14-4.20 (m, 2 H),

3.81-4.09 (m, 4 H), 3.62(s, 6 H), 2.49-2.51 (m, 1 H), 2.09-2.35 (m, 5 H), 1.94-2.04 (m, 4 H), 1.83 (s, 3 H), 0.83-0.96 (m, 12 H). **MS (ESI)** m/z (M+H)⁺ 753.5.

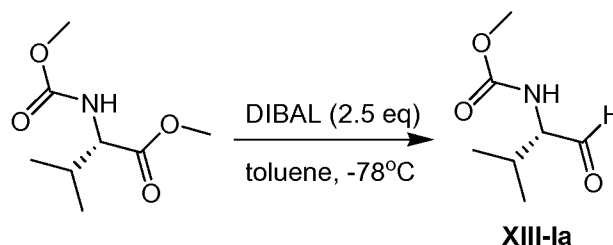
SECTION XIII

PREPARATION OF COMPOUNDS: SECTION XIII

Example XIII-I: Synthesis of Intermediates for the Preparation of Compound 900**Scheme XIII-I****Scheme XIII-Ia**

General Procedure XIII-A

[0226] To a stirred and cooled (0°C, ice bath) solution of L-Valine methyl ester hydrochloride (10 g, 60 mmol) in water (60 mL) were added dropwise aq. Na₂CO₃ (1 M solution, 66 mL) and methyl chloroformate (7 g, 72 mmol). The ice-bath was then removed and the mixture stirred at r.t. for 3 hours. Subsequently, the mixture was extracted with EtOAc (60 mL × 3), dried over MgSO₄ and concentrated to afford N-(methoxycarbonyl)-L-Valine methyl ester (10 g, yield 88%), used in next step without further purification. ¹H NMR (400MHz, CDCl₃): δ 5.22 (br d, 1 H), 4.29-4.24 (m, 1 H), 3.73 (s, 3 H), 3.69 (s, 3H), 2.18-2.10 (m, 1 H), 0.94 (d, *J*=8 Hz, 3 H), 0.88 (d, *J*=8 Hz, 3 H).

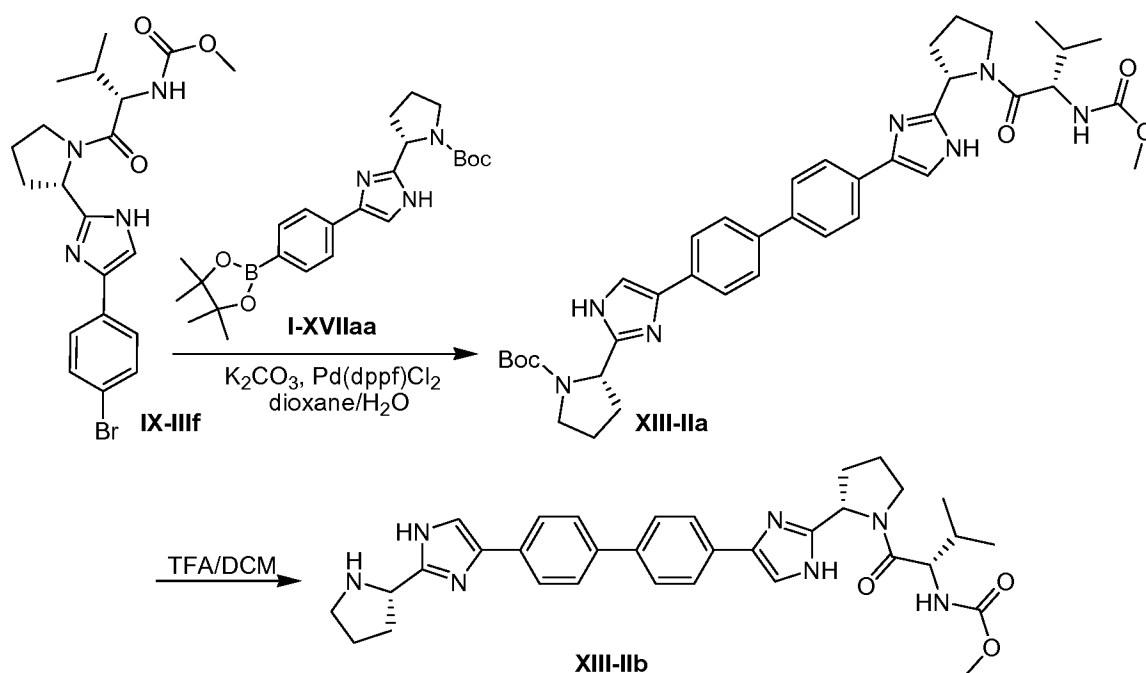
Scheme XIII-Ib

General Procedure XIII-B

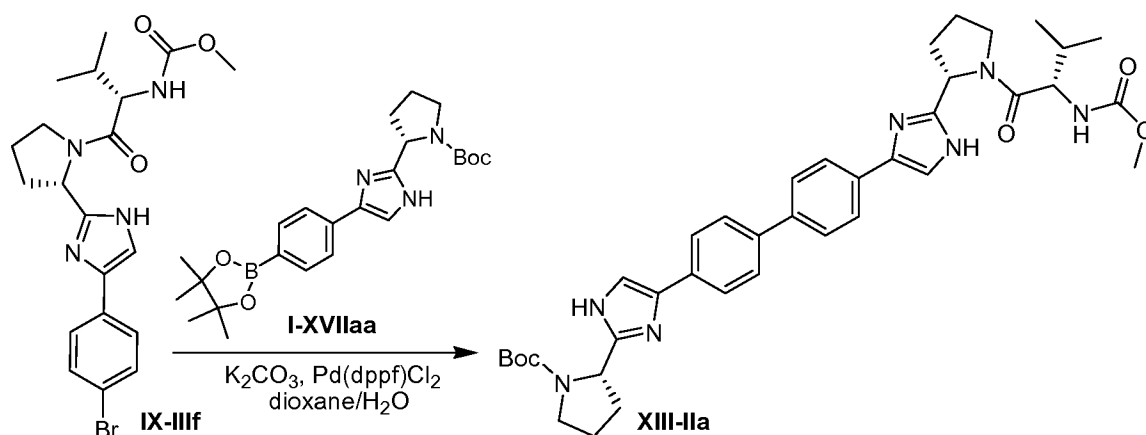
[0227] A solution of N-(methoxycarbonyl)-L-Valine methyl ester (0.95 g, 5 mmol) in toluene (10 mL) was degassed with nitrogen. Then it was cooled to -78°C using a dry ice-acetone bath. A solution of DIBAL in toluene (1 M, 12.5 mL, 12.5 mmol) was added dropwise at -78°C . After addition, the mixture was stirred at -78°C for 2 hrs. Subsequently, methanol (5 mL) was added slowly to quench the reaction while maintaining the temperature below -65°C . The resulting mixture was poured into 50 mL of aq. NaOH (1 M), then extracted with EtOAc ($50\text{ mL} \times 3$), the combined extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford aldehyde **XIII-Ia**. To prevent racemization, the crude product was used directly in next step without further purification (0.8 g, crude yield 100%). ^1H NMR (400MHz, CDCl_3): δ 9.62 (s, 1 H), 5.38 (brs, 1 H), 4.28 (brm, 1 H), 3.71 (s, 3H), 2.28 (m, 1H), 1.02 (d, $J=6.8$ Hz, 3 H), 0.90 (d, $J=6.8$ Hz, 3 H).

Example XIII-II: Synthesis of Intermediates for the Preparation of Compound **900**

Scheme XIII-II



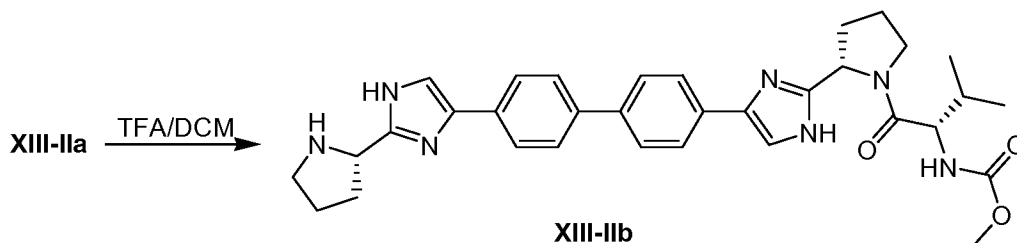
Scheme XIII-IIa



General Procedure XIII-C

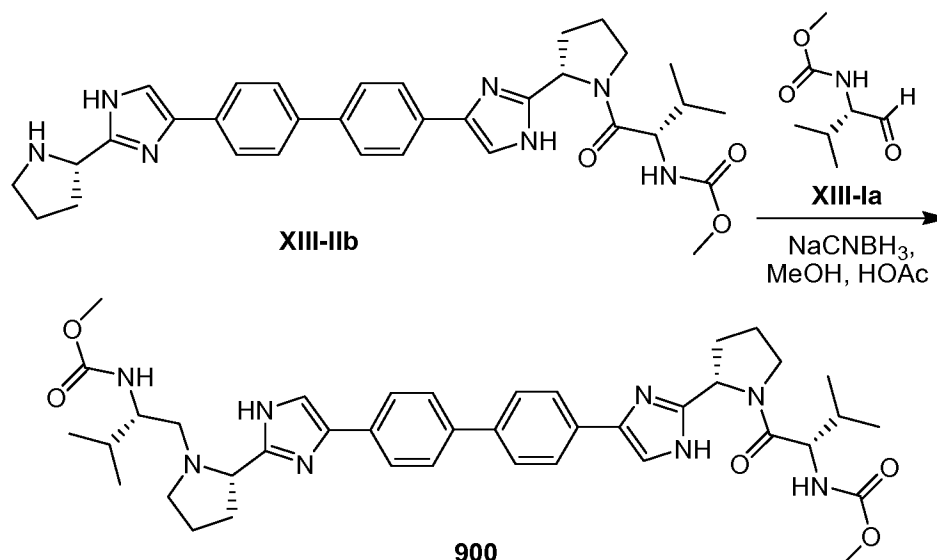
[0228] To a solution of compound **IX-III f** (0.2 g, 0.4 mmol), compound **I-XVIIaa** (0.2 g, 0.4 mmol), K_2CO_3 (0.13 g, 1.0 mmol) in dioxane/ H_2O (2 mL / 0.5 mL) was added $Pd(dppf)Cl_2$ (20 mg). The mixture was stirred at reflux overnight. After cooling to room temperature, the mixture was diluted with H_2O (20 mL), and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by Prep-TLC to afford compound **XIII-IIa** (0.15 g, yield 50%).

Scheme XIII-IIb



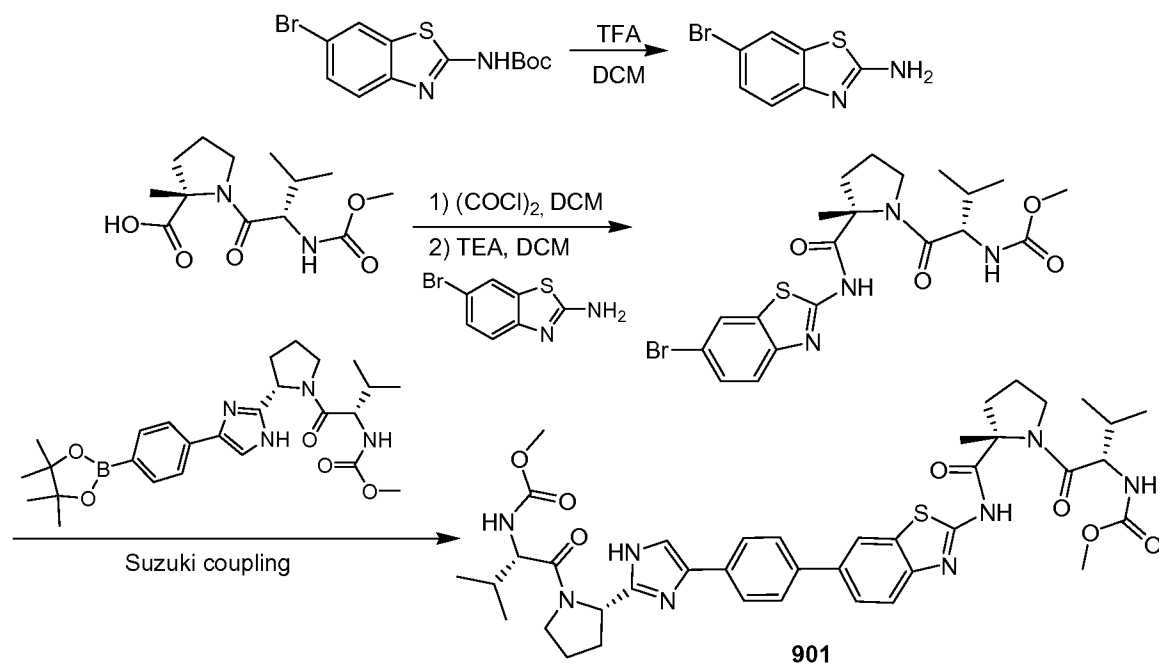
General Procedure XIII-D

[0229] A solution of compound **XIII-IIa** (0.15 g, 0.3 mmol) in TFA/DCM (2 mL/2 mL) was stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure to afford crude product (0.16 g, crude yield 100%) of which 30 mg of the crude product was purified by Prep-HPLC to afford 15 mg of compound **XIII-IIb**. ^1H NMR (400MHz, CD_3OD): δ 7.57-7.79 (m, 8 H), 7.29-7.36 (m, 2 H), 5.15-5.18 (m, 1 H), 4.34-4.37 (m, 1 H), 4.21-4.25 (m, 1 H), 3.98-4.01 (m, 1 H), 3.78-3.87 (m, 1 H), 3.67 (s, 3 H), 3.00-3.18 (m, 2 H), 2.14-2.48 (m, 4 H), 1.80-2.11 (m, 5 H), 0.97-0.93 (m, 6 H). MS (ESI) m/z ($M+H$) $^+$ 582.1.

Example XIII-III: Preparation of Compound 900**Scheme XIII-III****General Procedure XIII-E**

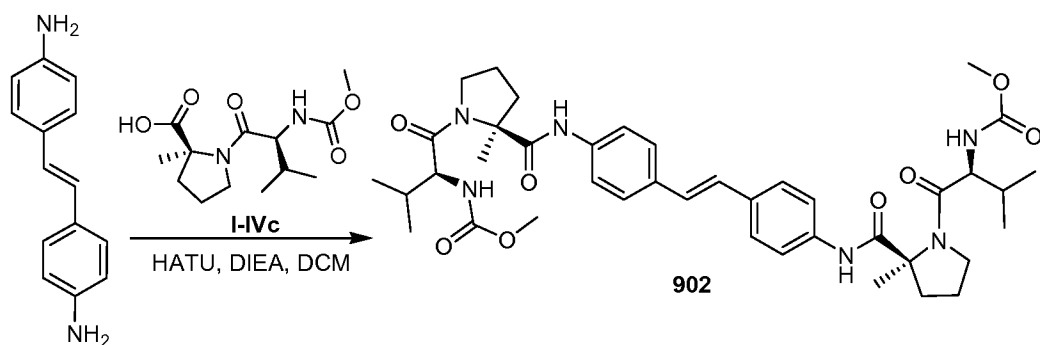
[0230] To a solution of compound **XIII-IIb** (0.1 g, 0.17 mmol) in CH₃OH (5 mL), CH₃COOH (0.5 mL) was added compound **XIII-Ia** (28 mg, 0.18 mmol) and stirred 30 min. Subsequently, NaCNBH₃ (0.033 g, 0.52 mmol) was added to the stirring mixture. The mixture was stirred at room temperature for an additional 3 hours. The mixture was then concentrated, and the residue was diluted with H₂O, and extracted with DCM. The organic layer was separated, dried over Na₂SO₄ and concentrated, the residue was purified by Prep-HPLC to afford compound **900** (25 mg, yield 21%). ¹H NMR (400MHz, CD₃OD): δ 7.63-7.79 (m, 8H), 7.37 (s, 1 H), 7.30 (s, 1 H), 5.15-5.18 (m, 1H), 4.22 (d, *J*=7.6 Hz, 1 H), 3.68-3.97 (m, 2 H), 3.62 (s, 3 H), 3.65 (s, 3 H), 3.49-3.55 (m, 2 H), 2.65-2.70 (m, 1 H), 1.87-2.39 (m, 13 H), 0.87-0.99 (m, 6 H), 0.67-0.86 (m, 6 H). **MS (ESI)** *m/z* (M+H)⁺ 725.4.

[0231] Example IX-IV: Compound **901** can be prepared according to the following Scheme:



[0232] Example IX-V: Preparation of compound **902**:

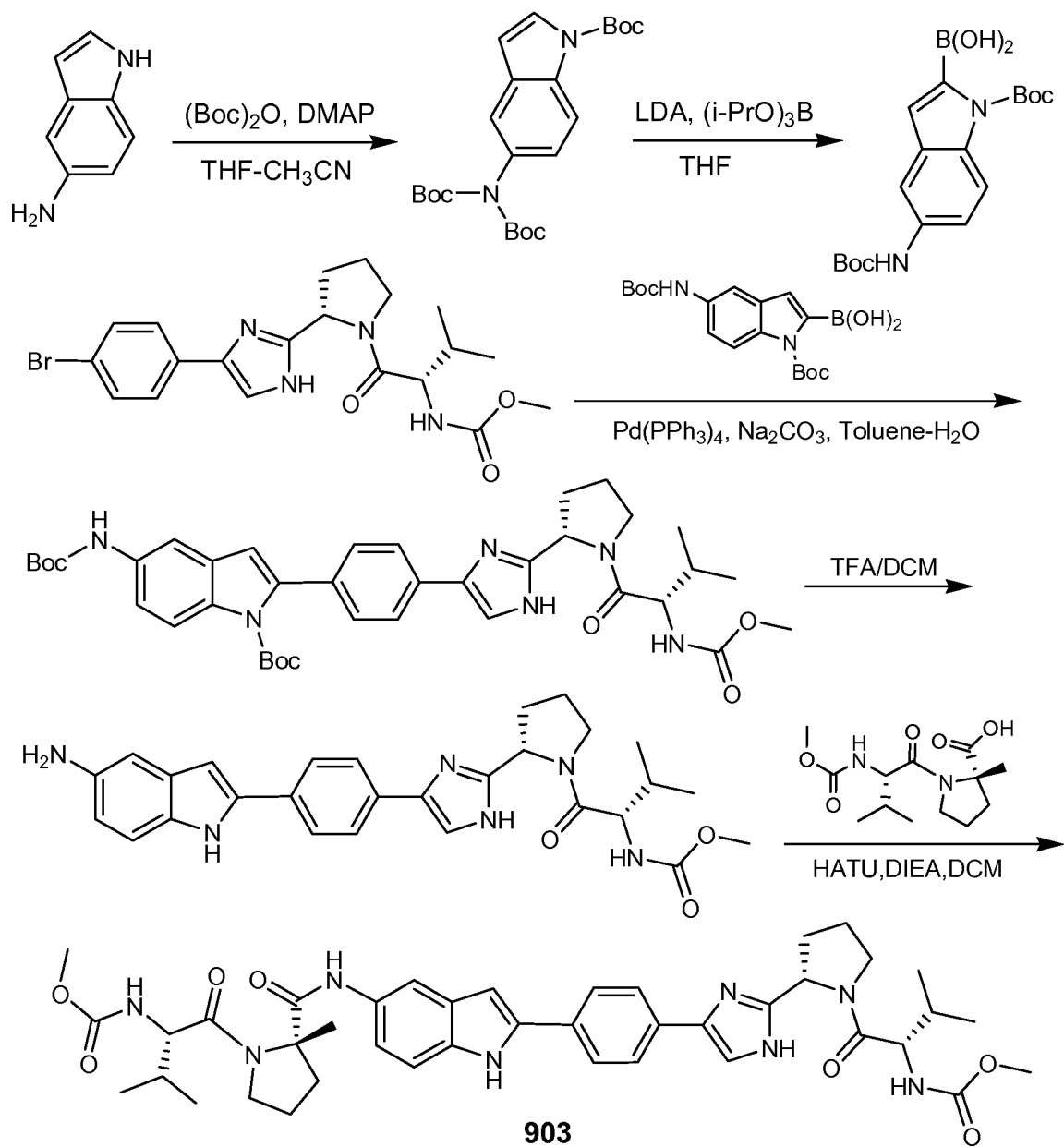
Scheme XIII-V



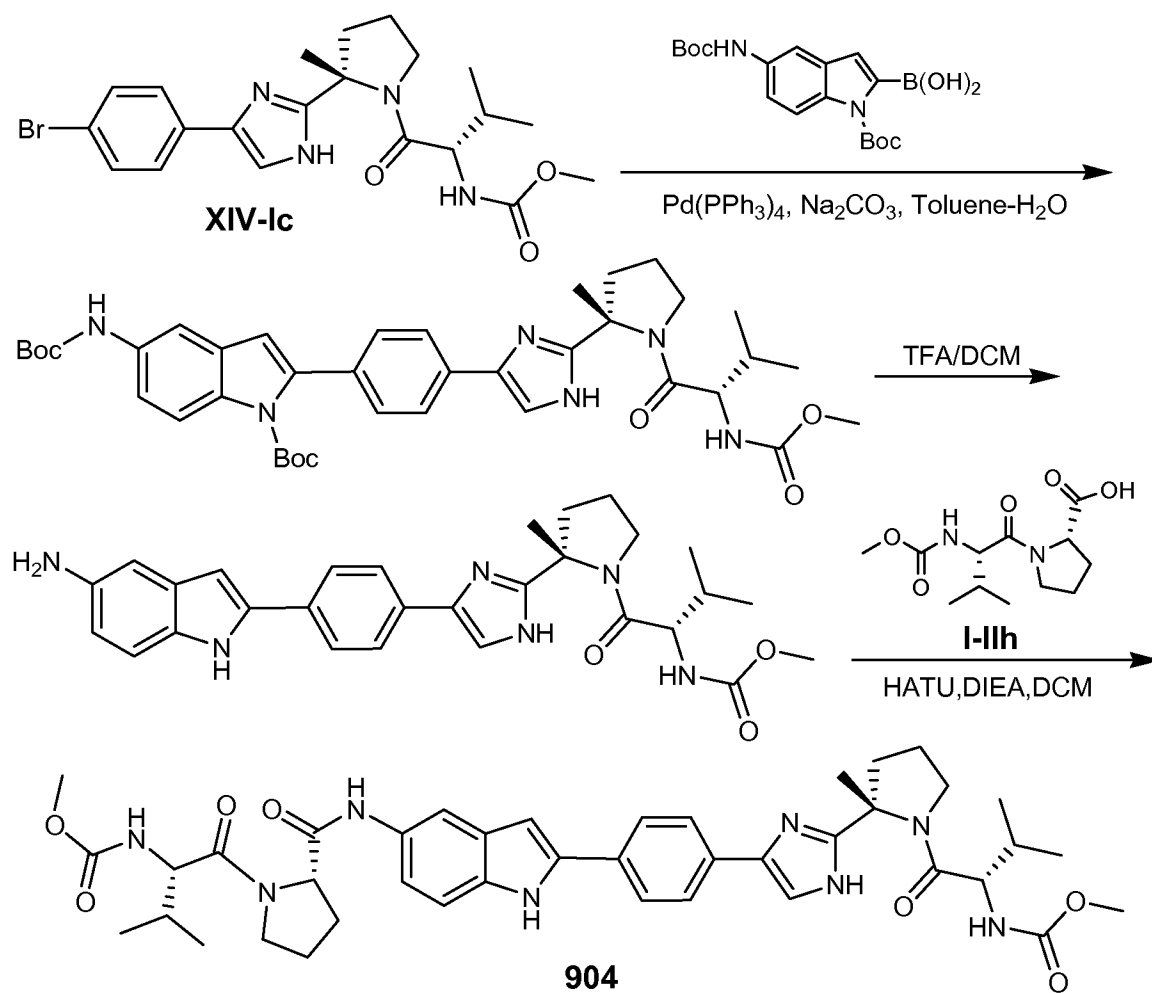
General Procedure XIII-F

[0233] A solution of 4,4'-stilbenediamine (50 mg, 0.174 mmol) in anhydrous DCM (3 mL) was treated with compound **I-IVc** (115 mg, 0.4 mmol), HATU (166 mg, 0.436 mmol) and DIEA (90 mg, 0.697 mmol). The resulting mixture was stirred at r.t. for 4 hours. The mixture was diluted with water (10 mL) and extracted with EtOAc (30 mL $\times$ 2). The combined organic layers were dried over sodium sulfate, and concentrated *in vacuo* to give a residue. The residue was purified by Prep-HPLC to afford compound **902** (30 mg, yield 23%). ¹H NMR (400 MHz, CD₃OD): δ 7.49-7.56 (m, 8H), 7.09 (s, 2H), 4.19 (d, $J=7.6$ Hz, 2H), 3.98-3.99 (m, 2H), 3.83-3.89 (m, 2H), 3.68 (s, 6H), 2.34-2.41 (m, 2H), 2.08-2.16 (m, 6H), 1.91-2.00 (m, 2H), 1.69 (s, 6H), 1.03 (d, $J=6.4$ Hz, 6H), 0.97 (d, $J=6.4$ Hz, 6H). MS (ESI) m/z (M+H)⁺ 747.5.

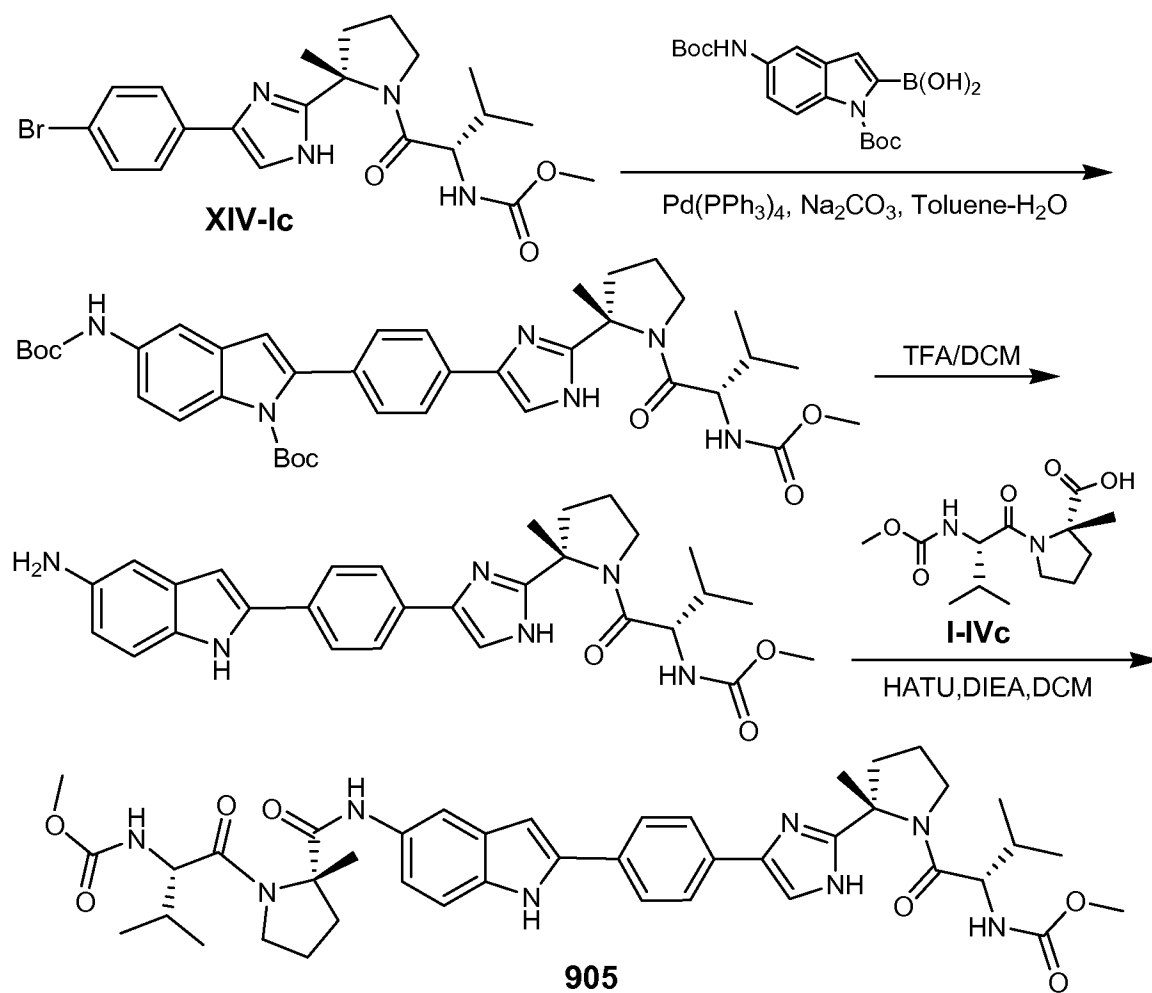
[0234] Example IX-VI: Compound **903** can be prepared according to the following Scheme:



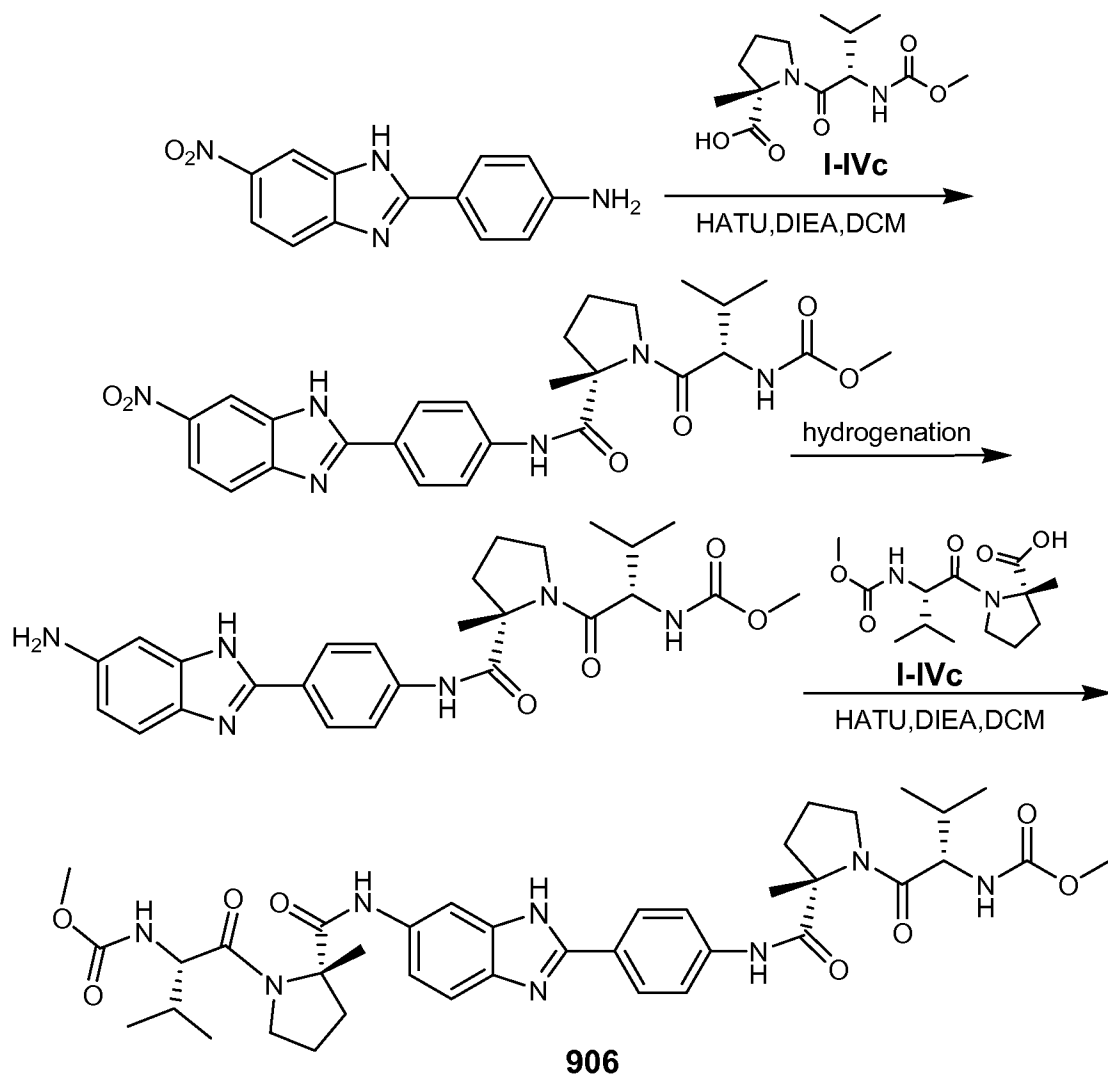
[0235] Example IX-VII: Compound **904** can be prepared according to the following Scheme:



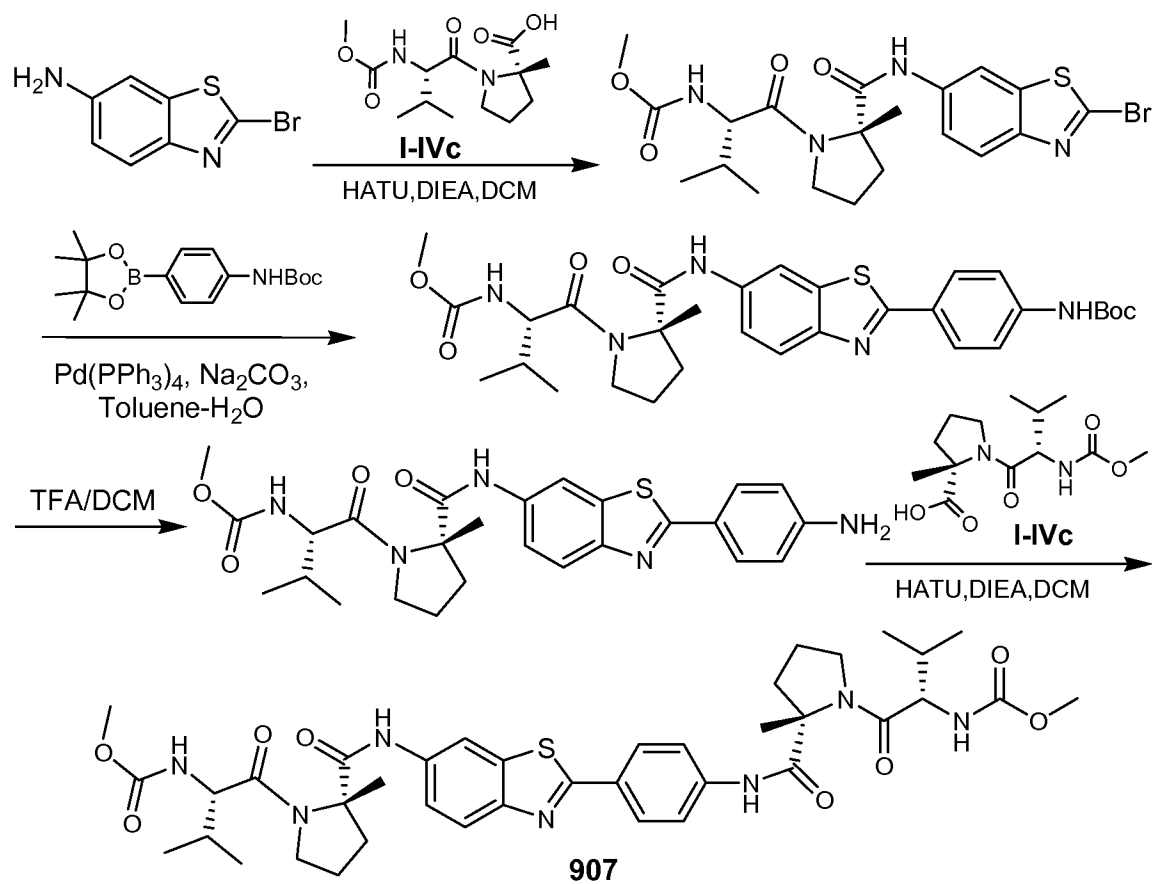
[0236] Example IX-VIII: Compound **905** can be prepared according to the following Scheme:



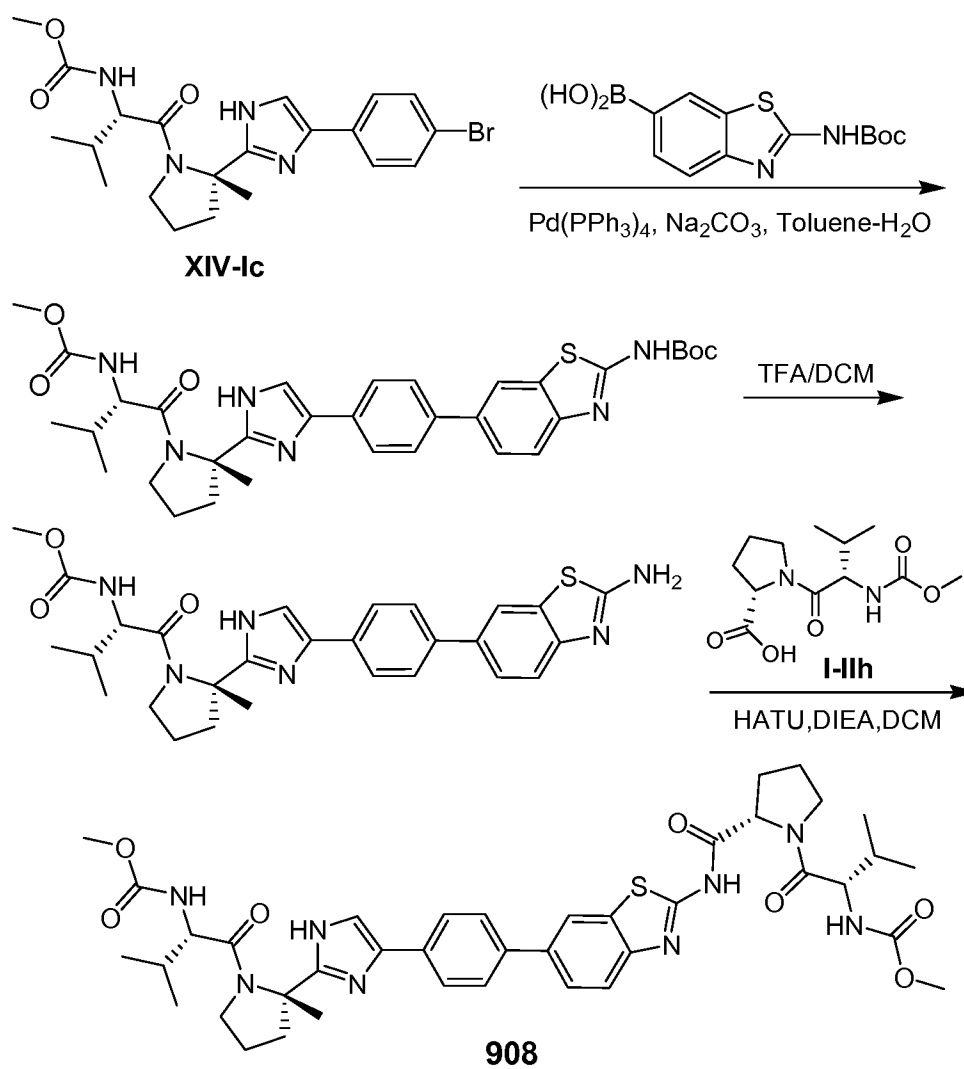
[0237] Example IX-IX: Compound **906** can be prepared according to the following Scheme:



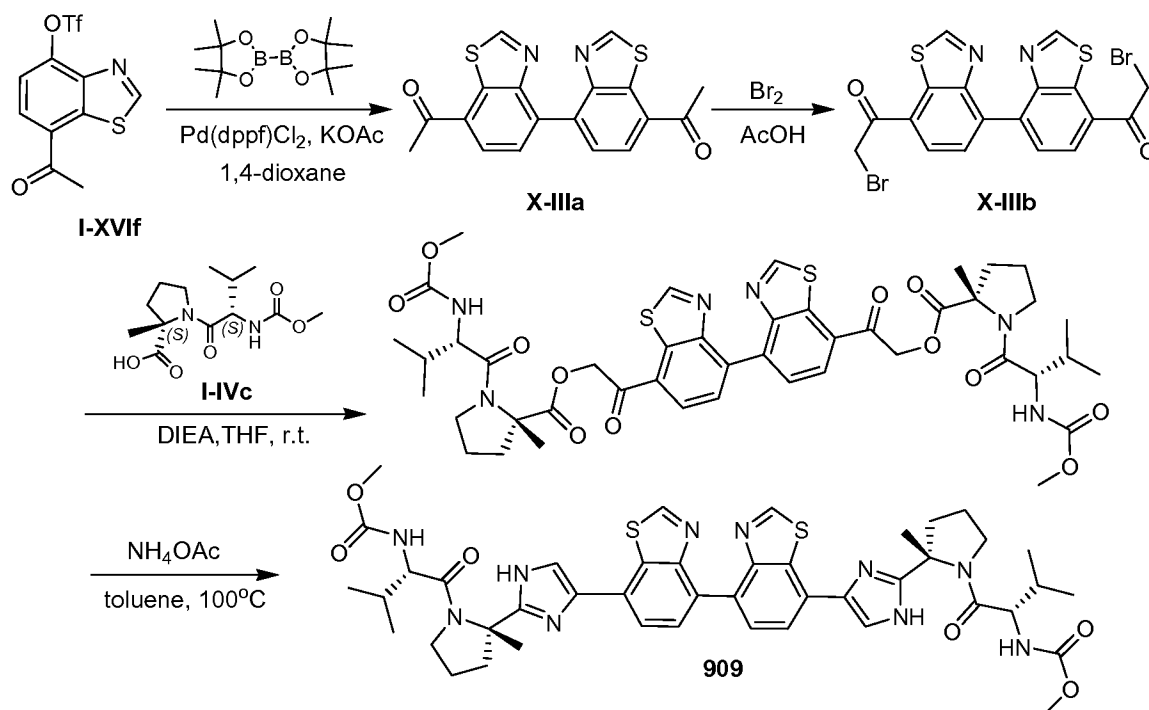
[0238] Example IX-X: Compound **907** can be prepared according to the following Scheme:



[0239] Example IX-XI: Compound **908** can be prepared according to the following Scheme:



Example IX-XII: Compound **909** can be prepared according to the following Scheme:

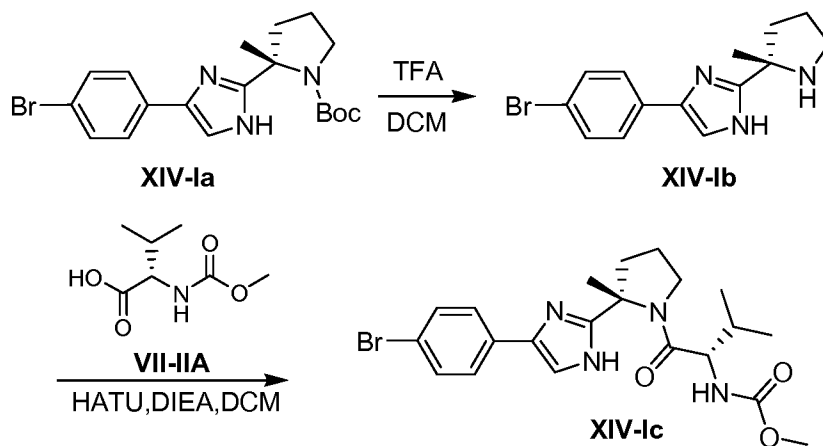


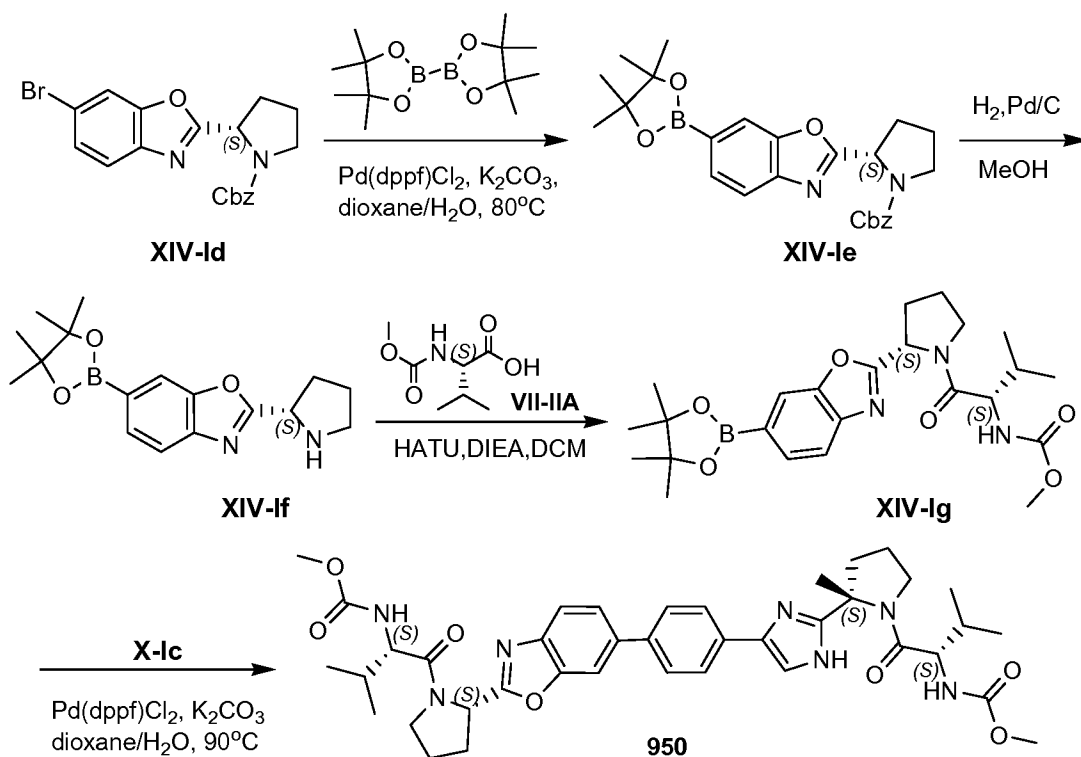
SECTION III

PREPARATION OF COMPOUNDS: SECTION III

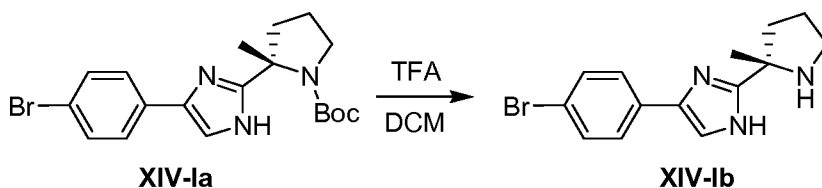
Example XIV-I: Synthesis of Compound **950**

Scheme XIV-I





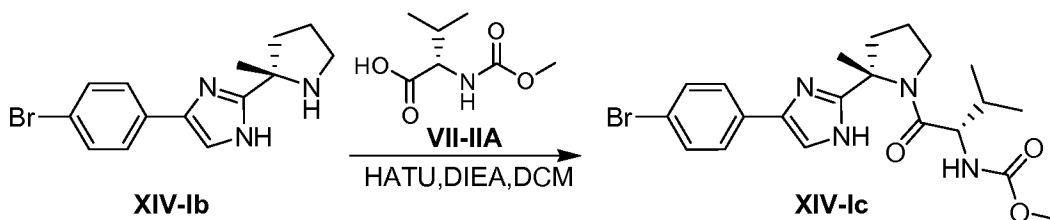
Scheme XIV-Ia



General Procedure XIV -A

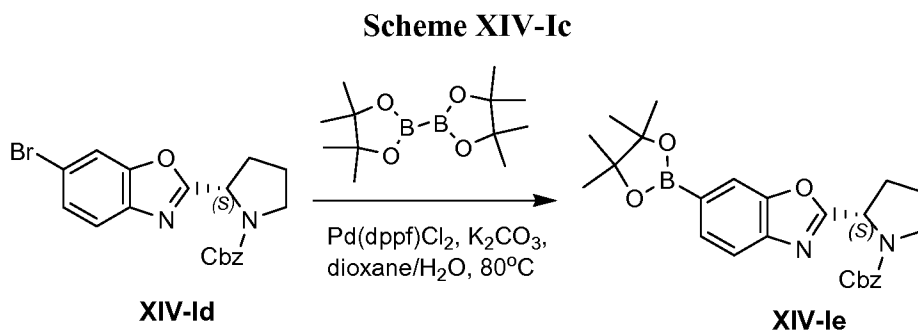
[0240] Compound **XIV-Ia** (80 mg, 0.2 mmol) was dissolved in a solution of TFA in DCM (30%, 2 mL). The resulting mixture was stirred at r.t. for 1 h. After concentration under reduced pressure, the residue was neutralized with *aq.* NaOH (1 M), and extracted with DCM (30 mL $\times$ 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to afford compound **XIV-Ib** (50 mg, yield 83.0%), which was used directly in the next step without further purification. **MS (ESI)** m/z (M+H)⁺ 306.

Scheme XIV-Ib



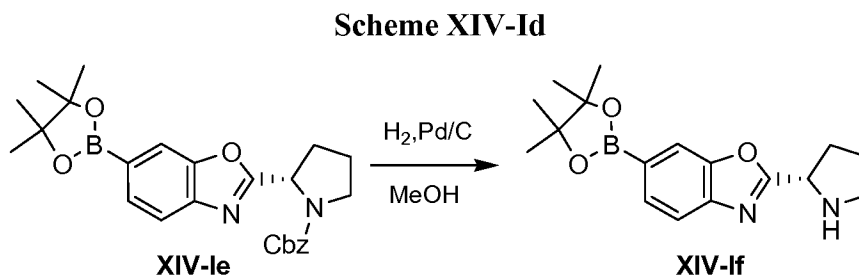
General Procedure XIV -B

[0241] A mixture of compound **XIV-Ib** (50 mg, 0.16 mmol), compound **VII-IIA** (43 mg, 0.25 mmol), HATU (95 mg, 0.25 mmol) and DIEA (65 mg, 0.5 mmol) in DCM was stirred at r.t for 2 hrs. The mixture was diluted with DCM (60 mL), and washed with brine. The organic layer was separated, dried over Na₂SO₄, filtered and concentrated. The residue was purified by prep-TLC (PE: EtOAc =1:2) to afford compound **XIV-Ic** (50 mg, yield 66%). **MS (ESI) *m/z* (M+H)⁺ 464.**



General Procedure XIV -C

[0242] A flask was charged with compound **XIV-Id** (300 mg, 0.75 mmol), bis(pinacolato)diboron (380 mg, 1.5 mmol), K₂CO₃ (205 mg, 1.5 mmol), 1,4-dioxane (10 mL) and H₂O (1mL), and then purged with nitrogen three times. Subsequently, the nitrogen protected mixture was treated with Pd(dppf)Cl₂ (50 mg, 0.068 mmol). The resulting mixture was stirred at 80°C for 3 hrs under nitrogen protection. After cooling to r.t., the mixture was diluted with EtOAc (100 mL), and washed with water and brine. The organic layer was separated, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE/ EtOAc =2/1) to afford the compound **X-Ie** (150 mg, yield 45%). **MS (ESI) *m/z* (M+H)⁺ 449.**

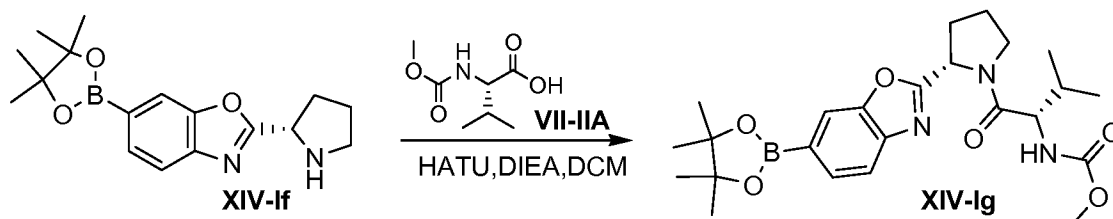


General Procedure XIV -D

[0243] A mixture of compound **XIV-Ie** (150 mg, 0.33 mmol) and 10% Pd/C (20 mg) in MeOH (20 mL) was hydrogenated under H₂ (45 psi) at 50°C. After stirring for 8 hrs, the mixture was cooled to r.t. and the H₂ was replaced with N₂ and then the catalyst

was removed by filtration. The filtrate was removed to afford compound **XIV-If** (70 mg, yield 67%), which was used in next step directly. **MS (ESI) m/z (M+H)⁺ 315.**

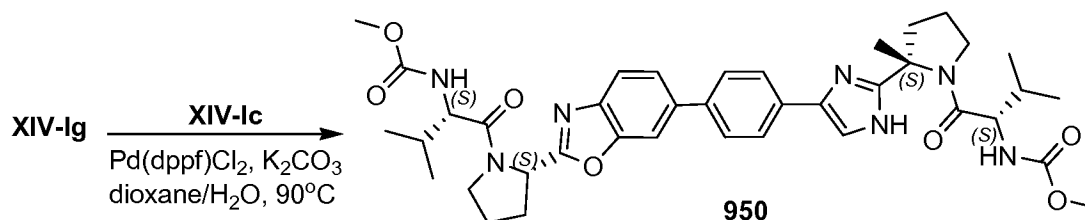
Scheme XIV-Ie



General Procedure X-E

[0244] A mixture of compound **XIV-If** (70 mg, 0.22 mmol), compound **VII-IIA** (46.2 mg, 0.26 mmol), HATU (99 mg, 0.26 mmol) and DIEA (67 mg, 0.52 mmol) in DCM was stirred at r.t for 2 hrs. Subsequently, the mixture was diluted with DCM (60 mL), and washed with water and brine. The organic layer was separated, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE: EtOAc =1:2) to afford compound **XIV-Ig** (50 mg, yield 48%). **MS (ESI) m/z (M+H)⁺ 472.**

Scheme XIV-If



General Procedure XIV -F

[0245] A flask was charged with compound **XIV-Ig** (50 mg, 0.11 mmol), compound **XIV-Ic** (50 mg, 0.1 mmol), K₂CO₃ (30 mg, 0.22 mmol), 1,4-dioxane (2 mL) and H₂O (0.5 mL), and then purged with nitrogen three times. Subsequently, the nitrogen protected mixture was treated with Pd(dppf)Cl₂ (10 mg, 0.0137 mmol). The resulting mixture was stirred at 90°C for 3 hrs under nitrogen protection. After cooling to r.t., the mixture was diluted with EtOAc (50 mL), and washed with water and brine. The organic layer was separated, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to afford compound **950** (8 mg, yield: 11%). **¹H NMR** (400MHz, CD₃OD): δ 7.73-7.83 (m, 3H), 7.62-7.69 (m, 4H), 7.31 (s, 1H), 5.28-5.32 (m, 1H), 4.17-4.27 (m, 2H), 4.04-4.10 (m, 2H), 3.90-3.94 (m, 2H), 3.64

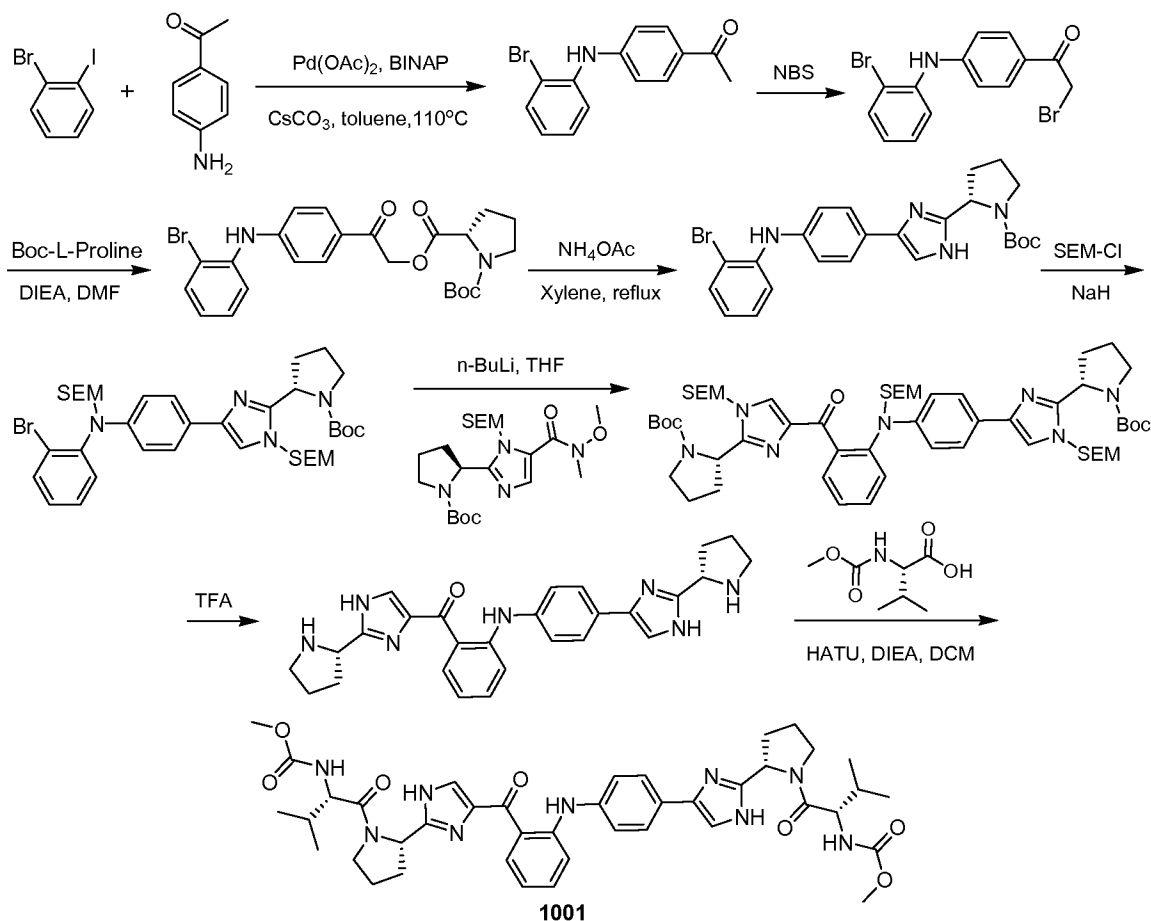
(s, 6H), 2.43-2.55 (m, 2H), 1.86-2.18 (m, 8H), 1.86 (s, 3H), 0.86-1.06 (m, 12H). MS (ESI) m/z (M+H)⁺728.5.

SECTION IV

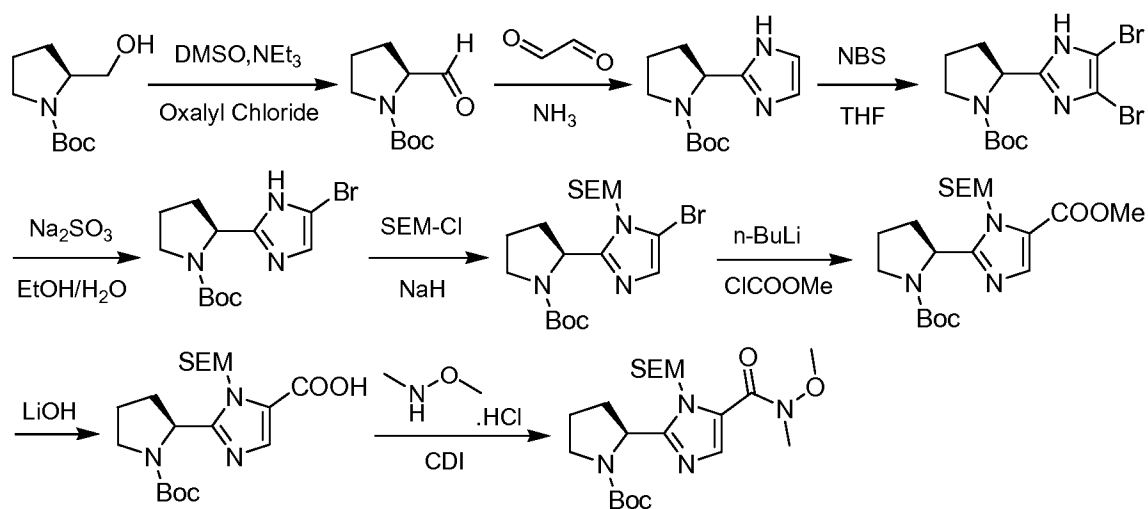
PREPARATION OF COMPOUNDS: SECTION IV

Example XV-I: Compound **1001** can be prepared according to the following Schemes:

Scheme XV-Ia

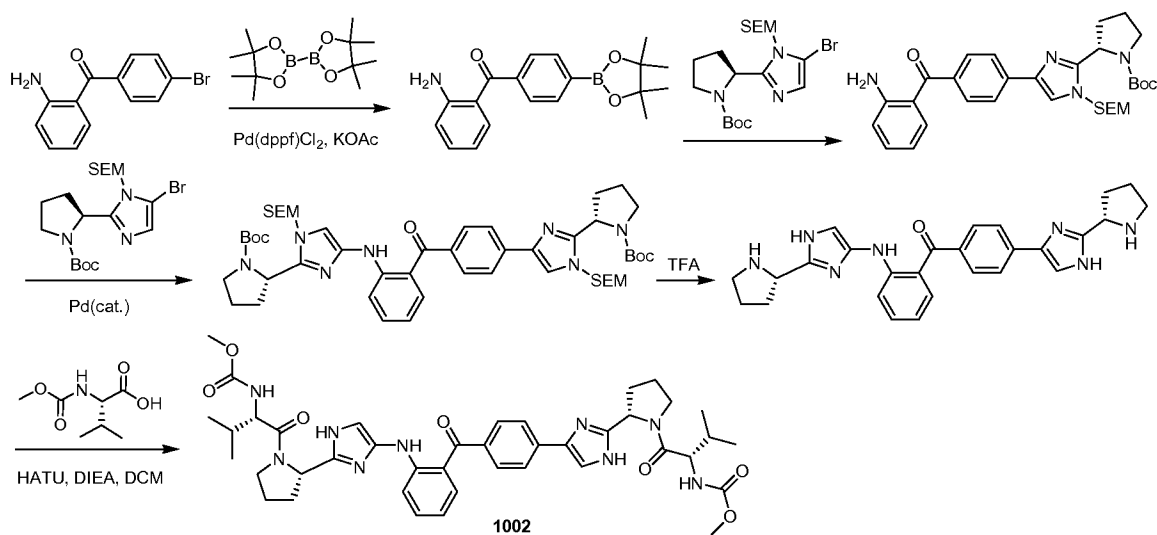


Scheme XV-Iaa



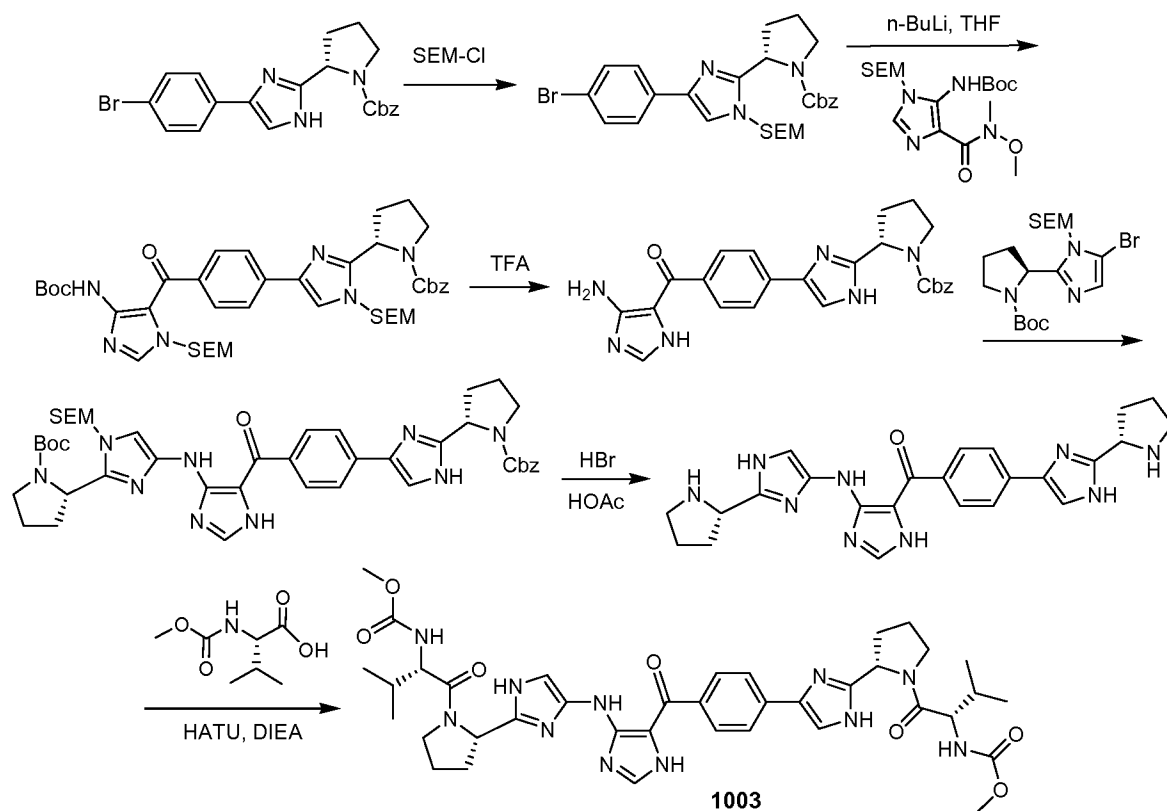
Example XV-II: Compound **1002** can be prepared according to the following Scheme:

Scheme XV-IIa

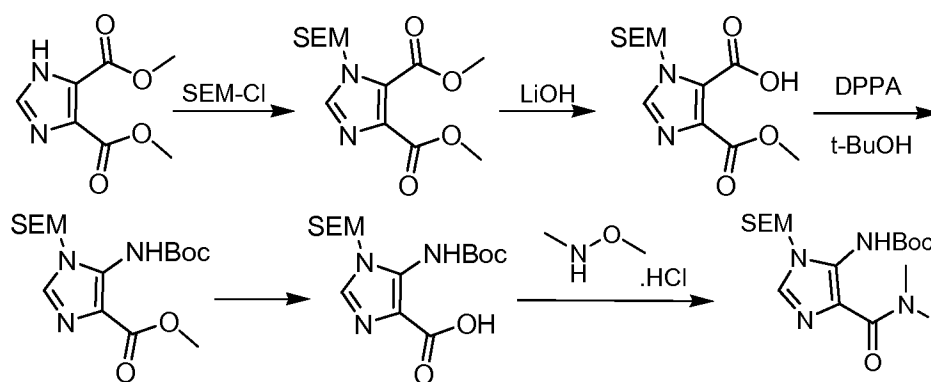


Example XV-III: Compound **1003** can be prepared according to the following Schemes:

Scheme XV-IIIa

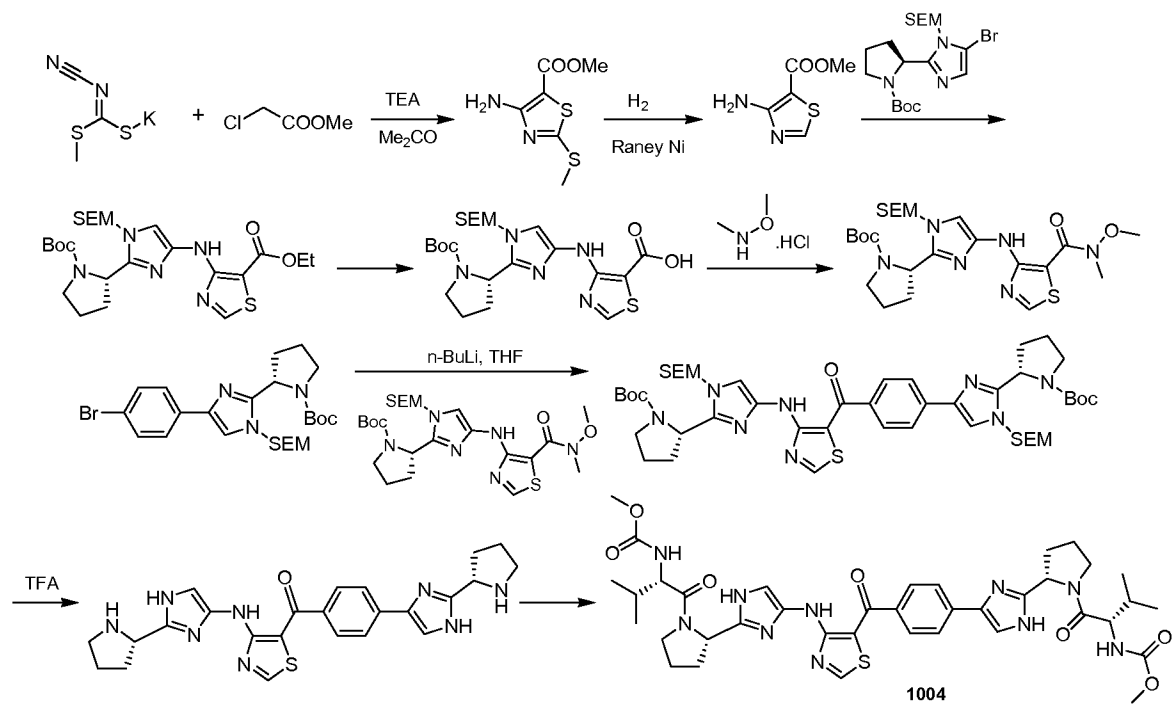


Scheme XV-IIIaa



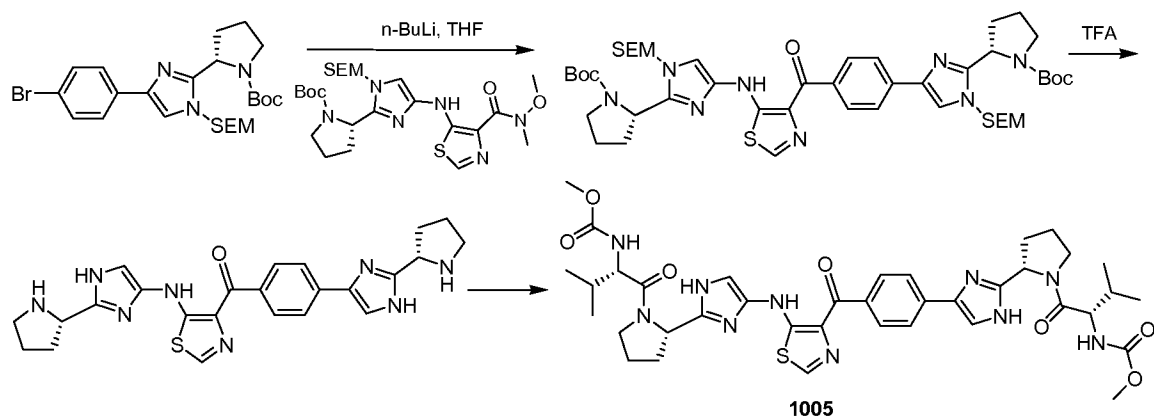
Example XV-IV: Compound **1004** can be prepared according to the following Schemes:

Scheme XV-IVa



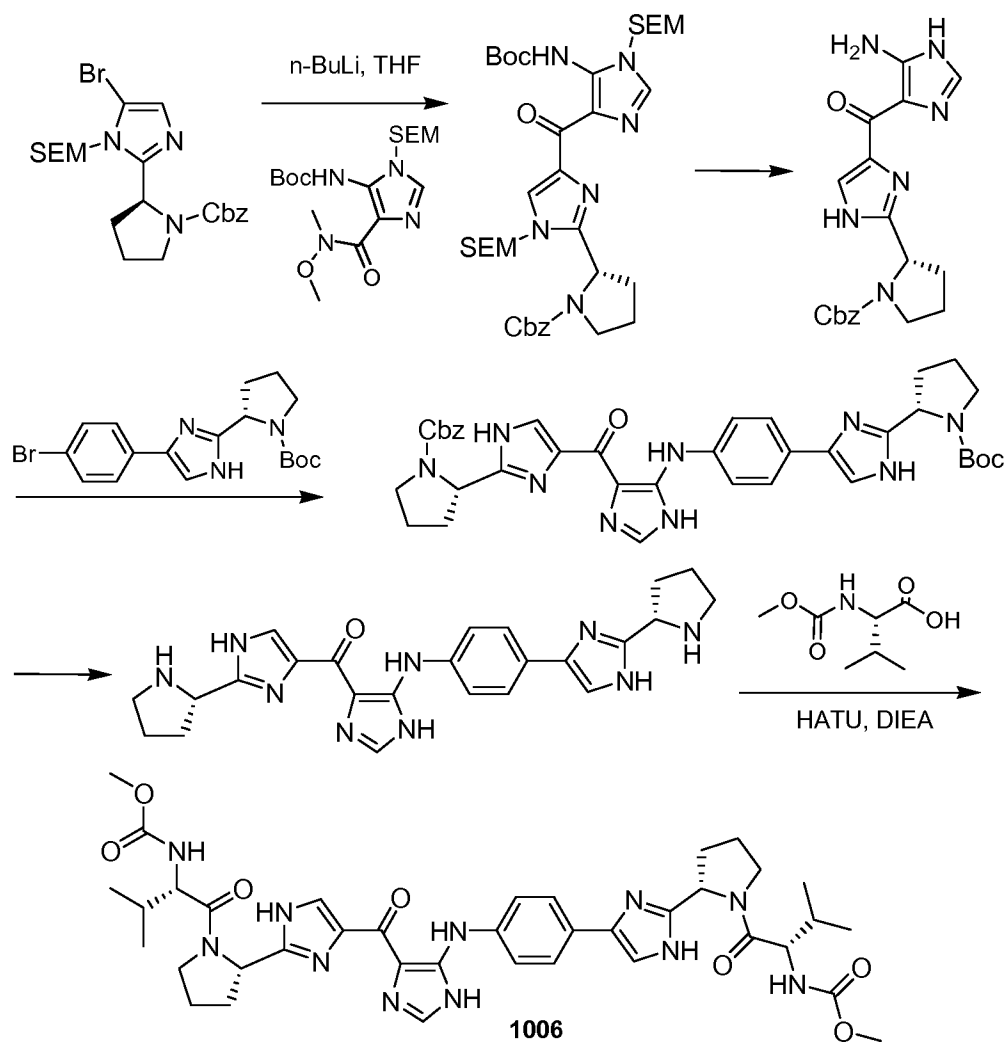
Example XV-V: Compound **1005** can be prepared according to the following Schemes:

Scheme XV-Va



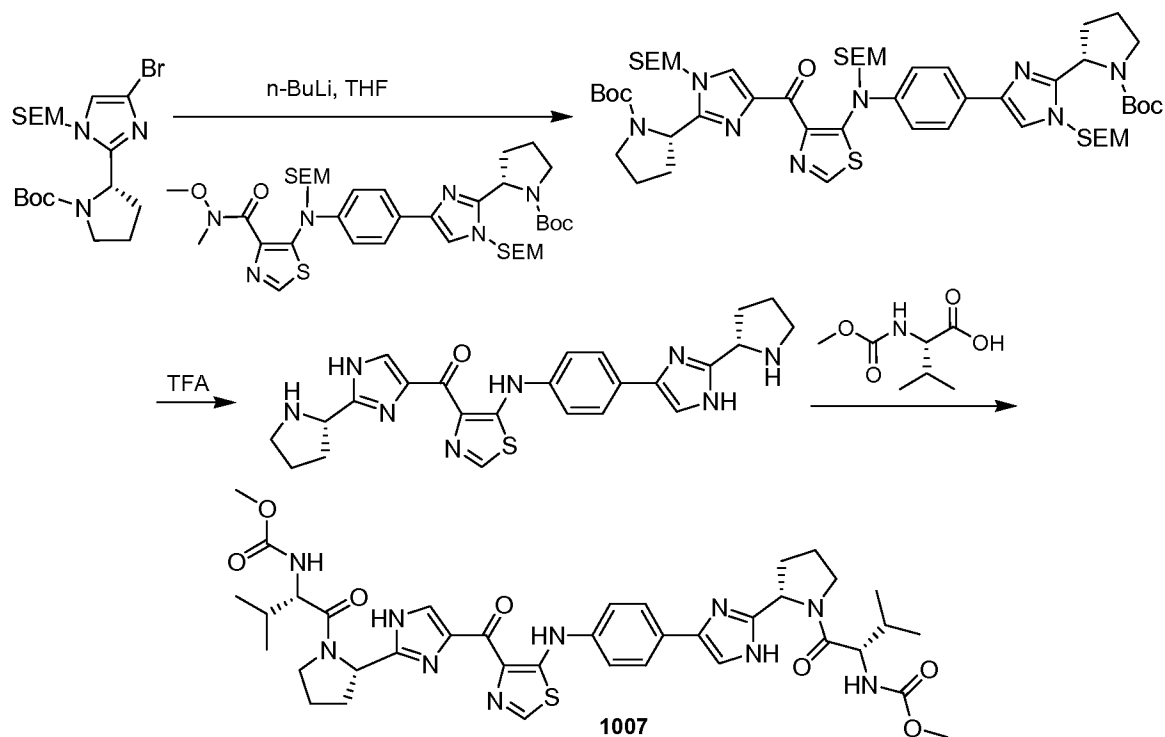
Example XV-VI: Compound **1006** can be prepared according to the following Scheme:

Scheme XV-VIa

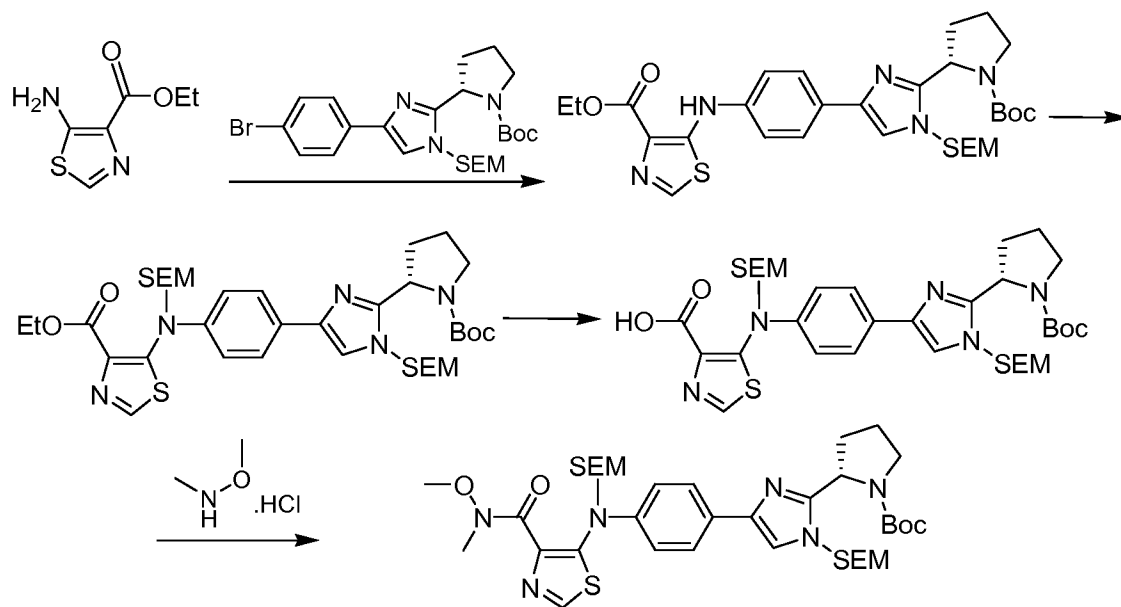


Example XV-VII: Compound **1007** can be prepared according to the following Schemes:

Scheme XV-VIIa

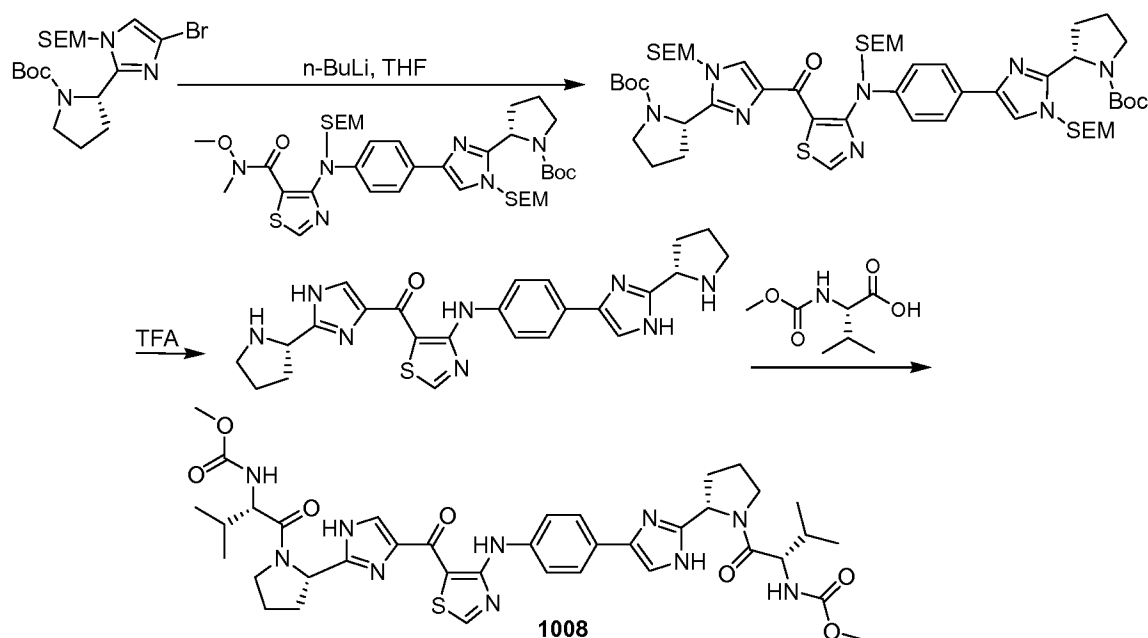


Scheme XV-VIIaa

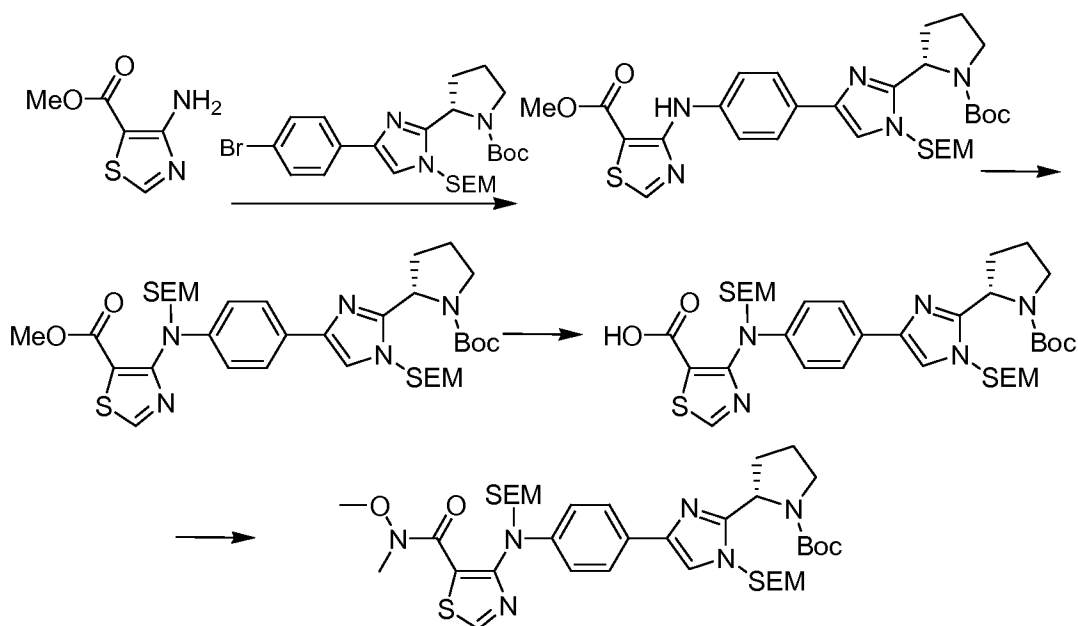


Example XV-VIII: Compound **1008** can be prepared according to the following Schemes:

Scheme XV-VIIIa



Scheme XV-VIIIaa



SECTION V

[0246] HCV Replicon Assay

[0247] Huh7 cells containing HCV replicons with an integrated luciferase reporter gene are maintained at 37°C in 5% CO₂ in Dulbecco's modified Eagle's medium (DMEM; Mediatech, Herndon, VA) containing 10% heat-inactivated fetal bovine serum (FBS; Mediatech, Herndon, VA), 2 mM L-glutamine (Cambrex Bioscience, Walkersville, MD), 1% non essential amino acids (Lonza, Walkersville, MD), 50 IU/mL penicillin

(Mediatech, Herndon, VA), 50 mg/mL streptomycin (Mediatech, Herndon, VA) and 0.5 mg/mL G418 (Promega, Madison, WI). Cells are sub-divided 1:3 or 4 every 2-3 days.

[0248] 24h prior to the assay, Huh7 cells containing sub-genomic HCV replicons are collected, counted, and plated in Nunclon 96-well tissue culture plates (ThermoFisher, Rochester, NY) at 5000 cells/well in 100mL standard maintenance medium (above) and incubated in the conditions above. To initiate the assay, culture medium is removed, and replaced with 90 mL maintenance media lacking G418. Test compounds are serially diluted three-fold in dimethyl sulfoxide (DMSO) in two duplicate rows for each EC₅₀ determination. These compound solutions are diluted ten-fold in DMEM lacking serum and G418. 10 mL of these compound solutions in media are added to duplicate tissue culture plates. The final volume is 100 μ L with a DMSO concentration of 1%. Compound concentrations are adjusted to appropriately define a dose response curve. Typical dilution series range from 100mM to 1.69 nM final concentrations to 1nM to 16.9 fM final. Plates are incubated at 37 °C for approximately 48 hr.

[0249] Following incubation, media is removed from one of the two duplicate plates and replicon-reporter luciferase activity is measured using a Bright-Glo luciferase assay kit (Promega, Madison, WI) according to manufacturer's instructions. Semi-log plots of luciferase activity versus the logarithm of compound concentration are fit to a 4-parameter logistic function using XLfit software (IDBS Inc., Guildford, UK) to determine EC₅₀.

[0250] Table 1: Examples of activity.

Compound	EC ₅₀ nM
701	B
702	B
703	B
704	B
705	B
706	B
707	C
708	B
709	A
710	C
711	B
712	C
713	A
714	B

715	B
716	C
717	B
718	B
719	B
720	C
721	C
808	C
809	C
900	B
902	A
904	C
905	C
906	A
907	B
908	C
909	C
1001	C

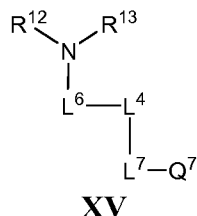
[0251] **A** indicates an EC₅₀ of 100 nM and greater than 100 nM

[0252] **B** indicates an EC₅₀ between 10 and 100 nM

[0253] **C** indicates an EC₅₀ of 10 nM and less than 10 nM

WHAT IS CLAIMED IS:

1. A compound having the structure of Formula **XV**:



or a pharmaceutically acceptable salt thereof,

wherein:

each $\text{R}^{12}\text{R}^{13}\text{N}$ is separately selected, wherein R^{12} and R^{13} are each separately selected from hydrogen, $-(\text{Y}^{14})(\text{C}(\text{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\text{R}^2)_2)_r]-[\text{Y}^{14}(\text{C}(\text{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\text{R}^2)_2)_r]_s-(\text{Y}^{14})_s-\text{R}^{80}$, $-(\text{Y}^{14})(\text{C}(\text{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\text{R}^2)_2)_r]-\text{Y}^{14}(\text{C}(\text{R}^2)_2)_r\text{O}(\text{C}(\text{R}^2)_2)_r-(\text{Y}^{14})_s-\text{R}^{80}$, alkoxyalkyl, alkoxyC(=O)-, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)-, C_{3-7} cycloalkylC(=O)-, C_{1-6} alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, $(\text{R}^e\text{R}^f\text{N})$ alkyl, $(\text{R}^e\text{R}^f\text{N})$ alkylC(=O)-, and $(\text{R}^e\text{R}^f\text{N})\text{C}(=\text{O})-$,

said alkoxyalkyl, alkoxyC(=O)-, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)-, C_{3-7} cycloalkylC(=O)-, C_{1-6} alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, and alkyl in $(\text{R}^e\text{R}^f\text{N})$ alkyl and $(\text{R}^e\text{R}^f\text{N})$ alkylC(=O)- are each optionally substituted with one or more R^{1ab} ;

or $\text{R}^{12}\text{R}^{13}\text{N}$ is a heterocyclyl linked through a ring nitrogen atom optionally substituted with one or more of oxo, $-(\text{Y}^{14})(\text{C}(\text{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\text{R}^2)_2)_r]-[\text{Y}^{14}(\text{C}(\text{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\text{R}^2)_2)_r]_s-(\text{Y}^{14})_s-\text{R}^{80}$, $-(\text{Y}^{14})(\text{C}(\text{R}^2)_2)_r(\text{NR}^2)_s(\text{C}(\text{R}^2)_2)_r]-\text{Y}^{14}(\text{C}(\text{R}^2)_2)_r\text{O}(\text{C}(\text{R}^2)_2)_r-(\text{Y}^{14})_s-\text{R}^{80}$, alkoxyalkyl, alkoxyC(=O)-, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)-, C_{3-7} cycloalkylC(=O)-, C_{1-6} alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl,

heterocyclalkyl, heterocyclalkylC(=O)–, heterocyclC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, ($R^e R^f N$)alkyl, ($R^e R^f N$)alkylC(=O)–, and ($R^e R^f N$)C(=O)–,

said alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocycl, heteroaryl, heteroarylalkyl, heterocyclalkyl, heterocyclalkylC(=O)–, heterocyclC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, and alkyl in ($R^e R^f N$)alkyl and ($R^e R^f N$)alkylC(=O)– are each optionally substituted with one or more R^{1ab} ;

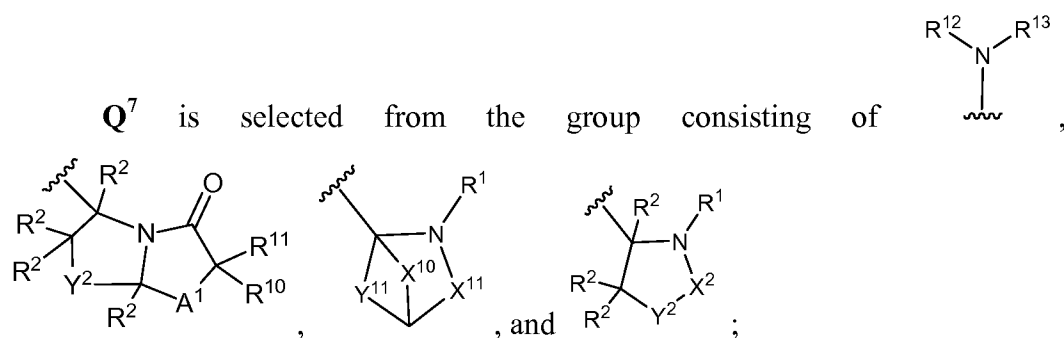
each R^{1ab} is separately selected from the group consisting of $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, $-C(R^{2a})_2NR^{3a}R^{3b}$, alkoxyalkyl, C_{1-6} alkylOC(=O)–, C_{1-6} alkylOC(=O) C_{1-6} alkyl, C_{1-6} alkylC(=O) C_{1-6} alkyl, aryl, aryl(CH₂)_n–, aryl(CH₂)_nO–, aryl(CH=CH)_m–, arylalkylO–, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)(CH=CH)_m–, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocycl, heterocycl(CH=CH)_m–, heterocyclalkoxy, heterocyclalkyl, heterocyclOalkyl, hydroxyalkyl, $R^c R^d N$ –, $R^c R^d N(CH_2)_n$ –, ($R^c R^d N$)(CH=CH)_m–, ($R^c R^d N$)alkyl, ($R^c R^d N$)C(=O)–, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9 halo;

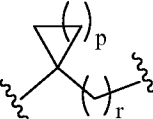
each R^{80} is separately selected from the group consisting of hydrogen, alkoxyalkyl, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, heterocyclalkyl, and ($R^e R^f N$)alkyl, said alkoxyalkyl, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroarylalkyl, heterocyclalkyl, and alkyl in ($R^e R^f N$)alkyl are each optionally substituted with one or more R^{1ac} ;

each R^{1ac} is separately selected from the group consisting of $-C(R^{2a})_2NR^{3a}R^{3b}$, alkoxyalkyl, C_{1-6} alkylOC(=O)–, C_{1-6} alkylOC(=O) C_{1-6} alkyl, C_{1-6} alkylC(=O) C_{1-6} alkyl, aryl, aryl(CH₂)_n–, aryl(CH₂)_nO–, aryl(CH=CH)_m–,

arylalkylO-, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)(CH=CH)_m-, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclyl, heterocyclyl(CH=CH)_m-, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, **R^cR^dN**-, **R^cR^dN**(CH₂)_n-, (**R^cR^dN**)(CH=CH)_m-, (**R^cR^dN**)alkyl, (**R^cR^dN**)C(=O)-, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each **Y¹⁴** is separately selected from the group consisting of -C(=O)-, -S(=O)-, -C(=S)-, -S(=O)₂-, -C(=O)O-, -C(=O)NR^{2c}-, -S(=O)₂NR^{2c}-, -C(=O)NR^{2c}C(=O)-, and -C(CF₃)₂NR^{2c}-,

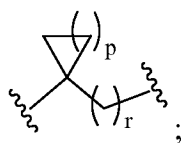


X² is (C(**R²**)₂)_q, , or **X²** is null;

Y² is selected from O (oxygen), S (sulfur), S(O), SO₂, NR², and C(**R²**)₂ with the proviso that when **X²** is null **Y²** is C(**R²**)₂;

each **X¹⁰** is (C(**R²**)₂)_q;

each **X¹¹** is separately selected from the group consisting of (C(**R²**)₂)_q, and



each **Y¹¹** is separately selected from the group consisting of -O(C(**R²**)₂)_n-, -S(C(**R²**)₂)_n-, -S(O)(C(**R²**)₂)_n-, -SO₂(C(**R²**)₂)_n-, -NR²(C(**R²**)₂)_n-, and (C(**R²**)₂)_q;

R¹ is selected from the group consisting of **R^{1aa}**, **R^{1a}C(=O)-** and **R^{1a}C(=S)-**;

each **R^{1a}** is separately selected from the group consisting of -C(**R^{2a}**)₂NR^{3a}R^{3b}, alkoxyalkyl, C₁₋₆alkylOC(=O)-, C₁₋₆alkylOC(=O)C₁₋₆alkyl,

C₁₋₆alkylC(=O)C₁₋₆alkyl, aryl, aryl(CH₂)_n-, aryl(CH₂)_nO-, aryl(CH=CH)_m-, arylalkylO-, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)(CH=CH)_m-, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclyl, heterocyclyl(CH=CH)_m-, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, **R^cR^dN**-, **R^cR^dN**(CH₂)_n-, (**R^cR^dN**)(CH=CH)_m-, (**R^cR^dN**)alkyl, (**R^cR^dN**)C(=O)-, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

R^{1aa} is $-\text{[(Y}^{14}\text{)(C(R}^2\text{)}_2\text{)}_r\text{(NR}^2\text{)}_s\text{(C(R}^2\text{)}_2\text{)}_r\text{]-[Y}^{14}\text{(C(R}^2\text{)}_2\text{)}_r\text{(NR}^2\text{)}_s\text{(C(R}^2\text{)}_2\text{)}_r\text{]-}$ $\text{(Y}^{14}\text{)}_s\text{-R}^{80}$, $-\text{[(Y}^{14}\text{)(C(R}^2\text{)}_2\text{)}_r\text{(NR}^2\text{)}_s\text{(C(R}^2\text{)}_2\text{)}_r\text{]-Y}^{14}\text{(C(R}^2\text{)}_2\text{)}_r\text{O(C(R}^2\text{)}_2\text{)}_r\text{-(Y}^{14}\text{)}_s\text{-R}^{80}$, alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, (**R^eR^fN**)alkyl, (**R^eR^fN**)alkylC(=O)-, and (**R^eR^fN**)C(=O)-,

said alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, and alkyl in (**R^eR^fN**)alkyl and (**R^eR^fN**)alkylC(=O)- are each optionally substituted with one or more **R^{1ab}**;

each **R¹⁰** is **R^cR^dN**-;

each **R¹¹** is separately selected from the group consisting of H (hydrogen), alkoxyalkyl, C₁₋₆alkylOC(=O)C₁₋₆alkyl, C₁₋₆alkylC(=O)C₁₋₆alkyl, aryl(CH₂)_n-, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, **R^cR^dN**(CH₂)_n-, (**R^cR^dN**)alkyl, and C₁₋₆alkyl optionally substituted with up to 9 halo;

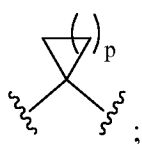
each **R^cR^dN** is separately selected, wherein **R^c** and **R^d** are each separately selected from hydrogen, alkoxyC(=O)-, C₁₋₆alkyl, C₁₋₆alkylC(=O)-,

C₁₋₆alkylsulfonyl, arylalkylOC(=O)–, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclalkyl, heterocyclalkylC(=O)–, heterocyclC(=O)–, (R^eR^fN)alkyl, (R^eR^fN)alkylC(=O)–, and (R^eR^fN)C(=O)–, wherein the alkyl part of arylalkyl, arylalkylC(=O)–, heterocyclalkyl, and heterocyclalkylC(=O)– are each optionally substituted with one R^eR^fN– group; and wherein the aryl part of arylalkyl, arylalkylC(=O)–, arylC(=O)–, and arylsulfonyl, and the heterocycl part of heterocyclalkyl, heterocyclalkylC(=O)–, and heterocyclC(=O)– are each optionally substituted with up to three substituents each independently selected from the group consisting of cyano, halo, nitro, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each R^eR^fN is separately selected, wherein R^e and R^f are each separately selected from hydrogen, C₁₋₆alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycl, heterocyclalkyl, (R^xR^yN)alkyl, and (R^xR^yN)C(=O)–;

each R^xR^yN is separately selected, wherein R^x and R^y are each separately selected from hydrogen, C₁₋₆alkylOC(=O)–, C₁₋₆alkyl, C₁₋₆alkylC(=O)–, aryl, arylalkyl, cycloalkyl, and heterocycl;

each C(R^{2a})₂ is separately selected, wherein each R^{2a} is separately selected from the group consisting of hydrogen, C₁₋₆alkyl optionally substituted with up to 9 halo, aryl(CH₂)_n–, and heteroaryl(CH₂)_n–, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9

halo, or optionally C(R^{2a})₂ is ;

each R^{3a} is separately selected from the group consisting of hydrogen, and optionally substituted C₁₋₆alkyl;

each R^{3b} is separately selected from the group consisting of optionally substituted C₁₋₆alkyl, heteroaryl, –(CH₂)_nC(=O)NR^{4a}R^{4b}, –(CH₂)_nC(=O)OR^{5a}, and –(CH₂)_nC(=O)R^{6a} said heteroaryl optionally substituted with cyano, halo, nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each $\mathbf{R}^{4a}\mathbf{R}^{4b}\mathbf{N}$ is separately selected, wherein $\mathbf{R}^{4a}$ and $\mathbf{R}^{4b}$ are each separately selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, and $\text{aryl}(\text{CH}_2)_n-$;

each $\mathbf{R}^{5a}$ is separately selected from the group consisting of optionally substituted C_{1-6} alkyl, and $\text{aryl}(\text{CH}_2)_n-$;

each $\mathbf{R}^{6a}$ is separately selected from the group consisting of optionally substituted C_{1-6} alkyl, and $\text{aryl}(\text{CH}_2)_n-$;

each $\mathbf{A}^1$ is separately selected from the group consisting of C_{2-6} alkenyl, C_{1-6} alkyl, and $-(\text{CH}_2)_n-\text{O}-(\text{CH}_2)_m-$, each optionally substituted with one or more $\mathbf{R}^2$;

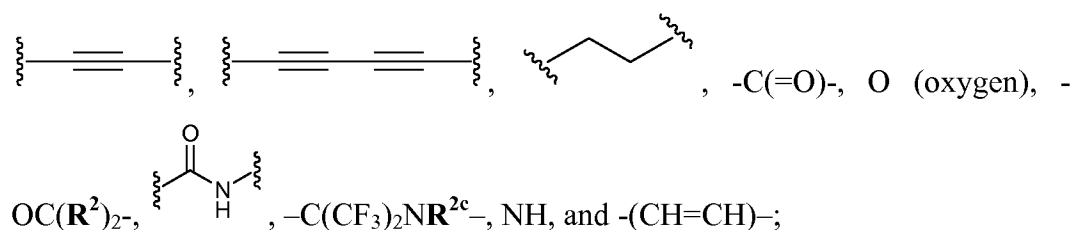
each $\mathbf{R}^2$ is separately selected, wherein $\mathbf{R}^2$ is selected from the group consisting of hydrogen, halo, hydroxy, C_{1-6} alkoxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, alkoxyalkyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, $(\mathbf{R}^e\mathbf{R}^f\mathbf{N})\text{alkyl}$, and $\mathbf{R}^a\mathbf{R}^b\mathbf{N}-$, said C_{1-6} alkyl optionally substituted with one or more halo, $-\text{OR}^{2b}$, $-\text{C}(=\text{O})\text{OR}^{2b}$, $-\text{C}(=\text{O})\text{NHR}^{2b}$, $-\text{NHC}(=\text{NH})\text{NHR}^{2b}$, $-\text{NHR}^{2b}$, SR^{2b} , imidazolyl, indolyl, $-\text{SCH}_3$, phenyl, and 4-hydroxyphenyl, said C_{1-6} alkoxy, alkoxyalkyl, aryl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and alkyl in $(\mathbf{R}^e\mathbf{R}^f\mathbf{N})\text{alkyl}$ each optionally substituted with one or more $\mathbf{R}^4$, or optionally two vicinal $\mathbf{R}^2$ and the carbons to which they are attached are together a fused three- to six-membered carbocyclic ring optionally substituted with up to two C_{1-6} alkyl groups;

$\mathbf{R}^{2b}$ is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

each $\mathbf{R}^{2c}$ is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, said alkyl optionally substituted with $\mathbf{R}^e\mathbf{R}^f\mathbf{N}-$, alkoxy, or $\text{C}_{1-6}\text{alkylS}-$;

each $\mathbf{R}^a\mathbf{R}^b\mathbf{N}$ is separately selected, wherein $\mathbf{R}^a$ and $\mathbf{R}^b$ are each separately selected from the group consisting of hydrogen, C_{2-6} alkenyl, and C_{1-6} alkyl;

$\mathbf{L}^4$ is selected from the group consisting of $-(\mathbf{J}^2)_s-(\mathbf{L}^5)_s-(\mathbf{J}^2)_s-(\mathbf{L}^5)_s-\mathbf{J}^2$.

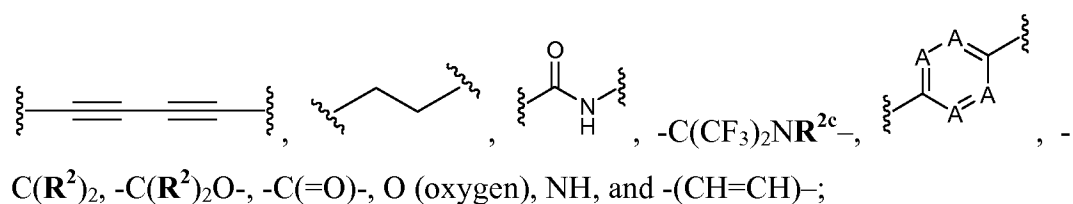


J² is aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, or polycyclic hydrocarbon, each optionally substituted with one or more **R**¹⁵;

each **R**¹⁴ is separately selected from the group consisting of hydroxy, C₁₋₆alkoxy optionally substituted with up to 9 fluoro, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC(=O)–, arylalkylOC(=O)–, –COOH, halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each **R**¹⁵ is separately selected from the group consisting of halo, hydroxy, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC(=O)–, arylalkylOC(=O)–, –COOH, **R**⁹, **R**^x**R**^yN, **R**^x**R**^yNC(=O), **R**^x**R**^yNC₁₋₆alkyl, heteroaryl, aryl, C₁₋₆alkyl optionally substituted with up to 9 halo, C₁₋₆alkyl substituted with up to 5 hydroxy, C₁₋₆alkoxy optionally substituted with up to 9 halo, C₁₋₆haloalkyl, **R**^a**R**^bN–, (**R**^a**R**^bN)alkyl, (**R**^a**R**^bN)C(=O)–, C₁₋₆alkyl substituted with up to 5 hydroxy, said substituent aryl and heteroaryl are each optionally substituted with one or more **R**¹⁴, or optionally two vicinal **R**¹⁵ and the carbons to which they are attached are together a fused three– to six–membered carbocyclic ring optionally substituted with up to two C₁₋₆alkyl groups, or optionally two geminal **R**¹⁵ and the carbon to which they are attached are together a three– to six–membered carbocyclic ring optionally substituted with up to two C₁₋₆alkyl groups, or optionally two geminal **R**¹⁵ are together oxo;

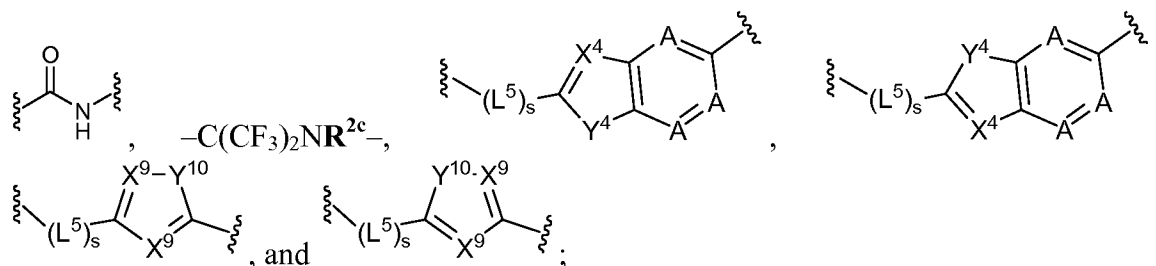
each $\mathbf{L}^5$ is separately selected from the group consisting of ,



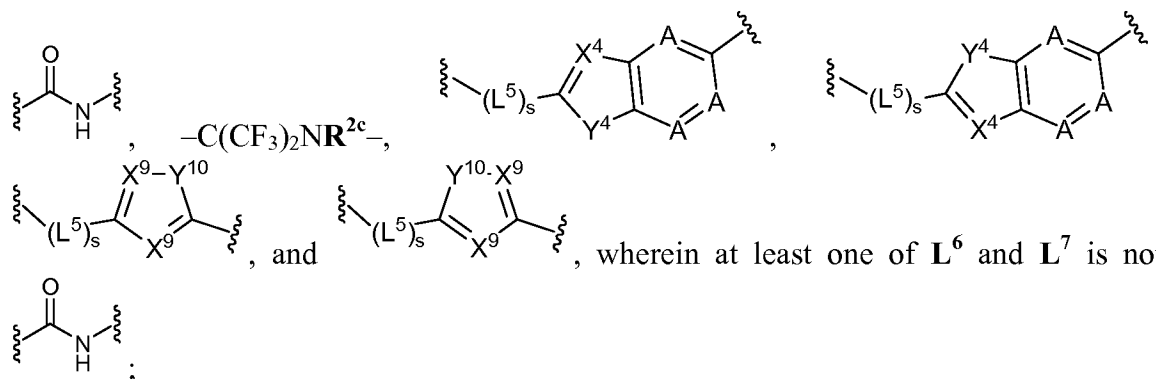
each **A** is separately selected from the group consisting of **CR**³ and N (nitrogen);

each R^3 is separately selected from the group consisting of hydrogen, C_{1-6} alkoxy, C_{1-6} alkylOC $_{1-6}$ alkyl, C_{1-6} alkylOC(=O)–, arylalkylOC(=O)–, –COOH, halo, hydroxy, R^aR^bN –, (R^aR^bN) alkyl, $(R^aR^bN)C(=O)$ –, C_{1-6} alkyl optionally substituted with up to 9 halo and up to 5 hydroxy;

L^6 is selected from the group consisting of



L^7 is selected from the group consisting of



each X^4 is separately selected from the group consisting of CR^4 and N (nitrogen);

each Y^4 is separately selected from the group consisting of $C(R^4)_2$, NR^4 , O (oxygen), and S (sulfur);

each X^9 is separately selected from the group consisting of CH and N (nitrogen);

each Y^{10} is separately selected from the group consisting of $-CH_2-$ and $-NH-$;

each m separately is 1 or 2;

each n separately is 0, 1 or 2;

each p separately is 1, 2, 3 or 4;

each q separately is 1, 2, 3, 4 or 5;

each r separately is 0, 1, 2, 3, or 4;

each s separately is 0 or 1;

each R^4 is separately selected from the group consisting of H (hydrogen), C_{1-6} alkoxy, C_{1-6} alkylOC $_{1-6}$ alkyl, C_{1-6} alkylOC(=O)–, arylalkylOC(=O)–, –COOH, halo, C_{1-6} haloalkyl, hydroxy, R^aR^bN –, (R^aR^bN) alkyl, $(R^aR^bN)C(=O)$ –, C_{1-6} alkyl optionally substituted with up to 9 halo and up to 5 hydroxy, or optionally two geminal R^4 are together oxo;

R^9 is selected from the group consisting of hydrogen and $-C(=O)R^{9a}$;

R^{9a} is selected from the group consisting of $-NR^{9b}R^{9c}$, $-OR^{9d}$, C_{1-6} alkyl optionally substituted with up to 9 halo, and optionally substituted aryl;

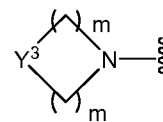
R^{9b} is selected from the group consisting of hydrogen, C_{1-6} alkyl optionally substituted with up to 9 halo, and optionally substituted aryl;

R^{9c} is selected from the group consisting of C_{1-6} alkyl optionally substituted with up to 9 halo, and optionally substituted aryl; and

R^{9d} is selected from the group consisting of C_{1-6} alkyl optionally substituted with up to 9 halo, and optionally substituted aryl.

2. The compound of Claim 1, wherein at least one $R^{12}R^{13}N$ is a nitrogen containing heterocyclyl optionally including one or more $-C(=O)$ –, O (oxygen), S (sulfur), S(O), SO_2 , or NH groups in the heterocyclyl ring and optionally substituted with one or more of $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, (R^eR^fN) alkyl, (R^eR^fN) alkylC(=O)–, and $(R^eR^fN)C(=O)$ –,

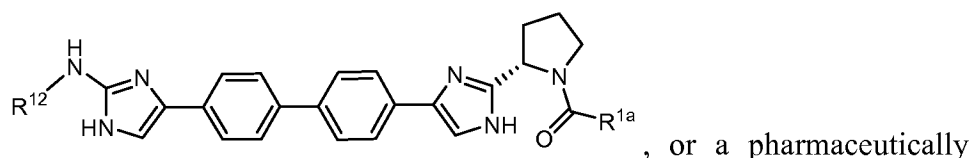
said alkoxyalkyl, alkoxyC(=O)–, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)–, C_{3-7} cycloalkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)–, heterocyclylC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, and alkyl in (R^eR^fN) alkyl and (R^eR^fN) alkylC(=O)– are each optionally substituted with one or more R^1 .



3. The compound of Claim 1, wherein at least one $R^{12}R^{13}N$ is optionally substituted with one or more of $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-$, $[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-$, $Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, (R^eR^fN) alkyl, (R^eR^fN) alkylC(=O)-, and $(R^eR^fN)C(=O)-$,

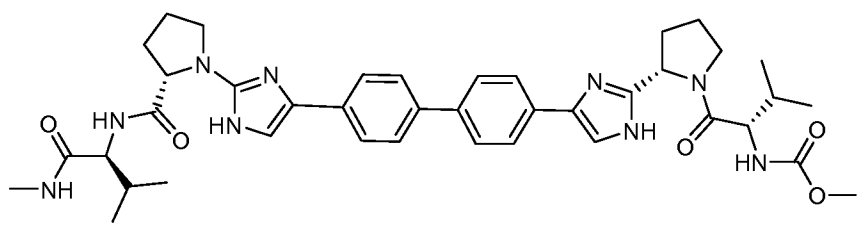
said alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, and alkyl in (R^eR^fN) alkyl and (R^eR^fN) alkylC(=O)- are each optionally substituted with one or more R^1 ; wherein Y^3 is O (oxygen), S (sulfur), S(O), SO₂, -C(=O)-, -NH-, -CH₂-, -NHCH₂-, -OCH₂-, -SCH₂-, -NHCH₂-, -NHC(=O)-, or -NHSO₂-.

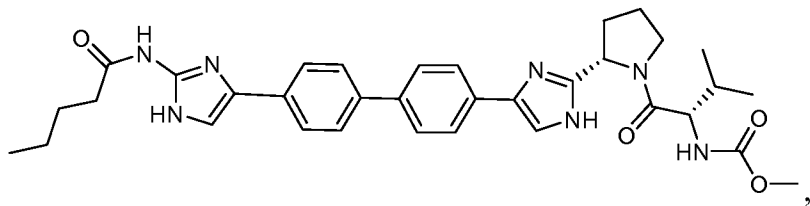
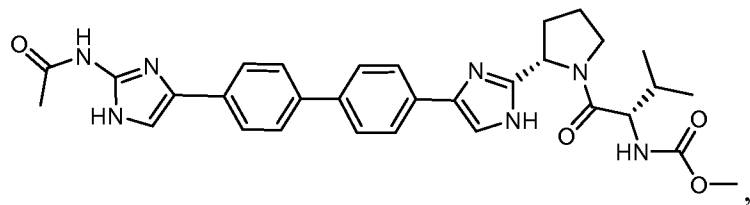
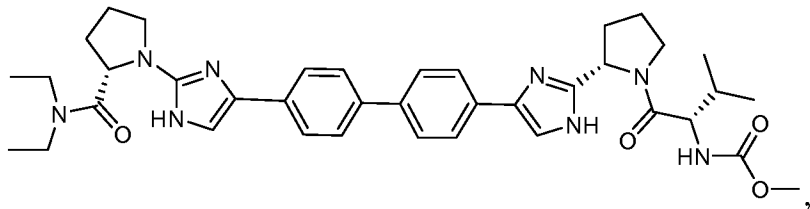
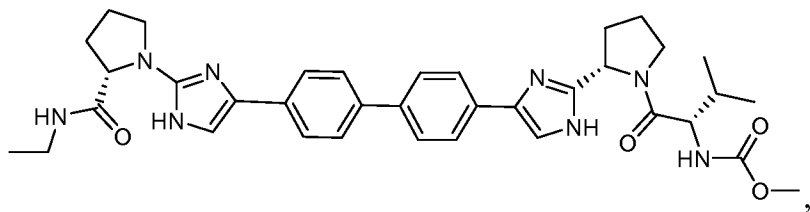
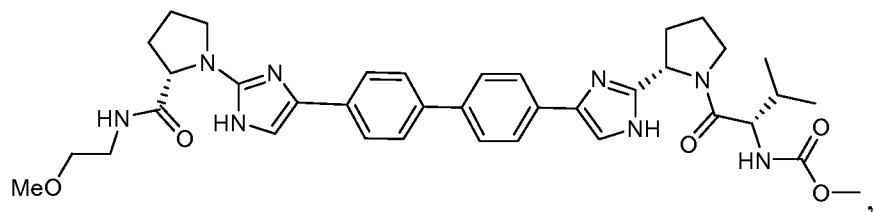
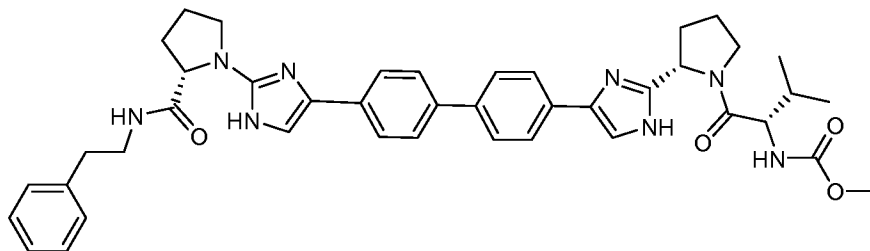
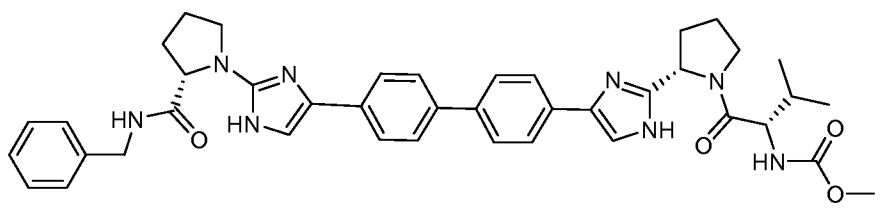
4. The compound of Claim 1 having the Formula **XVa**:

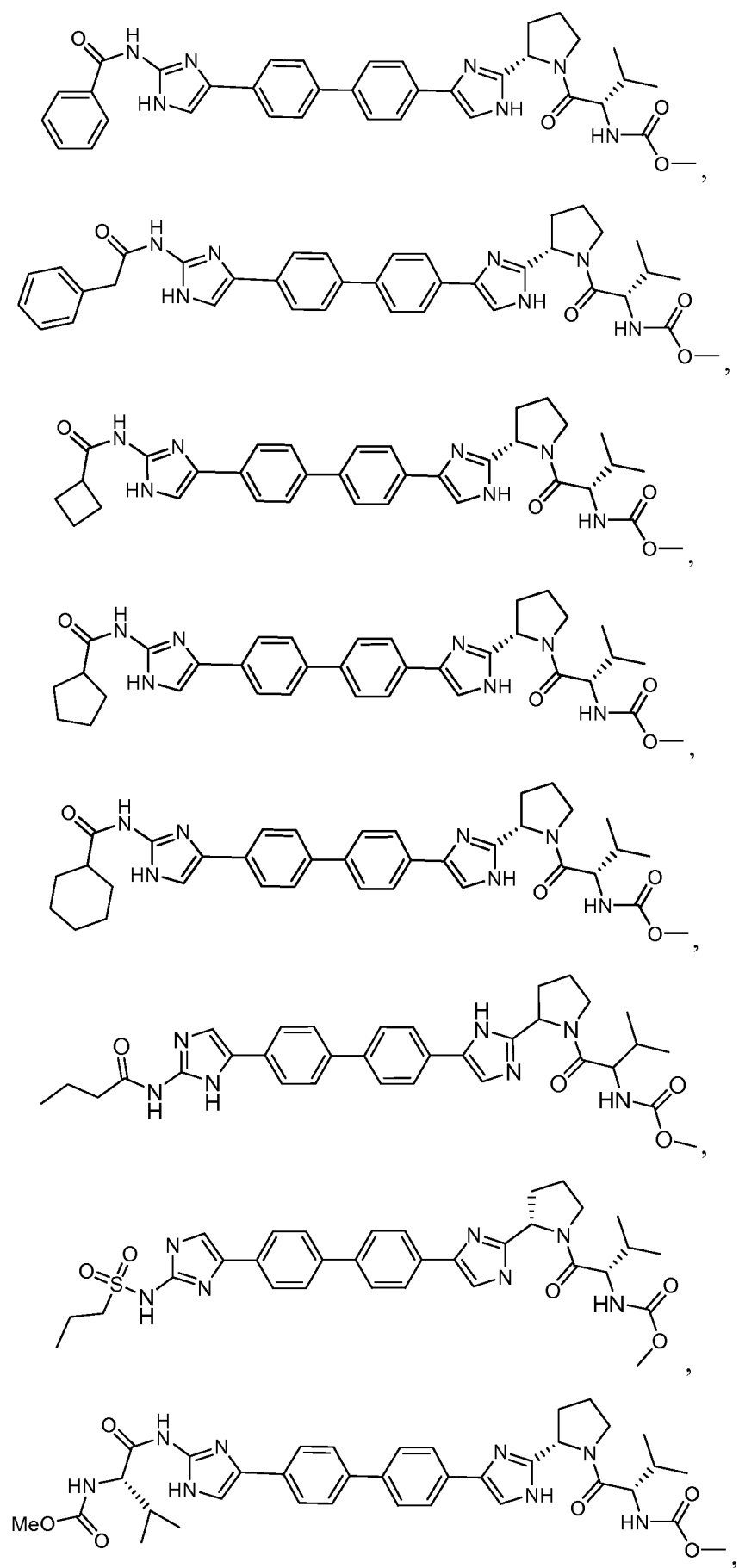


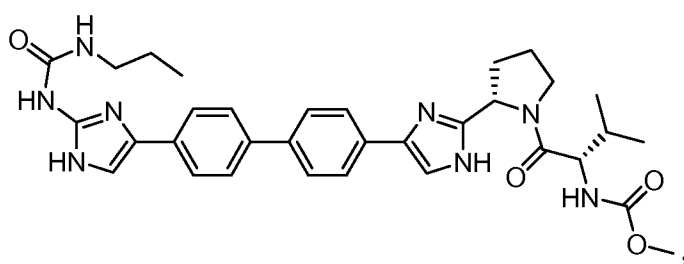
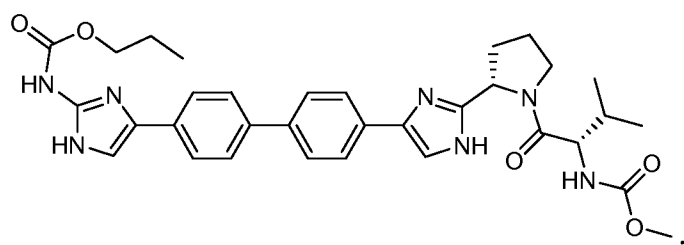
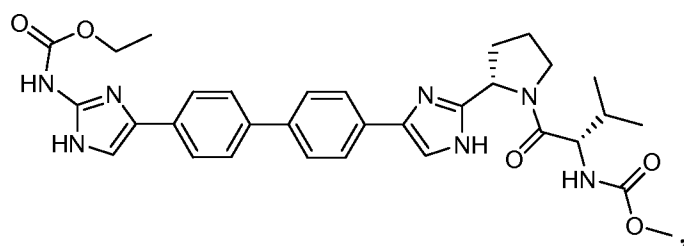
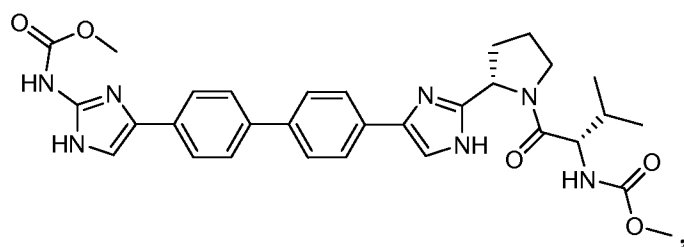
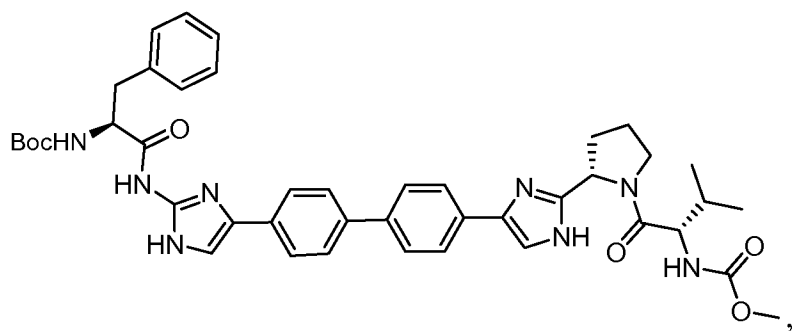
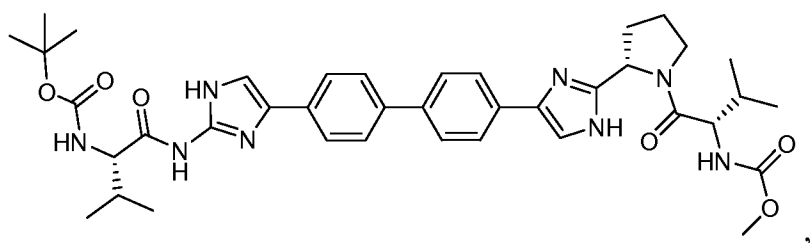
acceptable salt thereof.

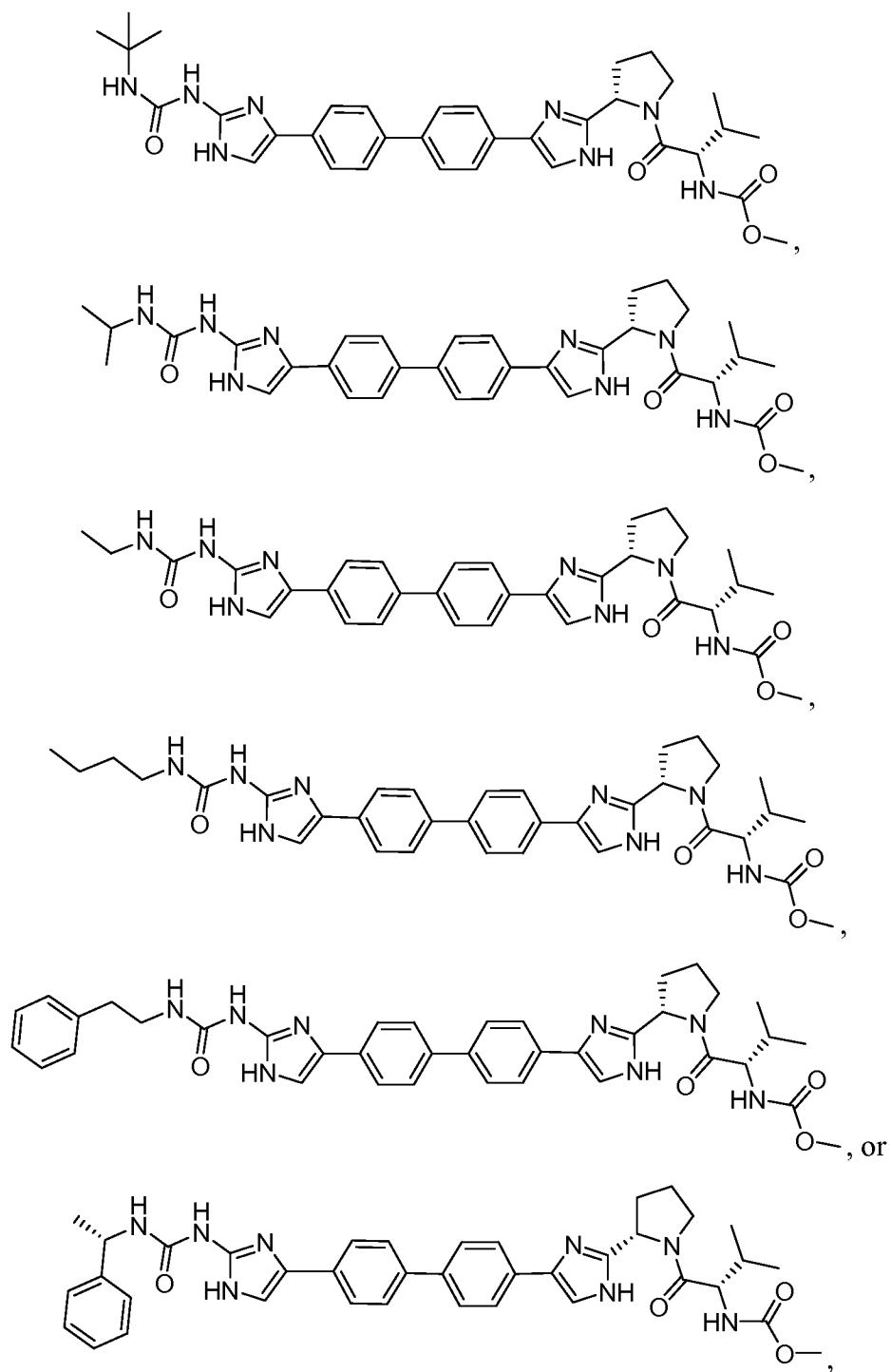
5. The compound of Claim 1, having the structure:



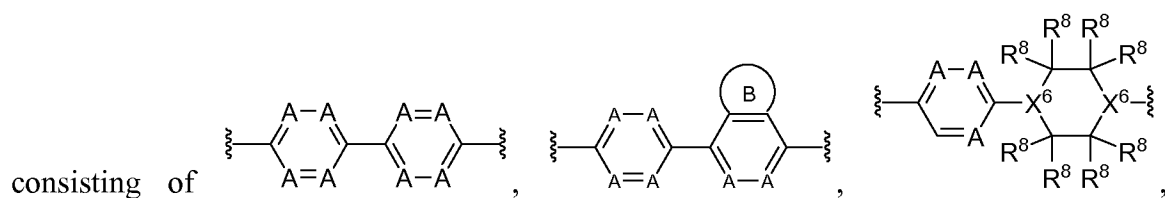


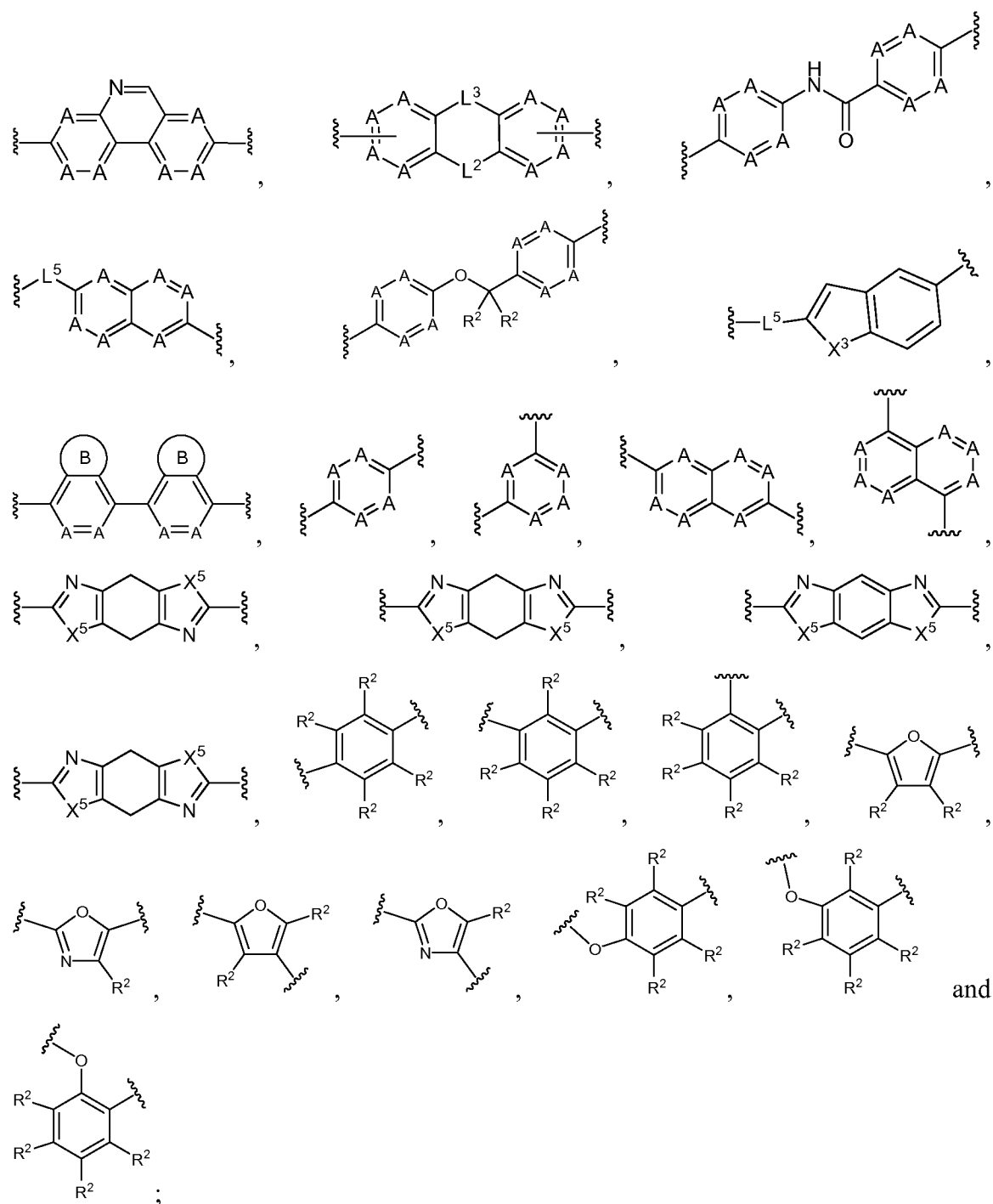






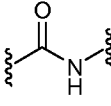
6. The compound of Claim 1, wherein L^4 is selected from the group





each **B** is separately selected, wherein **B** is a fused optionally substituted saturated or unsaturated three- to seven-membered carbocyclic ring or a fused optionally substituted saturated or unsaturated three- to seven-membered heterocyclic ring, each optionally substituted with one or more **R**⁴;

L^2 is selected from the group consisting of $-C(=O)-$, $-(CH_2CH_2)-$, $-(CH_2O)-$, $-(CH_2S)-$, $-(CH=CH)-$, $-(CH=N)-$, $-NH-$, O (oxygen), S (sulfur), and $-CH_2-$;

L^3 is selected from the group consisting of , $-(NR^9)-$, O (oxygen), S (sulfur), and $-CH_2-$;

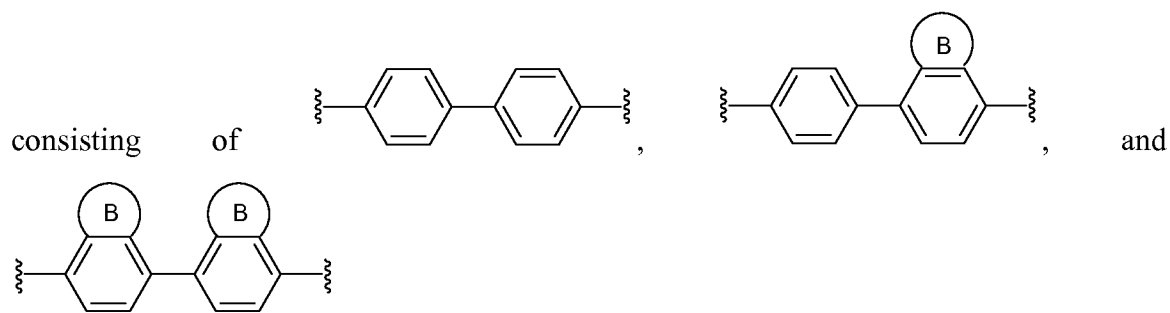
X^3 is selected from the group consisting of NH, O (oxygen), and S (sulfur);

each X^5 is separately selected from the group consisting of $-NH-$, O (oxygen), S (sulfur), and $-CH_2-$;

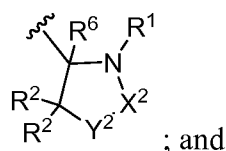
each X^6 is separately selected from the group consisting of N (nitrogen), and CR^8 ; and

each R^8 is separately selected from the group consisting of hydrogen, $C_{1-6}alkylOC_{1-6}alkyl$, $C_{1-6}alkylOC(=O)-$, arylalkyl $OC(=O)-$, halo, $(R^aR^bN)alkyl$, $(R^aR^bN)C(=O)-$, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo and up to 5 hydroxy.

7. The compound of Claim 6, wherein L^4 is selected from the group



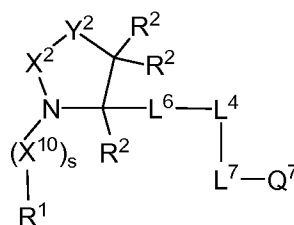
8. The compound of Claim 1, wherein Q^7 is:



R^6 is $C_{1-6}alkyl$ optionally substituted with up to 9 halo.

9. The compound of Claim 8, wherein R^6 is methyl.

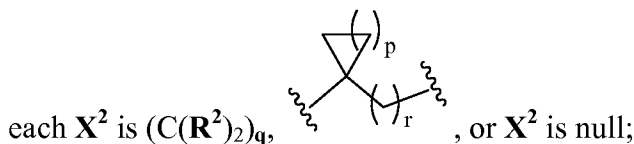
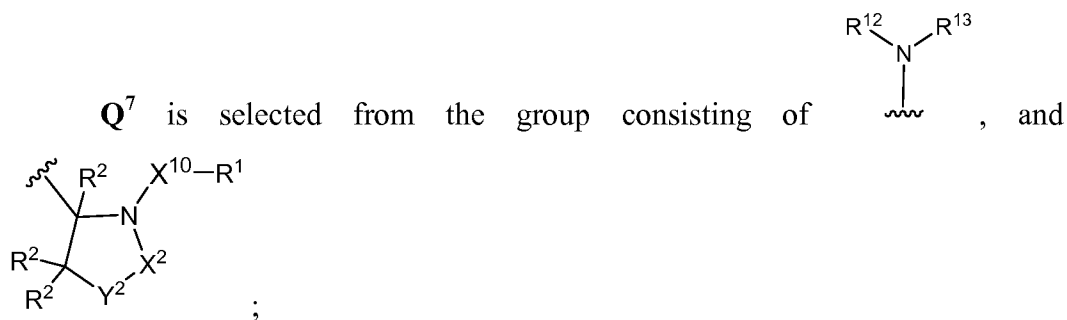
10. A compound having the structure of Formula XVI:



XVI

or a pharmaceutically acceptable salt thereof,

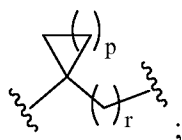
wherein:



each Y^2 is selected from O (oxygen), S (sulfur), S(O), SO₂, NR², and C(R²)₂ with the proviso that when X^2 is null Y^2 is C(R²)₂;

each X^{10} is $(C(R^2)_2)_q$;

each X^{11} is separately selected from the group consisting of $(C(R^2)_2)_q$, and



each Y^{11} is separately selected from the group consisting of -O(C(R²)₂)_n-, -S(C(R²)₂)_n-, -S(O)(C(R²)₂)_n-, -SO₂(C(R²)₂)_n-, -NR²(C(R²)₂)_n-, and (C(R²)₂)_q;

each $R^{12}R^{13}N$ is separately selected, wherein R^{12} and R^{13} are each separately selected from hydrogen, -[(Y¹⁴)(C(R²)₂)_r(NR²)_s(C(R²)₂)_r]-[Y¹⁴(C(R²)₂)_r(NR²)_s(C(R²)₂)_r]-s-(Y¹⁴)_s-R⁸⁰, -[(Y¹⁴)(C(R²)₂)_r(NR²)_s(C(R²)₂)_r]-Y¹⁴(C(R²)₂)_rO(C(R²)₂)_r-(Y¹⁴)_s-R⁸⁰, alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, (R^eR^fN)alkyl, (R^eR^fN)alkylC(=O)-, and (R^eR^fN)C(=O)-,

said alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl,

heterocyclalkylC(=O)–, heterocyclC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, and alkyl in (R^eR^fN)alkyl and (R^eR^fN)alkylC(=O)– are each optionally substituted with one or more R^{1ab};

or R¹²R¹³N is a heterocycl linked through a ring nitrogen atom optionally substituted with one or more of oxo, –[(Y¹⁴)(C(R²)₂)_r(NR²)_s(C(R²)₂)_r]–[Y¹⁴(C(R²)₂)_r(NR²)_s(C(R²)₂)_r]–(Y¹⁴)_s–R⁸⁰, –[(Y¹⁴)(C(R²)₂)_r(NR²)_s(C(R²)₂)_r]–Y¹⁴(C(R²)₂)_rO(C(R²)₂)_r–(Y¹⁴)_s–R⁸⁰, alkoxyalkyl, alkoxyC(=O)–, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)–, C₃₋₇cycloalkylC(=O)–, C₁₋₆alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocycl, heteroaryl, heteroarylalkyl, heterocyclalkyl, heterocyclalkylC(=O)–, heterocyclC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, (R^eR^fN)alkyl, (R^eR^fN)alkylC(=O)–, and (R^eR^fN)C(=O)–,

said alkoxyalkyl, alkoxyC(=O)–, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)–, C₃₋₇cycloalkylC(=O)–, C₁₋₆alkylsulfonyl, arylalkylOC(=O)–, aryl, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocycl, heteroaryl, heteroarylalkyl, heterocyclalkyl, heterocyclalkylC(=O)–, heterocyclC(=O)–, heteroarylC(=O)–, heteroarylalkylC(=O)–, and alkyl in (R^eR^fN)alkyl and (R^eR^fN)alkylC(=O)– are each optionally substituted with one or more R^{1ab};

each R^{1ab} is separately selected from the group consisting of –[(Y¹⁴)(C(R²)₂)_r(NR²)_s(C(R²)₂)_r]–[Y¹⁴(C(R²)₂)_r(NR²)_s(C(R²)₂)_r]–(Y¹⁴)_s–R⁸⁰, –[(Y¹⁴)(C(R²)₂)_r(NR²)_s(C(R²)₂)_r]–Y¹⁴(C(R²)₂)_rO(C(R²)₂)_r–(Y¹⁴)_s–R⁸⁰, –C(R^{2a})₂NR^{3a}R^{3b}, alkoxyalkyl, C₁₋₆alkylOC(=O)–, C₁₋₆alkylOC(=O)C₁₋₆alkyl, C₁₋₆alkylC(=O)C₁₋₆alkyl, aryl, aryl(CH₂)_n–, aryl(CH₂)_nO–, aryl(CH=CH)_m–, arylalkylO–, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)(CH=CH)_m–, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocycl, heterocycl(CH=CH)_m–, heterocyclalkoxy, heterocyclalkyl, heterocyclOalkyl, hydroxyalkyl, R^cR^dN–, R^cR^dN(CH₂)_n–, (R^cR^dN)(CH=CH)_m–, (R^cR^dN)alkyl, (R^cR^dN)C(=O)–, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted

with cyano, halo, nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each **R**⁸⁰ is separately selected from the group consisting of hydrogen, alkoxyalkyl, C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and (**R**^e**R**^fN)alkyl, said alkoxyalkyl, C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and alkyl in (**R**^e**R**^fN)alkyl are each optionally substituted with one or more **R**^{1ac};

each **R**^{1ac} is separately selected from the group consisting of -C(**R**^{2a})₂N**R**^{3a}**R**^{3b}, alkoxyalkyl, C₁₋₆alkylOC(=O)-, C₁₋₆alkylOC(=O)C₁₋₆alkyl, C₁₋₆alkylC(=O)C₁₋₆alkyl, aryl, aryl(CH₂)_n-, aryl(CH₂)_nO-, aryl(CH=CH)_m-, arylalkylO-, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)(CH=CH)_m-, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclyl, heterocyclyl(CH=CH)_m-, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, **R**^c**R**^dN-, **R**^c**R**^dN(CH₂)_n-, (**R**^c**R**^dN)(CH=CH)_m-, (**R**^c**R**^dN)alkyl, (**R**^c**R**^dN)C(=O)-, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each **Y**¹⁴ is separately selected from the group consisting of -C(=O)-, -S(=O)-, -C(=S)-, -S(=O)₂-, -C(=O)O-, -C(=O)N**R**^{2c}-, -S(=O)₂N**R**^{2c}-, -C(=O)N**R**^{2c}C(=O)-, and -C(CF₃)₂N**R**^{2c}-;

R¹ is selected from the group consisting of **R**^{1aa}, **R**^{1a}C(=O)- and **R**^{1a}C(=S)-;

each **R**^{1a} is separately selected from the group consisting of -C(**R**^{2a})₂N**R**^{3a}**R**^{3b}, alkoxyalkyl, C₁₋₆alkylOC(=O)-, C₁₋₆alkylOC(=O)C₁₋₆alkyl, C₁₋₆alkylC(=O)C₁₋₆alkyl, aryl, aryl(CH₂)_n-, aryl(CH₂)_nO-, aryl(CH=CH)_m-, arylalkylO-, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)(CH=CH)_m-, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclyl, heterocyclyl(CH=CH)_m-, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, **R**^c**R**^dN-, **R**^c**R**^dN(CH₂)_n-, (**R**^c**R**^dN)(CH=CH)_m-, (**R**^c**R**^dN)alkyl, (**R**^c**R**^dN)C(=O)-, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted

with cyano, halo, nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

R^{1aa} is selected from the group consisting of -C(**R^{2a}**)₂N**R^{3a}R^{3b}**, -[(**Y¹⁴**)(C(**R²**)₂)_r(N**R²**)_s(C(**R²**)₂)_r)-[**Y¹⁴**(C(**R²**)₂)_r(N**R²**)_s(C(**R²**)₂)_r)]_s-(**Y¹⁴**)_s-**R⁸⁰**, -[(**Y¹⁴**)(C(**R²**)₂)_r(N**R²**)_s(C(**R²**)₂)_r)-**Y¹⁴**(C(**R²**)₂)_rO(C(**R²**)₂)_r-(**Y¹⁴**)_s-**R⁸⁰**, alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, (**R^eR^fN**)alkyl, (**R^eR^fN**)alkylC(=O)-, and (**R^eR^fN**)C(=O)-,

said alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, and alkyl in (**R^eR^fN**)alkyl and (**R^eR^fN**)alkylC(=O)- are each optionally substituted with one or more **R^{1ab}**;

each **R¹⁰** is **R^cR^dN**-;

each **R¹¹** is separately selected from the group consisting of H (hydrogen), alkoxyalkyl, C₁₋₆alkylOC(=O)C₁₋₆alkyl, C₁₋₆alkylC(=O)C₁₋₆alkyl, aryl(CH₂)_n-, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, **R^cR^dN**(CH₂)_n-, (**R^cR^dN**)alkyl, and C₁₋₆alkyl optionally substituted with up to 9 halo;

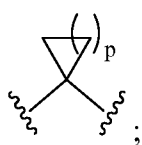
each **R^cR^dN** is separately selected, wherein **R^c** and **R^d** are each separately selected from hydrogen, alkoxyC(=O)-, C₁₋₆alkyl, C₁₋₆alkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, (**R^eR^fN**)alkyl, (**R^eR^fN**)alkylC(=O)-, and (**R^eR^fN**)C(=O)-, wherein the alkyl part of arylalkyl, arylalkylC(=O)-, heterocyclylalkyl, and heterocyclylalkylC(=O)- are each optionally substituted with one **R^eR^fN**- group; and wherein the aryl part of arylalkyl, arylalkylC(=O)-, arylC(=O)-, and arylsulfonyl, and the heterocyclyl

part of heterocyclalkyl, heterocyclalkylC(=O)–, and heterocyclC(=O)– are each optionally substituted with up to three substituents each independently selected from the group consisting of cyano, halo, nitro, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each **R^eR^fN** is separately selected, wherein **R^e** and **R^f** are each separately selected from hydrogen, C₁₋₆alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycl, heterocyclalkyl, (**R^xR^yN**)alkyl, and (**R^xR^yN**)C(=O)–;

each **R^xR^yN** is separately selected, wherein **R^x** and **R^y** are each separately selected from hydrogen, C₁₋₆alkylOC(=O)–, C₁₋₆alkyl, C₁₋₆alkylC(=O)–, aryl, arylalkyl, cycloalkyl, and heterocycl;

each **C(R^{2a})₂** is separately selected, wherein each **R^{2a}** is separately selected from the group consisting of hydrogen, C₁₋₆alkyl optionally substituted with up to 9 halo, aryl(CH₂)_n–, and heteroaryl(CH₂)_n–, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9

halo, or optionally **C(R^{2a})₂** is  ;

each **R^{3a}** is separately selected from the group consisting of hydrogen, and optionally substituted C₁₋₆alkyl;

each **R^{3b}** is separately selected from the group consisting of optionally substituted C₁₋₆alkyl, heteroaryl, –(CH₂)_nC(=O)NR^{4a}R^{4b}, –(CH₂)_nC(=O)OR^{5a}, and –(CH₂)_nC(=O)R^{6a} said heteroaryl optionally substituted with cyano, halo, nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each **R^{4a}R^{4b}N** is separately selected, wherein **R^{4a}** and **R^{4b}** are each separately selected from the group consisting of hydrogen, optionally substituted C₁₋₆alkyl, and aryl(CH₂)_n–;

each **R^{5a}** is separately selected from the group consisting of optionally substituted C₁₋₆alkyl, and aryl(CH₂)_n–;

each **R^{6a}** is separately selected from the group consisting of optionally substituted C₁₋₆alkyl, and aryl(CH₂)_n–;

each A^1 is separately selected from the group consisting of C_{2-6} alkenyl, C_{1-6} alkyl, and $-(CH_2)_n-O-(CH_2)_m-$, each optionally substituted with one or more R^2 ;

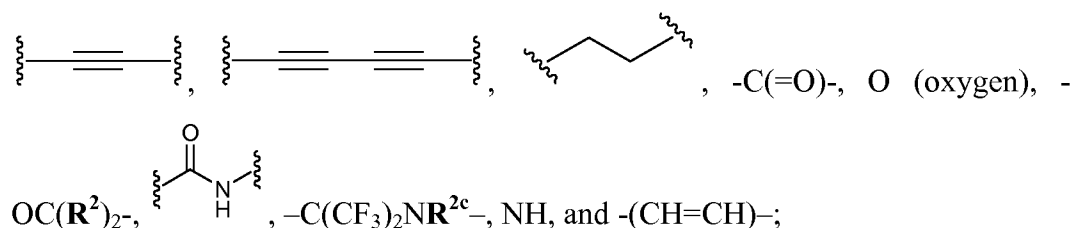
each R^2 is separately selected, wherein R^2 is selected from the group consisting of hydrogen, halo, hydroxy, C_{1-6} alkoxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, alkoxyalkyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclalkyl, $(R^e R^f N)$ alkyl, $R^a R^b N-$, said C_{1-6} alkyl optionally substituted with one or more halo, $-OR^{2b}$, $-C(=O)OR^{2b}$, $-C(=O)NHR^{2b}$, $-NHC(=NH)NHR^{2b}$, $-NHR^{2b}$, SR^{2b} , imidazolyl, indolyl, $-SCH_3$, phenyl, and 4-hydroxyphenyl, said C_{1-6} alkoxy, alkoxyalkyl, aryl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclalkyl, and alkyl in $(R^e R^f N)$ alkyl each optionally substituted with one or more R^4 , or optionally two vicinal R^2 and the carbons to which they are attached are together a fused three- to six-membered carbocyclic ring optionally substituted with up to two C_{1-6} alkyl groups;

R^{2b} is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclalkyl;

each R^{2c} is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclalkyl, said alkyl optionally substituted with $R^e R^f N-$, alkoxy, or C_{1-6} alkylS-;

each $R^a R^b N$ is separately selected, wherein R^a and R^b are each separately selected from the group consisting of hydrogen, C_{2-6} alkenyl, and C_{1-6} alkyl;

L^4 is selected from the group consisting of $-(J^2)_s-(L^5)_s-(J^2)_s-(L^5)_s-J^2-$,

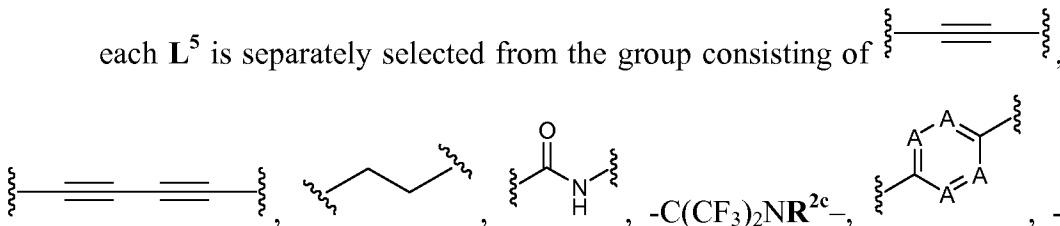


J^2 is aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, or polycyclic hydrocarbon, each optionally substituted with one or more R^{15} ;

each R^{14} is separately selected from the group consisting of hydroxy, C_{1-6} alkoxy optionally substituted with up to 9 fluoro, C_{1-6} alkylOC $_{1-6}$ alkyl,

C₁₋₆alkylOC(=O)–, arylalkylOC(=O)–, –COOH, halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

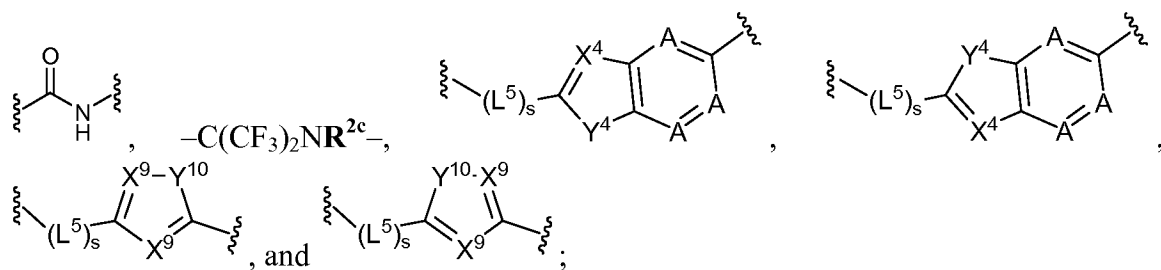
each **R**¹⁵ is separately selected from the group consisting of halo, hydroxy, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC(=O)–, arylalkylOC(=O)–, –COOH, **R**⁹, **R**^x**R**^yN, **R**^x**R**^yNC(=O), **R**^x**R**^yNC₁₋₆alkyl, heteroaryl, aryl, C₁₋₆alkyl optionally substituted with up to 9 halo, C₁₋₆alkyl substituted with up to 5 hydroxy, C₁₋₆alkoxy optionally substituted with up to 9 halo, C₁₋₆haloalkyl, **R**^a**R**^bN–, (**R**^a**R**^bN)alkyl, (**R**^a**R**^bN)C(=O)–, C₁₋₆alkyl substituted with up to 5 hydroxy, said substituent aryl and heteroaryl are each optionally substituted with one or more **R**¹⁴, or optionally two vicinal **R**¹⁵ and the carbons to which they are attached are together a fused three- to six-membered carbocyclic ring optionally substituted with up to two C₁₋₆alkyl groups, or optionally two geminal **R**¹⁵ and the carbon to which they are attached are together a three- to six-membered carbocyclic ring optionally substituted with up to two C₁₋₆alkyl groups, or optionally two geminal **R**¹⁵ are together oxo;

each **L**⁵ is separately selected from the group consisting of ,
C(**R**²)₂, –C(**R**²)₂O–, –C(=O)–, O (oxygen), NH, and –(CH=CH)–;

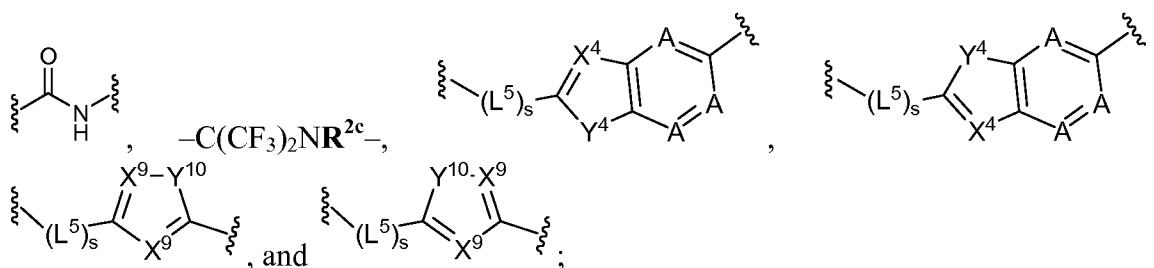
each **A** is separately selected from the group consisting of **CR**³ and N (nitrogen);

each **R**³ is separately selected from the group consisting of hydrogen, C₁₋₆alkoxy, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC(=O)–, arylalkylOC(=O)–, –COOH, halo, hydroxy, **R**^a**R**^bN–, (**R**^a**R**^bN)alkyl, (**R**^a**R**^bN)C(=O)–, C₁₋₆alkyl optionally substituted with up to 9 halo and up to 5 hydroxy;

L⁶ is selected from the group consisting of



L⁷ is selected from the group consisting of



each **X**⁴ is separately selected from the group consisting of **CR**⁴ and N (nitrogen);

each **Y**⁴ is separately selected from the group consisting of **C(R**⁴**)**₂, **NR**⁴, O (oxygen), and S (sulfur);

each **X**⁹ is separately selected from the group consisting of CH and N (nitrogen);

each **Y**¹⁰ is separately selected from the group consisting of **−CH**₂**−** and **−NH−**;

each **m** separately is 1 or 2;

each **n** separately is 0, 1 or 2;

each **p** separately is 1, 2, 3 or 4;

each **q** separately is 1, 2, 3, 4 or 5;

each **r** separately is 0, 1, 2, 3, or 4;

each **s** separately is 0 or 1;

each **R**⁴ is separately selected from the group consisting of H (hydrogen), C₁₋₆alkoxy, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC(=O)−, arylalkylOC(=O)−, **−COOH**, halo, C₁₋₆haloalkyl, hydroxy, **R**^a**R**^b**N**−, (**R**^a**R**^b**N**)alkyl, (**R**^a**R**^b**N**)C(=O)−, C₁₋₆alkyl optionally substituted with up to 9 halo and up to 5 hydroxy, or optionally two geminal **R**⁴ are together oxo;

R⁹ is selected from the group consisting of hydrogen and **−C(=O)R**^{9a};

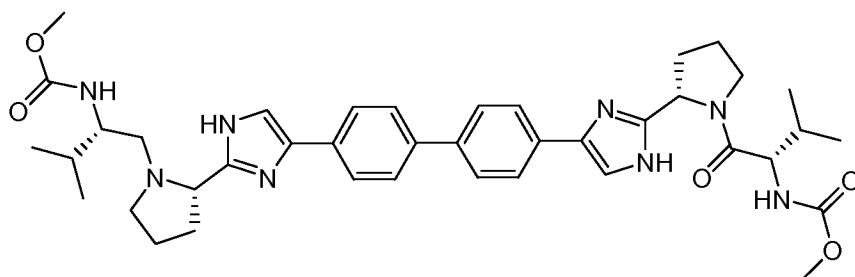
R^{9a} is selected from the group consisting of **−NR**^{9b}**R**^{9c}, **−OR**^{9d}, C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl;

R^{9b} is selected from the group consisting of hydrogen, C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl;

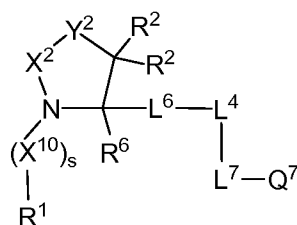
R^{9c} is selected from the group consisting of C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl; and

R^{9d} is selected from the group consisting of C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl.

11. The compound of Claim 10, having the structure:



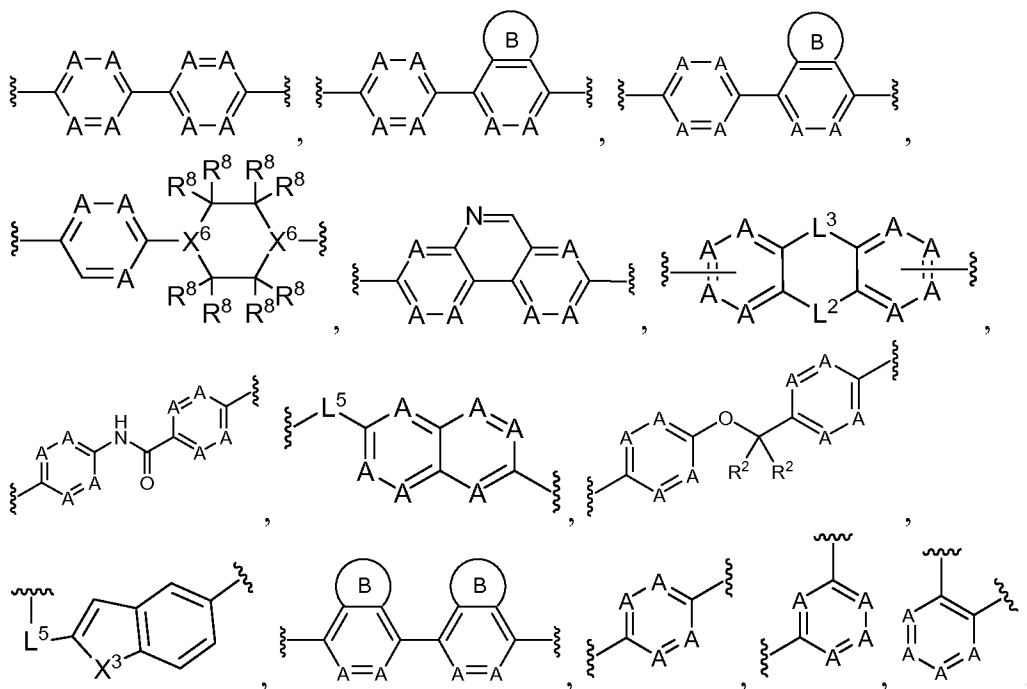
12. The compound of Claim 10, wherein R^6 is methyl.
13. The compound of Claim 10 having the structure of Formula **XVIa**:

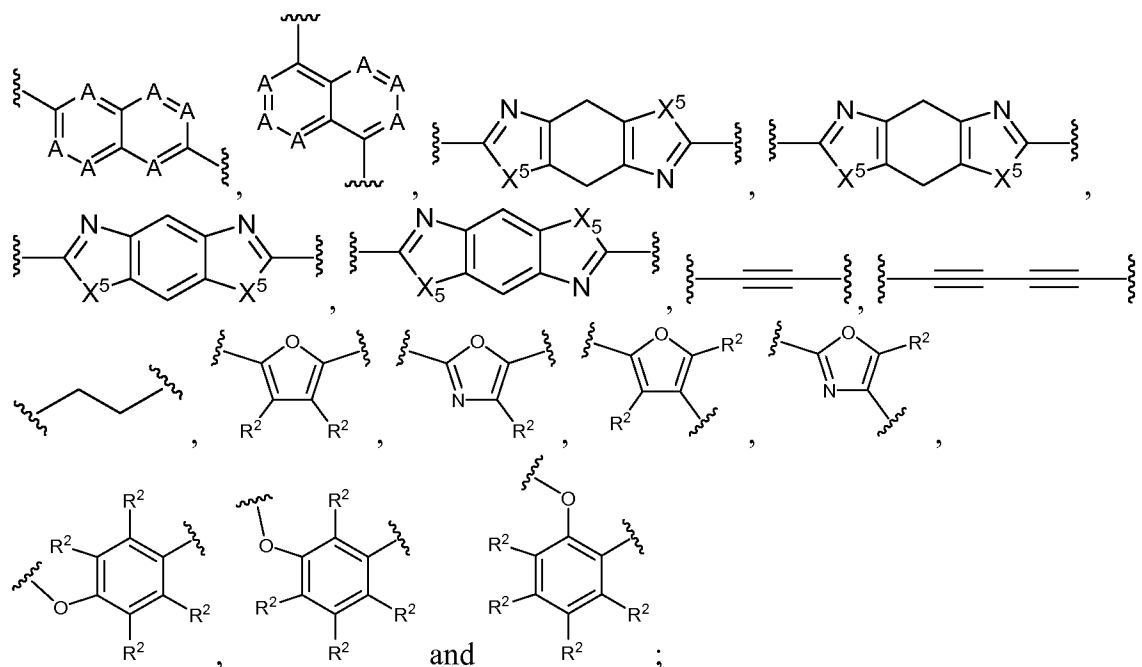


XVIa

or a pharmaceutically acceptable salt thereof, wherein R^6 is C_{1-6} alkyl optionally substituted with up to 9 halo.

14. The compound of Claim 10, wherein L^4 is selected from the group consisting of





$\mathbf{L}^2$ is selected from the group consisting of $-\text{C}(=\text{O})-$, $-(\text{CH}_2\text{CH}_2)-$, $-(\text{CH}_2\text{O})-$, $-(\text{CH}_2\text{S})-$, $-(\text{CH}=\text{CH})-$, $-(\text{CH}=\text{N})-$, $-\text{NH}-$, O (oxygen), S (sulfur), and $-\text{CH}_2-$;

L^3 is selected from the group consisting of , $-(NR^9)-$, O (oxygen), S (sulfur), and $-CH_2-$;

L^5 is selected from the group consisting of , , O (oxygen), NH, and $-(CH=CH)-$;

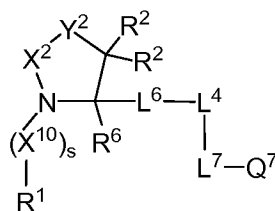
each $\mathbf{X}^3$ is separately selected from the group consisting of NH, O (oxygen), and S (sulfur);

each $\mathbf{X}^5$ is separately selected from the group consisting of $-\text{NH}-$, O (oxygen), S (sulfur), and $-\text{CH}_2-$;

each $\mathbf{X}^6$ is separately selected from the group consisting of N (nitrogen), and $\mathbf{CR}^8$; and

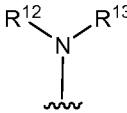
each **B** is separately selected, wherein **B** is a fused optionally substituted saturated or unsaturated three- to seven-membered carbocyclic ring or a fused optionally substituted saturated or unsaturated three- to seven-membered heterocyclic ring, each optionally substituted with one or more **R**⁴.

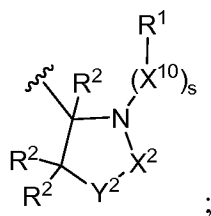
15. A compound having the structure of Formula XVII:

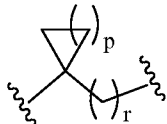


XVII

or a pharmaceutically acceptable salt thereof,
wherein:

Q^7 is selected from the group consisting of , and

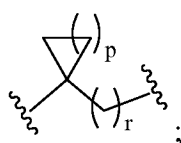


each X^2 is $(C(R^2)_2)_q$, , or X^2 is null;

each Y^2 is selected from O (oxygen), S (sulfur), S(O), SO₂, NR², and C(R²)₂ with the proviso that when X^2 is null Y^2 is C(R²)₂;

each X^{10} is $(C(R^2)_2)_q$;

each X^{11} is separately selected from the group consisting of $(C(R^2)_2)_q$, and



each Y^{11} is separately selected from the group consisting of -O(C(R²)₂)_n-, -S(C(R²)₂)_n-, -S(O)(C(R²)₂)_n-, -SO₂(C(R²)₂)_n-, -NR²(C(R²)₂)_n-, and (C(R²)₂)_q;

each $R^{12}R^{13}N$ is separately selected, wherein R^{12} and R^{13} are each separately selected from hydrogen, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-$, $[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-(Y^{14})_s-R^{80}$, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl,

heterocyclalkyl, heterocyclalkylC(=O)-, heterocyclC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, ($R^e R^f N$)alkyl, ($R^e R^f N$)alkylC(=O)-, and ($R^e R^f N$)C(=O)-,

said alkoxyalkyl, alkoxyC(=O)-, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)-, C_{3-7} cycloalkylC(=O)-, C_{1-6} alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocycl, heteroaryl, heteroarylalkyl, heterocyclalkyl, heterocyclalkylC(=O)-, heterocyclC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, and alkyl in ($R^e R^f N$)alkyl and ($R^e R^f N$)alkylC(=O)- are each optionally substituted with one or more R^{1ab} ;

or $R^{12} R^{13} N$ is a heterocycl linked through a ring nitrogen atom optionally substituted with one or more of oxo, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-$, $[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-$, $Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxyC(=O)-, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)-, C_{3-7} cycloalkylC(=O)-, C_{1-6} alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocycl, heteroaryl, heteroarylalkyl, heterocyclalkyl, heterocyclalkylC(=O)-, heterocyclC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, ($R^e R^f N$)alkyl, ($R^e R^f N$)alkylC(=O)-, and ($R^e R^f N$)C(=O)-,

said alkoxyalkyl, alkoxyC(=O)-, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkylC(=O)-, C_{3-7} cycloalkylC(=O)-, C_{1-6} alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocycl, heteroaryl, heteroarylalkyl, heterocyclalkyl, heterocyclalkylC(=O)-, heterocyclC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, and alkyl in ($R^e R^f N$)alkyl and ($R^e R^f N$)alkylC(=O)- are each optionally substituted with one or more R^{1ab} ;

each R^{1ab} is separately selected from the group consisting of $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-$, $[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-$, $Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, $-C(R^{2a})_2NR^{3a}R^{3b}$, alkoxyalkyl, C_{1-6} alkylOC(=O)-, C_{1-6} alkylOC(=O) C_{1-6} alkyl,

C₁₋₆alkylC(=O)C₁₋₆alkyl, aryl, aryl(CH₂)_n-, aryl(CH₂)_nO-, aryl(CH=CH)_m-, arylalkylO-, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)(CH=CH)_m-, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclyl, heterocyclyl(CH=CH)_m-, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, **R^cR^dN**-, **R^cR^dN**(CH₂)_n-, (**R^cR^dN**)(CH=CH)_m-, (**R^cR^dN**)alkyl, (**R^cR^dN**)C(=O)-, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each **R⁸⁰** is separately selected from the group consisting of hydrogen, alkoxyalkyl, C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and (**R^eR^fN**)alkyl, said alkoxyalkyl, C₁₋₆alkyl, C₃₋₇cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and alkyl in (**R^eR^fN**)alkyl are each optionally substituted with one or more **R^{1ac}**;

each **R^{1ac}** is separately selected from the group consisting of -C(**R^{2a}**)₂N**R^{3a}R^{3b}**, alkoxyalkyl, C₁₋₆alkylOC(=O)-, C₁₋₆alkylOC(=O)C₁₋₆alkyl, C₁₋₆alkylC(=O)C₁₋₆alkyl, aryl, aryl(CH₂)_n-, aryl(CH₂)_nO-, aryl(CH=CH)_m-, arylalkylO-, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)(CH=CH)_m-, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclyl, heterocyclyl(CH=CH)_m-, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, **R^cR^dN**-, **R^cR^dN**(CH₂)_n-, (**R^cR^dN**)(CH=CH)_m-, (**R^cR^dN**)alkyl, (**R^cR^dN**)C(=O)-, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each **Y¹⁴** is separately selected from the group consisting of -C(=O)-, -S(=O)-, -C(=S)-, -S(=O)₂-, -C(=O)O-, -C(=O)N**R^{2c}**-, -S(=O)₂N**R^{2c}**-, -C(=O)N**R^{2c}**C(=O)-, and -C(CF₃)₂N**R^{2c}**-,

R¹ is selected from the group consisting of **R^{1aa}**, **R^{1a}C(=O)-** and **R^{1a}C(=S)-**;

each **R^{1a}** is separately selected from the group consisting of -C(**R^{2a}**)₂N**R^{3a}R^{3b}**, alkoxyalkyl, C₁₋₆alkylOC(=O)-, C₁₋₆alkylOC(=O)C₁₋₆alkyl,

C₁₋₆alkylC(=O)C₁₋₆alkyl, aryl, aryl(CH₂)_n-, aryl(CH₂)_nO-, aryl(CH=CH)_m-, arylalkylO-, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)(CH=CH)_m-, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclyl, heterocyclyl(CH=CH)_m-, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, **R^cR^dN**-, **R^cR^dN**(CH₂)_n-, (**R^cR^dN**)(CH=CH)_m-, (**R^cR^dN**)alkyl, (**R^cR^dN**)C(=O)-, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

R^{1aa} is selected from the group consisting of -C(**R^{2a}**)₂NR^{3a}**R^{3b}**, -[(Y¹⁴)(C(**R²**)₂)_r(NR²)_s(C(**R²**)₂)_r)-[Y¹⁴(C(**R²**)₂)_r(NR²)_s(C(**R²**)₂)_r)]_s-(Y¹⁴)_s-**R⁸⁰**, -[(Y¹⁴)(C(**R²**)₂)_r(NR²)_s(C(**R²**)₂)_r)-Y¹⁴(C(**R²**)₂)_rO(C(**R²**)₂)_r-(Y¹⁴)_s-**R⁸⁰**, alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, (**R^eR^fN**)alkyl, (**R^eR^fN**)alkylC(=O)-, and (**R^eR^fN**)C(=O)-,

said alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, and alkyl in (**R^eR^fN**)alkyl and (**R^eR^fN**)alkylC(=O)- are each optionally substituted with one or more **R^{1ab}**;

each **R¹⁰** is **R^cR^dN**-;

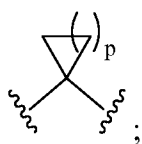
each **R¹¹** is separately selected from the group consisting of H (hydrogen), alkoxyalkyl, C₁₋₆alkylOC(=O)C₁₋₆alkyl, C₁₋₆alkylC(=O)C₁₋₆alkyl, aryl(CH₂)_n-, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclylalkyl, heterocyclylOalkyl, hydroxyalkyl, **R^cR^dN**(CH₂)_n-, (**R^cR^dN**)alkyl, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each $\mathbf{R}^c\mathbf{R}^d\mathbf{N}$ is separately selected, wherein $\mathbf{R}^c$ and $\mathbf{R}^d$ are each separately selected from hydrogen, alkoxyC(=O)–, C_{1-6} alkyl, C_{1-6} alkylC(=O)–, C_{1-6} alkylsulfonyl, arylalkylOC(=O)–, arylalkyl, arylalkylC(=O)–, arylC(=O)–, arylsulfonyl, heterocyclalkyl, heterocyclalkylC(=O)–, heterocyclC(=O)–, $(\mathbf{R}^e\mathbf{R}^f\mathbf{N})$ alkyl, $(\mathbf{R}^e\mathbf{R}^f\mathbf{N})$ alkylC(=O)–, and $(\mathbf{R}^e\mathbf{R}^f\mathbf{N})\text{C}(=\text{O})$ –, wherein the alkyl part of arylalkyl, arylalkylC(=O)–, heterocyclalkyl, and heterocyclalkylC(=O)– are each optionally substituted with one $\mathbf{R}^e\mathbf{R}^f\mathbf{N}$ – group; and wherein the aryl part of arylalkyl, arylalkylC(=O)–, arylC(=O)–, and arylsulfonyl, and the heterocycl part of heterocyclalkyl, heterocyclalkylC(=O)–, and heterocyclC(=O)– are each optionally substituted with up to three substituents each independently selected from the group consisting of cyano, halo, nitro, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9 halo;

each $\mathbf{R}^e\mathbf{R}^f\mathbf{N}$ is separately selected, wherein $\mathbf{R}^e$ and $\mathbf{R}^f$ are each separately selected from hydrogen, C_{1-6} alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycl, heterocyclalkyl, $(\mathbf{R}^x\mathbf{R}^y\mathbf{N})$ alkyl, and $(\mathbf{R}^x\mathbf{R}^y\mathbf{N})\text{C}(=\text{O})$ –;

each $\mathbf{R}^x\mathbf{R}^y\mathbf{N}$ is separately selected, wherein $\mathbf{R}^x$ and $\mathbf{R}^y$ are each separately selected from hydrogen, C_{1-6} alkylOC(=O)–, C_{1-6} alkyl, C_{1-6} alkylC(=O)–, aryl, arylalkyl, cycloalkyl, and heterocycl;

each $\text{C}(\mathbf{R}^{2a})_2$ is separately selected, wherein each $\mathbf{R}^{2a}$ is separately selected from the group consisting of hydrogen, C_{1-6} alkyl optionally substituted with up to 9 halo, aryl $(\text{CH}_2)_n$ –, and heteroaryl $(\text{CH}_2)_n$ –, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9

halo, or optionally $\text{C}(\mathbf{R}^{2a})_2$ is ;

each $\mathbf{R}^{3a}$ is separately selected from the group consisting of hydrogen, and optionally substituted C_{1-6} alkyl;

each $\mathbf{R}^{3b}$ is separately selected from the group consisting of optionally substituted C_{1-6} alkyl, heteroaryl, $-(\text{CH}_2)_n\text{C}(=\text{O})\text{NR}^{4a}\mathbf{R}^{4b}$, $-(\text{CH}_2)_n\text{C}(=\text{O})\text{OR}^{5a}$, and $-(\text{CH}_2)_n\text{C}(=\text{O})\mathbf{R}^{6a}$ said heteroaryl optionally substituted with cyano, halo,

nitro, hydroxyl, C₁₋₆alkoxy optionally substituted with up to 9 halo, and C₁₋₆alkyl optionally substituted with up to 9 halo;

each **R**^{4a}**R**^{4b}N is separately selected, wherein **R**^{4a} and **R**^{4b} are each separately selected from the group consisting of hydrogen, optionally substituted C₁₋₆alkyl, and aryl(CH₂)_n-;

each **R**^{5a} is separately selected from the group consisting of optionally substituted C₁₋₆alkyl, and aryl(CH₂)_n-;

each **R**^{6a} is separately selected from the group consisting of optionally substituted C₁₋₆alkyl, and aryl(CH₂)_n-;

each **A**¹ is separately selected from the group consisting of C₂₋₆alkenyl, C₁₋₆alkyl, and -(CH₂)_n-O-(CH₂)_m-, each optionally substituted with one or more **R**²;

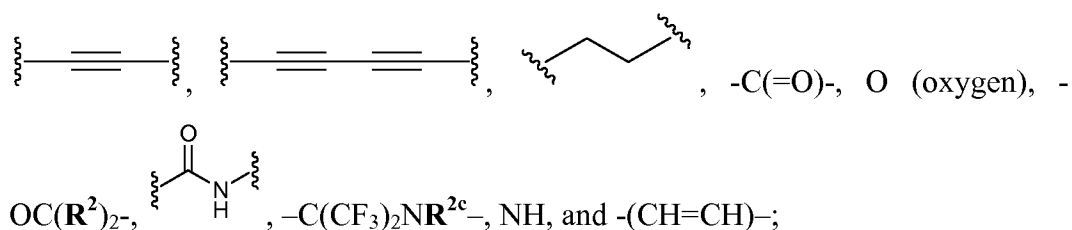
each **R**² is separately selected, wherein **R**² is selected from the group consisting of protium, halo, hydroxy, C₁₋₆alkoxy, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, alkoxyalkyl, C₃₋₇cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, (**R**^e**R**^fN)alkyl, **R**^a**R**^bN-, said C₁₋₆alkyl optionally substituted with one or more halo, -OR^{2b}, -C(=O)OR^{2b}, -C(=O)NHR^{2b}, -NHC(=NH)NHR^{2b}, -NHR^{2b}, SR^{2b}, imidazolyl, indolyl, -SCH₃, phenyl, and 4-hydroxyphenyl, said C₁₋₆alkoxy, alkoxyalkyl, aryl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and alkyl in (**R**^e**R**^fN)alkyl each optionally substituted with one or more **R**⁴, or optionally two vicinal **R**² and the carbons to which they are attached are together a fused three- to six-membered carbocyclic ring optionally substituted with up to two C₁₋₆alkyl groups;

R^{2b} is selected from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

each **R**^{2c} is selected from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, said alkyl optionally substituted with **R**^e**R**^fN-, alkoxy, or C₁₋₆alkylS-;

each **R**^a**R**^bN is separately selected, wherein **R**^a and **R**^b are each separately selected from the group consisting of hydrogen, C₂₋₆alkenyl, and C₁₋₆alkyl;

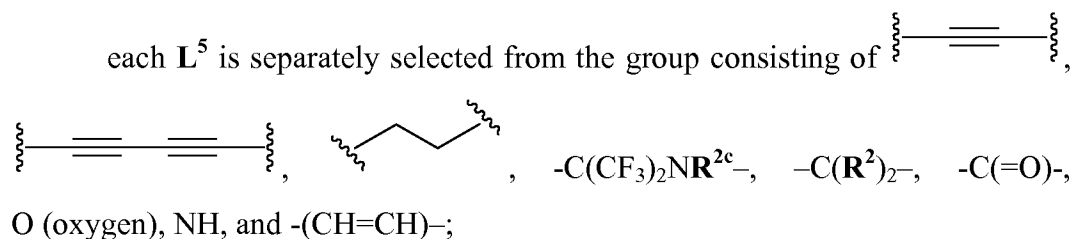
L^4 is selected from the group consisting of $-J^2-(L^5)_s-(J^2)_s-(L^5)_s-J^2-$, $-J^2-$,



each J^2 is phenyl optionally substituted with one or more R^{15} ;

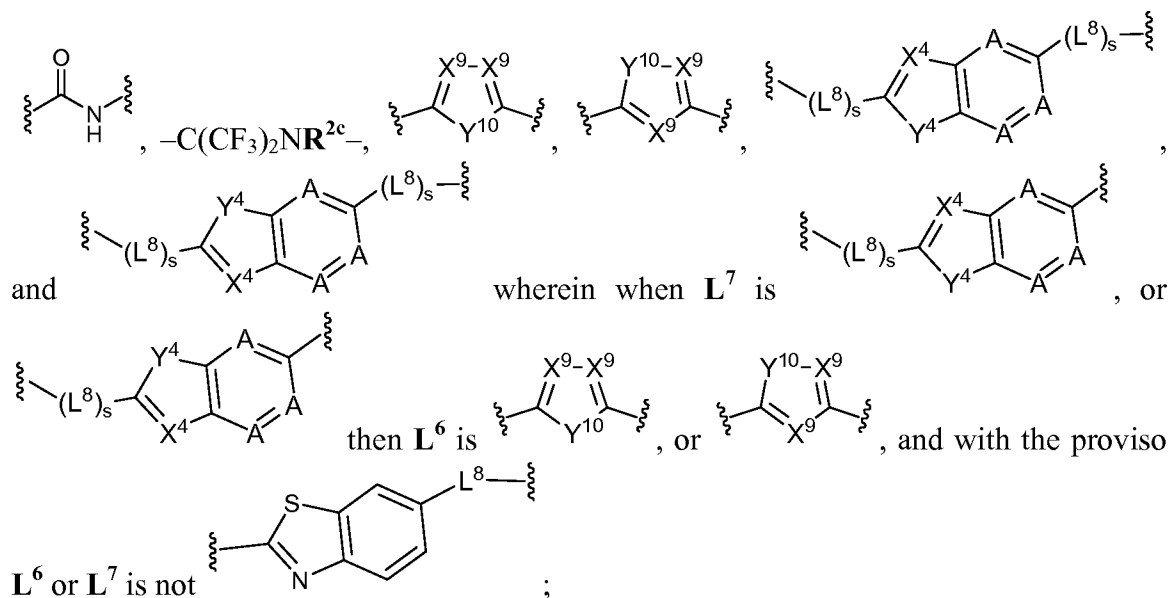
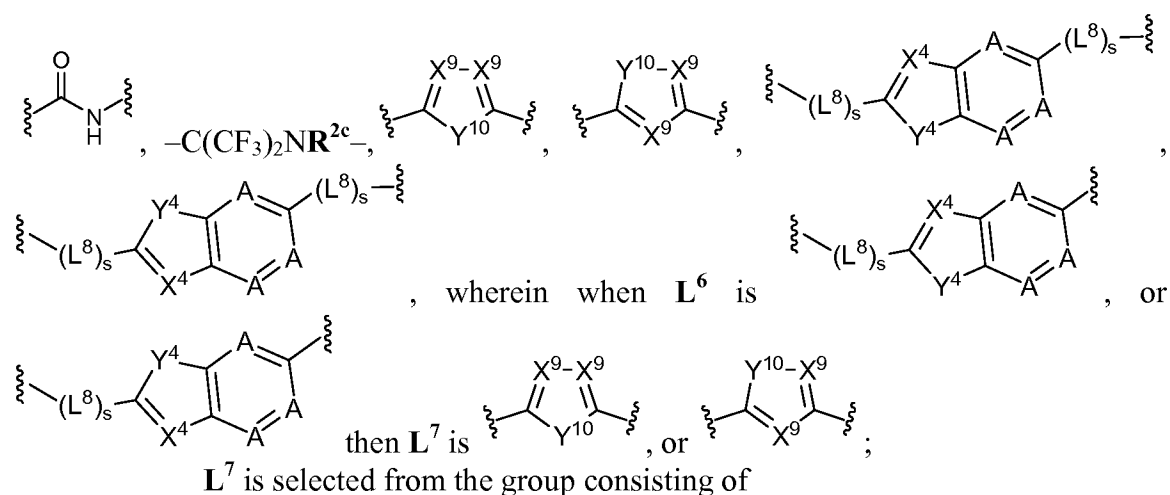
each R^{14} is separately selected from the group consisting of hydroxy, C_{1-6} alkoxy optionally substituted with up to 9 fluoro, $C_{1-6}alkylOC_{1-6}alkyl$, $C_{1-6}alkylOC(=O)-$, arylalkyl $OC(=O)-$, $-COOH$, halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo;

each R^{15} is separately selected from the group consisting of halo, hydroxy, $C_{1-6}alkylOC_{1-6}alkyl$, $C_{1-6}alkylOC(=O)-$, arylalkyl $OC(=O)-$, $-COOH$, R^9 , R^xR^yN , $R^xR^yNC(=O)$, $R^xR^yNC_{1-6}alkyl$, heteroaryl, aryl, $C_{1-6}alkyl$ optionally substituted with up to 9 halo, $C_{1-6}alkyl$ substituted with up to 5 hydroxy, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, $C_{1-6}haloalkyl$, R^aR^bN- , $(R^aR^bN)alkyl$, $(R^aR^bN)C(=O)-$, $C_{1-6}alkyl$ substituted with up to 5 hydroxy, said substituent aryl and heteroaryl are each optionally substituted with one or more R^{14} , or optionally two vicinal R^{15} and the carbons to which they are attached are together a fused three- to six-membered carbocyclic ring optionally substituted with up to two $C_{1-6}alkyl$ groups, or optionally two geminal R^{15} and the carbon to which they are attached are together a three- to six-membered carbocyclic ring optionally substituted with up to two $C_{1-6}alkyl$ groups, or optionally two geminal R^{15} are together oxo;

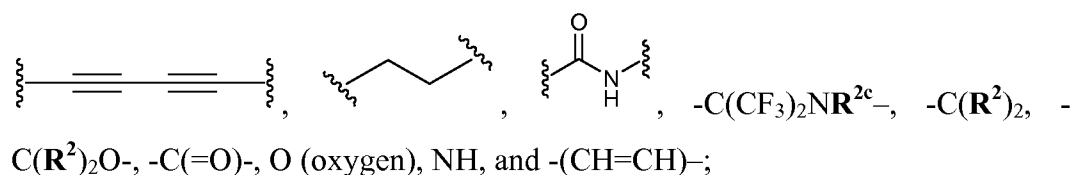


each A is separately selected from the group consisting of CR^3 and N (nitrogen);

L^6 is selected from the group consisting of



each L^8 is separately selected from the group consisting of $\text{---}\equiv\equiv\text{---}$,



each X^4 is separately selected from the group consisting of CR^4 and N (nitrogen);

each Y^4 is separately selected from the group consisting of $\text{C(R}^4)_2$, NR^4 , O (oxygen), and S (sulfur);

each X^9 is separately selected from the group consisting of CH and N (nitrogen);

each Y^{10} is separately selected from the group consisting of $\text{---CH}_2\text{---}$ and ---NH--- ;

each **m** separately is 1 or 2;

each **n** separately is 0, 1 or 2;

each **p** separately is 1, 2, 3 or 4;

each **q** separately is 1, 2, 3, 4 or 5;

each **r** separately is 0, 1, 2, 3, or 4;

each **s** separately is 0 or 1;

each **R**³ is separately selected from the group consisting of hydrogen, C₁₋₆alkoxy, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC(=O)–, arylalkylOC(=O)–, –COOH, halo, hydroxy, **R**^a**R**^bN–, (**R**^a**R**^bN)alkyl, (**R**^a**R**^bN)C(=O)–, C₁₋₆alkyl optionally substituted with up to 9 halo and up to 5 hydroxy;

each **R**⁴ is separately selected from the group consisting of H (hydrogen), C₁₋₆alkoxy, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC(=O)–, arylalkylOC(=O)–, –COOH, halo, C₁₋₆haloalkyl, hydroxy, **R**^a**R**^bN–, (**R**^a**R**^bN)alkyl, (**R**^a**R**^bN)C(=O)–, C₁₋₆alkyl optionally substituted with up to 9 halo and up to 5 hydroxy, or optionally two geminal **R**⁴ are together oxo;

R⁶ is C₁₋₆alkyl optionally substituted with up to 9 halo;

R⁹ is selected from the group consisting of hydrogen and –C(=O)**R**^{9a};

R^{9a} is selected from the group consisting of –NR^{9b}**R**^{9c}, –OR^{9d}, C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl;

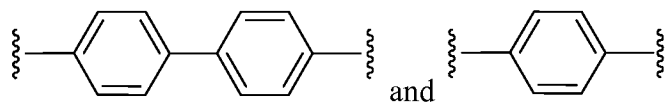
R^{9b} is selected from the group consisting of hydrogen, C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl;

R^{9c} is selected from the group consisting of C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl; and

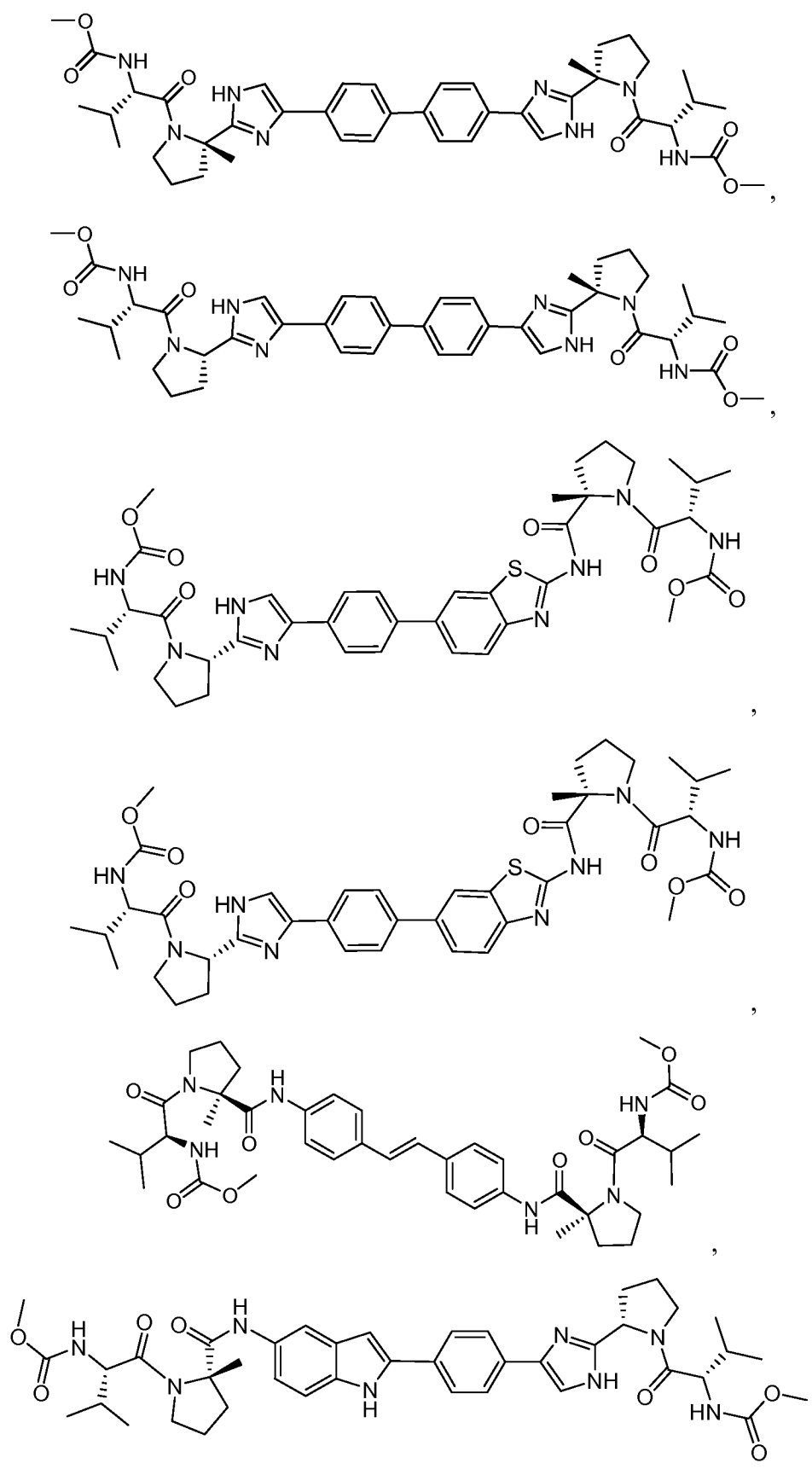
R^{9d} is selected from the group consisting of C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl.

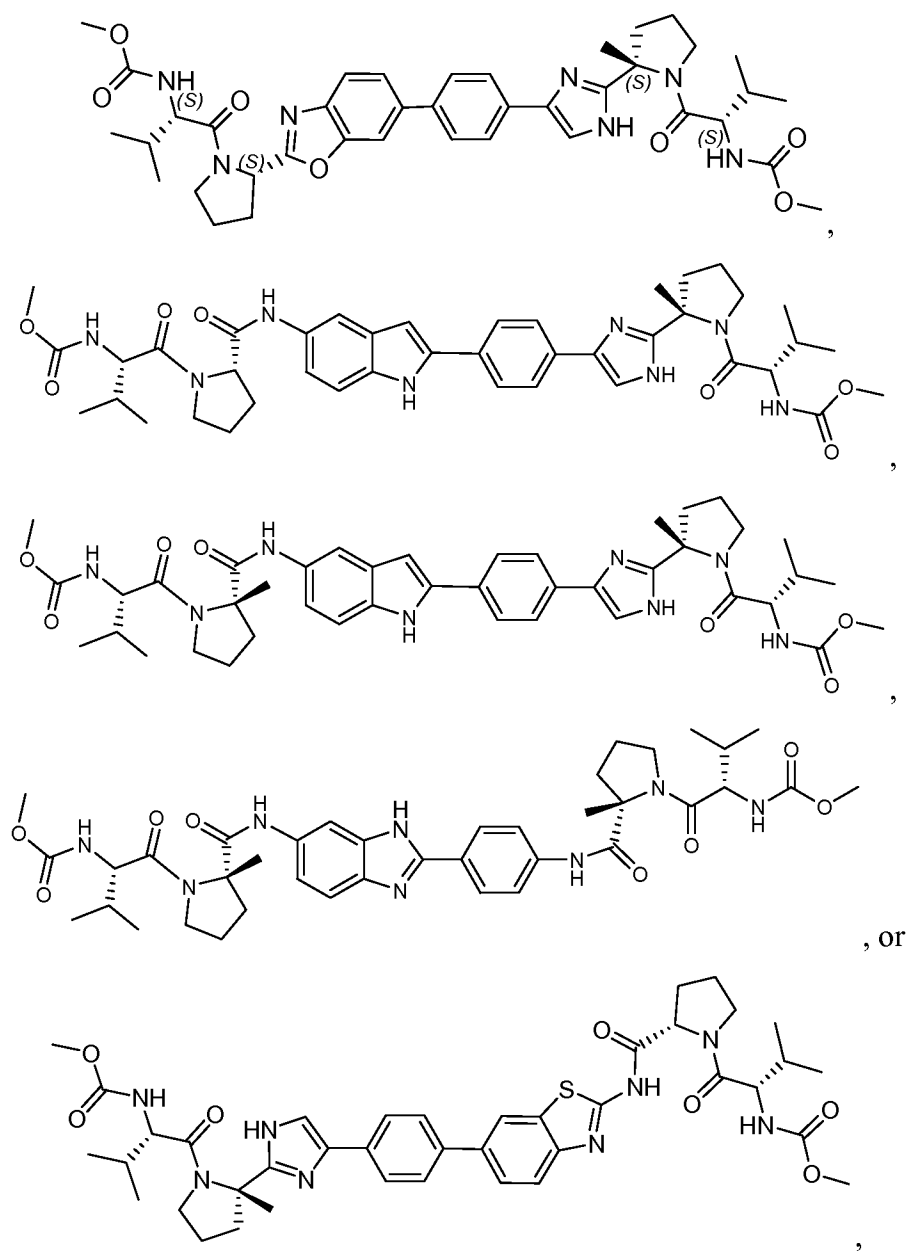
16. The compound of Claim 15, wherein

L⁴ is selected from the group consisting of



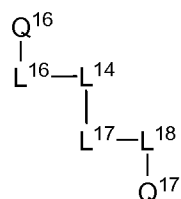
17. The compound of Claim 15, having the structure:





or a pharmaceutically acceptable salt thereof.

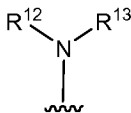
18. A compound having the structure of Formula **XVIII**:

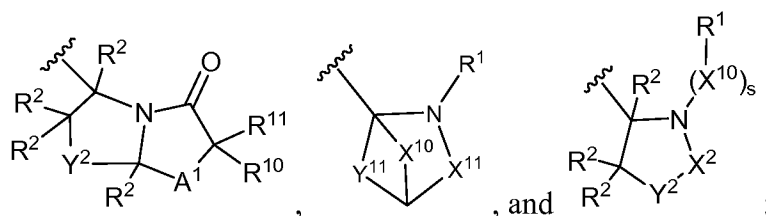


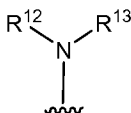
XVIII

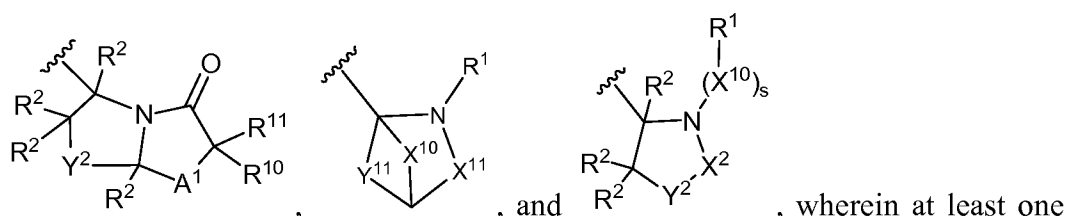
or a pharmaceutically acceptable salt thereof,

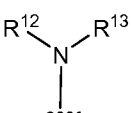
wherein:

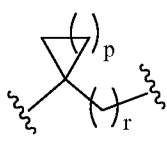
Q^{16} is selected from the group consisting of ,



Q^{17} is selected from the group consisting of ,



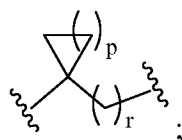
of Q^{16} and Q^{17} is not  ;

each X^2 is $(C(R^2)_2)_q$, , or X^2 is null;

each Y^2 is selected from O (oxygen), S (sulfur), S(O), SO_2 , NR^2 , and $C(R^2)_2$ with the proviso that when X^2 is null Y^2 is $C(R^2)_2$;

each X^{10} is $(C(R^2)_2)_q$;

each X^{11} is separately selected from the group consisting of $(C(R^2)_2)_q$, and



each Y^{11} is separately selected from the group consisting of $-O(C(R^2)_2)_n-$, $-S(C(R^2)_2)_n-$, $-S(O)(C(R^2)_2)_n-$, $-SO_2(C(R^2)_2)_n-$, $-NR^2(C(R^2)_2)_n-$, and $(C(R^2)_2)_q$;

each $R^{12}R^{13}N$ is separately selected, wherein R^{12} and R^{13} are each separately selected from hydrogen, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-$, $[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxyC(=O)-, C_{1-6} alkyl,

C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, (R^eR^fN)alkyl, (R^eR^fN)alkylC(=O)-, and (R^eR^fN)C(=O)-,

said alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, and alkyl in (R^eR^fN)alkyl and (R^eR^fN)alkylC(=O)- are each optionally substituted with one or more R^{1ab};

or R¹²R¹³N is a heterocyclyl linked through a ring nitrogen atom optionally substituted with one or more of oxo, -(Y¹⁴)(C(R²)₂)_r(NR²)_s(C(R²)₂)_r-[Y¹⁴(C(R²)₂)_r(NR²)_s(C(R²)₂)_r]_s-(Y¹⁴)_s-R⁸⁰, -(Y¹⁴)(C(R²)₂)_r(NR²)_s(C(R²)₂)_r]-Y¹⁴(C(R²)₂)_rO(C(R²)₂)_r-(Y¹⁴)_s-R⁸⁰, alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, (R^eR^fN)alkyl, (R^eR^fN)alkylC(=O)-, and (R^eR^fN)C(=O)-,

said alkoxyalkyl, alkoxyC(=O)-, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkylC(=O)-, C₃₋₇cycloalkylC(=O)-, C₁₋₆alkylsulfonyl, arylalkylOC(=O)-, aryl, arylalkyl, arylalkylC(=O)-, arylC(=O)-, arylsulfonyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkylC(=O)-, heterocyclylC(=O)-, heteroarylC(=O)-, heteroarylalkylC(=O)-, and alkyl in (R^eR^fN)alkyl and (R^eR^fN)alkylC(=O)- are each optionally substituted with one or more R^{1ab};

each R^{1ab} is separately selected from the group consisting of $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r-Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, $-C(R^{2a})_2NR^{3a}R^{3b}$, alkoxyalkyl, $C_{1-6}alkylOC(=O)-$, $C_{1-6}alkylOC(=O)C_{1-6}alkyl$, $C_{1-6}alkylC(=O)C_{1-6}alkyl$, aryl, $aryl(CH_2)_n-$, $aryl(CH_2)_nO-$, $aryl(CH=CH)_m-$, $arylalkylO-$, $arylalkyl$, $arylOalkyl$, cycloalkyl, $(cycloalkyl)(CH=CH)_m-$, $(cycloalkyl)alkyl$, $cycloalkylOalkyl$, heterocyclyl, $heterocyclyl(CH=CH)_m-$, $heterocyclylalkoxy$, $heterocyclylalkyl$, $heterocyclylOalkyl$, hydroxyalkyl, R^cR^dN- , $R^cR^dN(CH_2)_n-$, $(R^cR^dN)(CH=CH)_m-$, $(R^cR^dN)alkyl$, $(R^cR^dN)C(=O)-$, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo;

each R^{80} is separately selected from the group consisting of hydrogen, alkoxyalkyl, $C_{1-6}alkyl$, $C_{3-7}cycloalkyl$, aryl, $arylalkyl$, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and $(R^eR^fN)alkyl$, said alkoxyalkyl, $C_{1-6}alkyl$, $C_{3-7}cycloalkyl$, aryl, $arylalkyl$, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and alkyl in $(R^eR^fN)alkyl$ are each optionally substituted with one or more R^{1ac} ;

each R^{1ac} is separately selected from the group consisting of $-C(R^{2a})_2NR^{3a}R^{3b}$, alkoxyalkyl, $C_{1-6}alkylOC(=O)-$, $C_{1-6}alkylOC(=O)C_{1-6}alkyl$, $C_{1-6}alkylC(=O)C_{1-6}alkyl$, aryl, $aryl(CH_2)_n-$, $aryl(CH_2)_nO-$, $aryl(CH=CH)_m-$, $arylalkylO-$, $arylalkyl$, $arylOalkyl$, cycloalkyl, $(cycloalkyl)(CH=CH)_m-$, $(cycloalkyl)alkyl$, $cycloalkylOalkyl$, heterocyclyl, $heterocyclyl(CH=CH)_m-$, $heterocyclylalkoxy$, $heterocyclylalkyl$, $heterocyclylOalkyl$, hydroxyalkyl, R^cR^dN- , $R^cR^dN(CH_2)_n-$, $(R^cR^dN)(CH=CH)_m-$, $(R^cR^dN)alkyl$, $(R^cR^dN)C(=O)-$, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo;

each Y^{14} is separately selected from the group consisting of $-C(=O)-$, $-S(=O)-$, $-C(=S)-$, $-S(=O)_2-$, $-C(=O)O-$, $-C(=O)NR^{2c}-$, $-S(=O)_2NR^{2c}-$, $-C(=O)NR^{2c}C(=O)-$, and $-C(CF_3)_2NR^{2c}-$,

each R^1 is separately selected from the group consisting of R^{1aa} , $R^{1a}C(=O)-$ and $R^{1a}C(=S)-$;

each R^{1a} is separately selected from the group consisting of $-C(R^{2a})_2NR^{3a}R^{3b}$, alkoxyalkyl, $C_{1-6}alkylOC(=O)-$, $C_{1-6}alkylOC(=O)C_{1-6}alkyl$, $C_{1-6}alkylC(=O)C_{1-6}alkyl$, aryl, $aryl(CH_2)_n-$, $aryl(CH_2)_nO-$, $aryl(CH=CH)_m-$, $arylalkylO-$, $arylalkyl$, $arylOalkyl$, cycloalkyl, $(cycloalkyl)(CH=CH)_m-$, $(cycloalkyl)alkyl$, $cycloalkylOalkyl$, heterocyclyl, $heterocyclyl(CH=CH)_m-$, $heterocyclylalkoxy$, $heterocyclylalkyl$, $heterocyclylOalkyl$, hydroxyalkyl, R^cR^dN- , $R^cR^dN(CH_2)_n-$, $(R^cR^dN)(CH=CH)_m-$, $(R^cR^dN)alkyl$, $(R^cR^dN)C(=O)-$, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo;

each R^{1aa} is separately selected from the group consisting of $-C(R^{2a})_2NR^{3a}R^{3b}$, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-[Y^{14}(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]_s-(Y^{14})_s-R^{80}$, $-[(Y^{14})(C(R^2)_2)_r(NR^2)_s(C(R^2)_2)_r]-Y^{14}(C(R^2)_2)_rO(C(R^2)_2)_r-(Y^{14})_s-R^{80}$, alkoxyalkyl, alkoxy $C(=O)-$, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{3-7}cycloalkyl$, $C_{1-6}alkylC(=O)-$, $C_{3-7}cycloalkylC(=O)-$, $C_{1-6}alkylsulfonyl$, $arylalkylOC(=O)-$, aryl, $arylalkyl$, $arylalkylC(=O)-$, $arylC(=O)-$, $arylsulfonyl$, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkyl $C(=O)-$, heterocyclyl $C(=O)-$, heteroaryl $C(=O)-$, heteroarylalkyl $C(=O)-$, $(R^eR^fN)alkyl$, $(R^eR^fN)alkylC(=O)-$, and $(R^eR^fN)C(=O)-$,

said alkoxyalkyl, alkoxy $C(=O)-$, $C_{1-6}alkyl$, $C_{3-7}cycloalkyl$, $C_{1-6}alkylC(=O)-$, $C_{3-7}cycloalkylC(=O)-$, $C_{1-6}alkylsulfonyl$, $arylalkylOC(=O)-$, aryl, $arylalkyl$, $arylalkylC(=O)-$, $arylC(=O)-$, $arylsulfonyl$, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkyl $C(=O)-$, heterocyclyl $C(=O)-$, heteroaryl $C(=O)-$, heteroarylalkyl $C(=O)-$, and alkyl in $(R^eR^fN)alkyl$ and $(R^eR^fN)alkylC(=O)-$ are each optionally substituted with one or more R^{1ab} ;

each R^{10} is R^cR^dN- ;

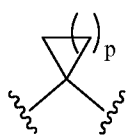
each R^{11} is separately selected from the group consisting of H (hydrogen), alkoxyalkyl, $C_{1-6}alkylOC(=O)C_{1-6}alkyl$, $C_{1-6}alkylC(=O)C_{1-6}alkyl$, $aryl(CH_2)_n-$, arylalkyl, arylOalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkylOalkyl, heterocyclalkyl, heterocyclOalkyl, hydroxyalkyl, $R^eR^dN(CH_2)_n-$, $(R^eR^dN)alkyl$, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo;

each R^eR^dN is separately selected, wherein R^e and R^d are each separately selected from hydrogen, $alkoxyC(=O)-$, $C_{1-6}alkyl$, $C_{1-6}alkylC(=O)-$, $C_{1-6}alkylsulfonyl$, $arylalkylOC(=O)-$, arylalkyl, $arylalkylC(=O)-$, $arylC(=O)-$, arylsulfonyl, heterocyclalkyl, $heterocyclalkylC(=O)-$, $heterocyclC(=O)-$, $(R^eR^fN)alkyl$, $(R^eR^fN)alkylC(=O)-$, and $(R^eR^fN)C(=O)-$, wherein the alkyl part of arylalkyl, $arylalkylC(=O)-$, heterocyclalkyl, and $heterocyclalkylC(=O)-$ are each optionally substituted with one R^eR^fN- group; and wherein the aryl part of arylalkyl, $arylalkylC(=O)-$, $arylC(=O)-$, and arylsulfonyl, and the heterocycl part of heterocyclalkyl, $heterocyclalkylC(=O)-$, and $heterocyclC(=O)-$ are each optionally substituted with up to three substituents each independently selected from the group consisting of cyano, halo, nitro, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9 halo;

each R^eR^fN is separately selected, wherein R^e and R^f are each separately selected from hydrogen, $C_{1-6}alkyl$, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycl, heterocyclalkyl, $(R^xR^yN)alkyl$, and $(R^xR^yN)C(=O)-$;

each R^xR^yN is separately selected, wherein R^x and R^y are each separately selected from hydrogen, $C_{1-6}alkylOC(=O)-$, $C_{1-6}alkyl$, $C_{1-6}alkylC(=O)-$, aryl, arylalkyl, cycloalkyl, and heterocycl;

each $C(R^{2a})_2$ is separately selected, wherein each R^{2a} is separately selected from the group consisting of hydrogen, $C_{1-6}alkyl$ optionally substituted with up to 9 halo, $aryl(CH_2)_n-$, and heteroaryl $(CH_2)_n-$, said aryl and heteroaryl each optionally substituted with cyano, halo, nitro, hydroxyl, $C_{1-6}alkoxy$ optionally substituted with up to 9 halo, and $C_{1-6}alkyl$ optionally substituted with up to 9

halo, or optionally $C(R^{2a})_2$ is ;

each R^{3a} is separately selected from the group consisting of hydrogen, and optionally substituted C_{1-6} alkyl;

each R^{3b} is separately selected from the group consisting of optionally substituted C_{1-6} alkyl, heteroaryl, $-(CH_2)_nC(=O)NR^{4a}R^{4b}$, $-(CH_2)_nC(=O)OR^{5a}$, and $-(CH_2)_nC(=O)R^{6a}$ said heteroaryl optionally substituted with cyano, halo, nitro, hydroxyl, C_{1-6} alkoxy optionally substituted with up to 9 halo, and C_{1-6} alkyl optionally substituted with up to 9 halo;

each $R^{4a}R^{4b}N$ is separately selected, wherein R^{4a} and R^{4b} are each separately selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, and aryl $(CH_2)_n-$;

each R^{5a} is separately selected from the group consisting of optionally substituted C_{1-6} alkyl, and aryl $(CH_2)_n-$;

each R^{6a} is separately selected from the group consisting of optionally substituted C_{1-6} alkyl, and aryl $(CH_2)_n-$;

each A^1 is separately selected from the group consisting of C_{2-6} alkenyl, C_{1-6} alkyl, and $-(CH_2)_n-O-(CH_2)_m-$, each optionally substituted with one or more R^2 ;

each R^2 is separately selected, wherein R^2 is selected from the group consisting of hydrogen, halo, hydroxy, C_{1-6} alkoxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, alkoxyalkyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, (R^eR^fN) alkyl, R^aR^bN- , said C_{1-6} alkyl optionally substituted with one or more halo, $-OR^{2b}$, $-C(=O)OR^{2b}$, $-C(=O)NHR^{2b}$, $-NHC(=NH)NHR^{2b}$, $-NHR^{2b}$, SR^{2b} , imidazolyl, indolyl, $-SCH_3$, phenyl, and 4-hydroxyphenyl, said C_{1-6} alkoxy, alkoxyalkyl, aryl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, arylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, and alkyl in (R^eR^fN) alkyl each optionally substituted with one or more R^4 , or optionally two vicinal R^2 and the carbons to which they are attached are together a fused three- to six-membered carbocyclic ring optionally substituted with up to two C_{1-6} alkyl groups;

R^{2b} is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

each R^{2c} is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, said alkyl optionally substituted with $R^e R^f N$ -, alkoxy, or C_{1-6} alkylS-;

each $R^a R^b N$ is separately selected, wherein R^a and R^b are each separately selected from the group consisting of hydrogen, C_{2-6} alkenyl, and C_{1-6} alkyl;

L^{14} is $-J^{11}-J^2-J^{12}-$;

J^2 is aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, or polycyclic hydrocarbon, each optionally substituted with one or more R^{15} ;

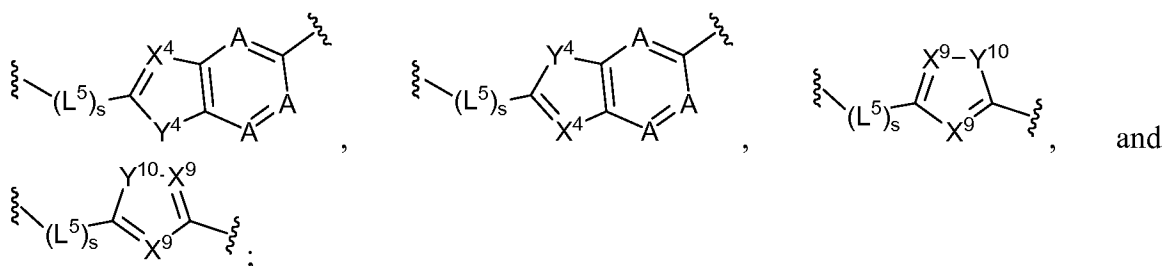
J^{11} is $C(R^4)_2$, NR^4 , O (oxygen), or S (sulfur);

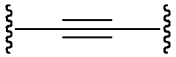
J^{12} is $-C(=O)-$, $S(O)$, SO_2 , or $-C(=NR^4)-$;

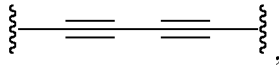
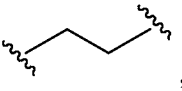
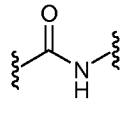
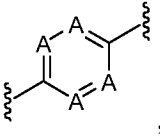
each R^{14} is separately selected from the group consisting of hydroxy, C_{1-6} alkoxy optionally substituted with up to 9 fluoro, C_{1-6} alkylOC $_{1-6}$ alkyl, C_{1-6} alkylOC(=O)-, arylalkylOC(=O)-, $-COOH$, halo, and C_{1-6} alkyl optionally substituted with up to 9 halo;

each R^{15} is separately selected from the group consisting of halo, hydroxy, C_{1-6} alkylOC $_{1-6}$ alkyl, C_{1-6} alkylOC(=O)-, arylalkylOC(=O)-, $-COOH$, R^9 , $R^x R^y N$, $R^x R^y NC(=O)$, $R^x R^y NC_{1-6}$ alkyl, heteroaryl, aryl, C_{1-6} alkyl optionally substituted with up to 9 halo, C_{1-6} alkyl substituted with up to 5 hydroxy, C_{1-6} alkoxy optionally substituted with up to 9 halo, C_{1-6} haloalkyl, $R^a R^b N$ -, $(R^a R^b N)$ alkyl, $(R^a R^b N)C(=O)-$, C_{1-6} alkyl substituted with up to 5 hydroxy, said substituent aryl and heteroaryl are each optionally substituted with one or more R^{14} , or optionally two vicinal R^{15} and the carbons to which they are attached are together a fused three- to six-membered carbocyclic ring optionally substituted with up to two C_{1-6} alkyl groups, or optionally two geminal R^{15} and the carbon to which they are attached are together a three- to six-membered carbocyclic ring optionally substituted with up to two C_{1-6} alkyl groups, or optionally two geminal R^{15} are together oxo;

L^{16} is selected from the group consisting of



each L^5 is separately selected from the group consisting of ,

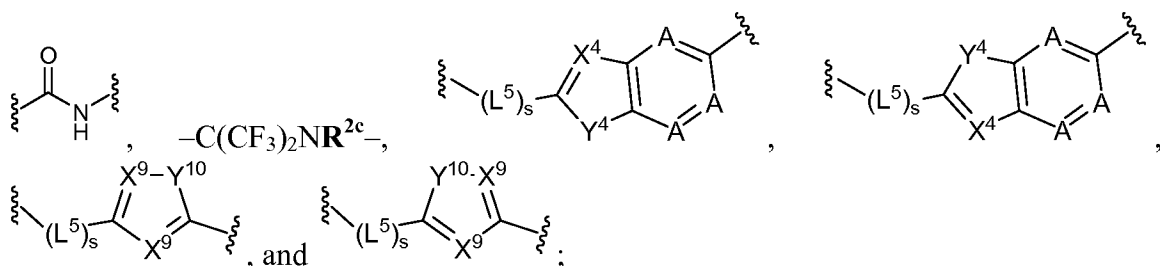
, , , $-C(CF_3)_2NR^{2c}-$, , $-C(R^2)_2$, $-C(R^2)_2O-$, $-C(=O)-$, O (oxygen), NH, and $-(CH=CH)-$;

each A is separately selected from the group consisting of CR^3 and N (nitrogen);

each R^3 is separately selected from the group consisting of hydrogen, C_{1-6} alkoxy, C_{1-6} alkylOC $_{1-6}$ alkyl, C_{1-6} alkylOC(=O)-, arylalkylOC(=O)-, $-COOH$, halo, hydroxy, R^aR^bN- , (R^aR^bN) alkyl, $(R^aR^bN)C(=O)-$, C_{1-6} alkyl optionally substituted with up to 9 halo and up to 5 hydroxy;

L^{17} is selected from the group consisting of aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, or polycyclic hydrocarbon, each optionally substituted with one or more R^{15} ;

L^{18} is selected from the group consisting of



each X^4 is separately selected from the group consisting of CR^4 and N (nitrogen);

each Y^4 is separately selected from the group consisting of $C(R^4)_2$, NR^4 , O (oxygen), and S (sulfur);

each X^9 is separately selected from the group consisting of CH and N (nitrogen);

each Y^{10} is separately selected from the group consisting of $-CH_2-$ and $-NH-$;

each **m** separately is 1 or 2;

each **n** separately is 0, 1 or 2;

each **p** separately is 1, 2, 3 or 4;

each **q** separately is 1, 2, 3, 4 or 5;

each **r** separately is 0, 1, 2, 3, or 4;

each **s** separately is 0 or 1;

each **R⁴** is separately selected from the group consisting of H (hydrogen), C₁₋₆alkoxy, C₁₋₆alkylOC₁₋₆alkyl, C₁₋₆alkylOC(=O)–, arylalkylOC(=O)–, –COOH, halo, C₁₋₆haloalkyl, hydroxy, **R^aR^bN–**, (**R^aR^bN**)alkyl, (**R^aR^bN**)C(=O)–, C₁₋₆alkyl optionally substituted with up to 9 halo and up to 5 hydroxy, or optionally two geminal **R⁴** are together oxo;

R⁹ is selected from the group consisting of hydrogen and –C(=O)**R^{9a}**;

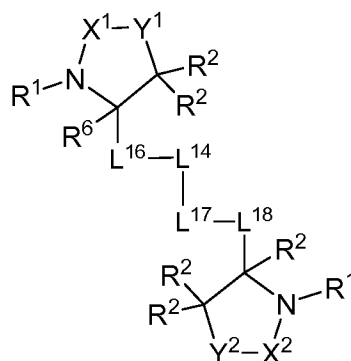
R^{9a} is selected from the group consisting of –NR^{9b}**R^{9c}**, –OR^{9d}, C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl;

R^{9b} is selected from the group consisting of hydrogen, C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl;

R^{9c} is selected from the group consisting of C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl; and

R^{9d} is selected from the group consisting of C₁₋₆alkyl optionally substituted with up to 9 halo, and optionally substituted aryl.

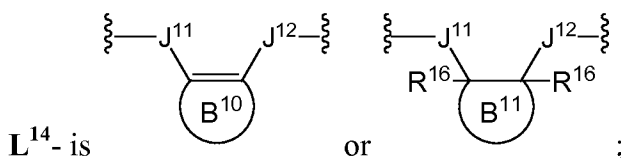
19. The compound of Claim 18 having the structure of Formula **XVIIIa**:



XVIIIa

or a pharmaceutically acceptable salt thereof,

wherein:

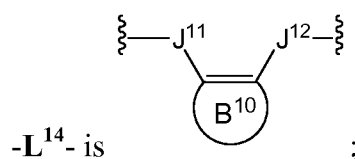


B^{10} is aryl, heteroaryl, or cycloalkenyl, each optionally substituted with one or more R^{15} ;

B^{11} is a heterocyclyl, cycloalkyl, or polycyclic hydrocarbon, each optionally substituted with one or more R^{15} ; and

each R^{16} is separately hydrogen or R^{15} .

20. The compound of Claim 19, wherein



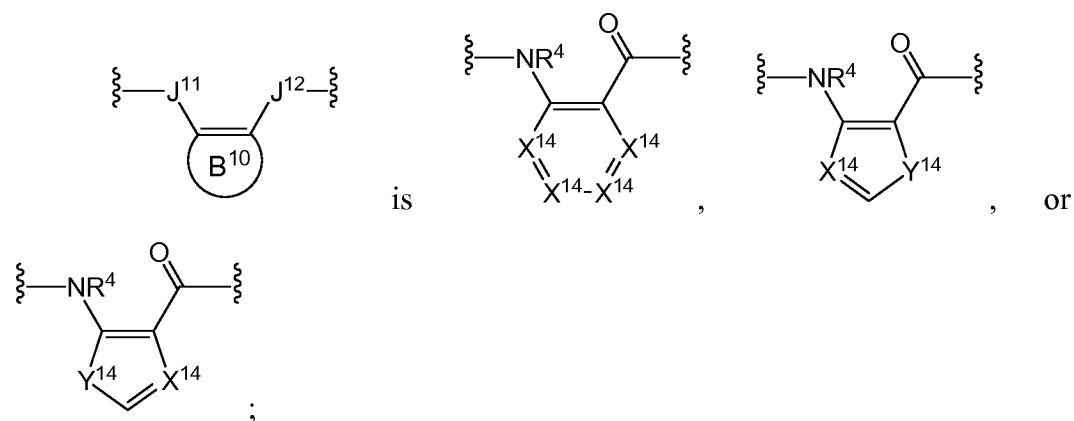
B^{10} is aryl, or heteroaryl;

J^{11} is NR^4 ; and

J^{12} is $-C(=O)-$.

21. The compound of Claim 20, wherein B^{10} is phenyl.

22. The compound of Claim 20, wherein

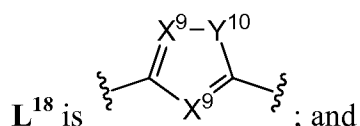
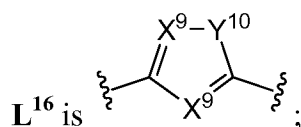


each X^{14} is separately selected from the group consisting of CR^{17} and N (nitrogen);

Y^{14} is selected from the group consisting of NR^{17} , O (oxygen), and S (sulfur);

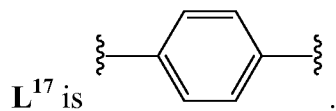
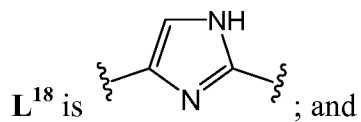
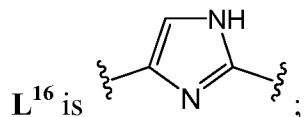
each R^{17} is separately hydrogen or R^{15} .

23. The compound of Claim 22, wherein



R^4 is separately hydrogen.

24. The compound of Claim 23, wherein



25. The compound of Claim 18 having the structure:

