

QUINOXALINE-CONTAINING COMPOUNDS AS HEPATITIS C VIRUS INHIBITORS

RELATED APPLICATIONS

5 This application claims the benefit of US provisional application number 60/987,958 filed on November 14, 2007 and US provisional application number 61/025,458 filed on February 1, 2008. The contents of the above applications are incorporated herein by reference.

TECHNICAL FIELD

10 The present invention relates to novel hepatitis C virus (HCV) protease inhibitor compounds having antiviral activity against HCV and useful in the treatment of HCV infections. More particularly, the invention relates to quinoxaline-containing compounds, compositions containing such compounds and methods for using the same, as well as processes for making such compounds.

BACKGROUND OF THE INVENTION

15 HCV is the principal cause of non-A, non-B hepatitis and is an increasingly severe public health problem both in the developed and developing world. It is estimated that the virus infects over 200 million people worldwide, surpassing the number of individuals infected with the human immunodeficiency virus (HIV) by nearly five fold. HCV infected
20 patients, due to the high percentage of individuals inflicted with chronic infections, are at an elevated risk of developing cirrhosis of the liver, subsequent hepatocellular carcinoma and terminal liver disease. HCV is the most prevalent cause of hepatocellular cancer and cause of patients requiring liver transplantations in the western world.

25 There are considerable barriers to the development of anti-HCV therapeutics, which include, but are not limited to, the persistence of the virus, the genetic diversity of the virus during replication in the host, the high incident rate of the virus developing drug-resistant mutants, and the lack of reproducible infectious culture systems and small-animal models for HCV replication and pathogenesis. In a majority of cases, given the mild course of the infection and the complex biology of the liver, careful consideration must be given to
30 antiviral drugs, which are likely to have significant side effects.

Only two approved therapies for HCV infection are currently available. The original treatment regimen generally involves a 3-12 month course of intravenous interferon- α (IFN- α), while a new approved second-generation treatment involves co-treatment with IFN- α and the general antiviral nucleoside mimics like ribavirin. Both of these treatments suffer from
5 interferon related side effects as well as low efficacy against HCV infections. There exists a need for the development of effective antiviral agents for treatment of HCV infection due to the poor tolerability and disappointing efficacy of existing therapies.

In a patient population where the majority of individuals are chronically infected and asymptomatic and the prognoses are unknown, an effective drug would desirably possess
10 significantly fewer side effects than the currently available treatments. The hepatitis C non-structural protein-3 (NS3) is a proteolytic enzyme required for processing of the viral polyprotein and consequently viral replication. Despite the huge number of viral variants associated with HCV infection, the active site of the NS3 protease remains highly conserved thus making its inhibition an attractive mode of intervention. Recent success in the treatment
15 of HIV with protease inhibitors supports the concept that the inhibition of NS3 is a key target in the battle against HCV.

HCV is a flaviridae type RNA virus. The HCV genome is enveloped and contains a single strand RNA molecule composed of circa 9600 base pairs. It encodes a polypeptide comprised of approximately 3010 amino acids.

The HCV polyprotein is processed by viral and host peptidase into 10 discreet peptides which serve a variety of functions. There are three structural proteins, C, E1 and E2. The P7 protein is of unknown function and is comprised of a highly variable sequence. There are six non-structural proteins. NS2 is a zinc-dependent metalloproteinase that functions in conjunction with a portion of the NS3 protein. NS3 incorporates two catalytic
25 functions (separate from its association with NS2): a serine protease at the N-terminal end, which requires NS4A as a cofactor, and an ATP-ase-dependent helicase function at the carboxyl terminus. NS4A is a tightly associated but non-covalent cofactor of the serine protease.

The NS3-NS4A protease is responsible for cleaving four sites on the viral
30 polyprotein. The NS3-NS4A cleavage is autocatalytic, occurring in cis. The remaining three hydrolyses, NS4A-NS4B, NS4B-NS5A and NS5A-NS5B all occur in trans. NS3 is a

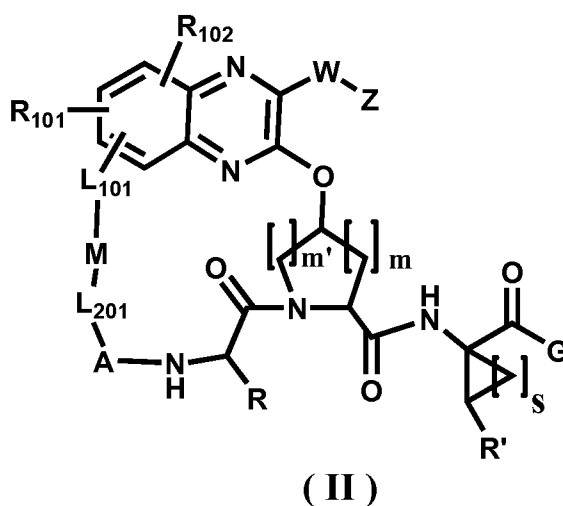
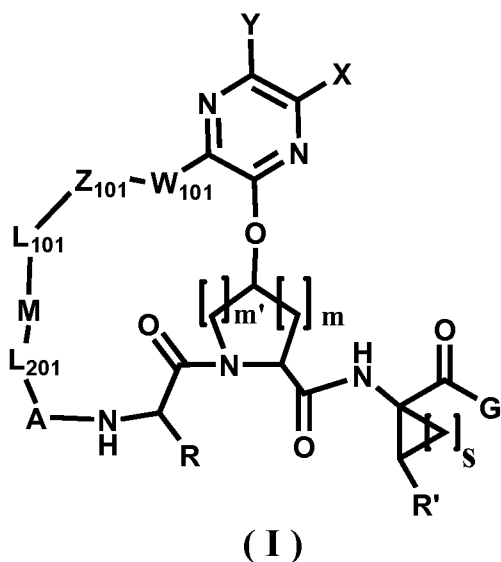
serine protease which is structurally classified as a chymotrypsin-like protease. While the NS serine protease possesses proteolytic activity by itself, the HCV protease enzyme is not an efficient enzyme in terms of catalyzing polyprotein cleavage. It has been shown that a central hydrophobic region of the NS4A protein is required for this enhancement. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficacy at all of the sites.

A general strategy for the development of antiviral agents is to inactivate virally encoded enzymes, including NS3, that are essential for the replication of the virus. Current efforts directed toward the discovery of NS3 protease inhibitors were reviewed by S. Tan, A. Pause, Y. Shi, N. Sonenberg, Hepatitis C Therapeutics: Current Status and Emerging Strategies, *Nature Rev. Drug Discov.* **1**, 867-881 (2002).

SUMMARY OF THE INVENTION

The present invention relates to quinoxaline-containing compounds and pharmaceutically acceptable salts, esters or prodrugs thereof, and methods of using the same to treat hepatitis C infection in a subject in need of such therapy. Compounds of the present invention interfere with the life cycle of the hepatitis C virus and are also useful as antiviral agents. The present invention further relates to pharmaceutical compositions comprising the aforementioned compounds, salts, esters or prodrugs for administration to a subject suffering from HCV infection. The present invention further features pharmaceutical compositions comprising a compound of the present invention (or a pharmaceutically acceptable salt, ester or prodrug thereof) and another anti-HCV agent, such as interferon (e.g., alpha-interferon, beta-interferon, consensus interferon, pegylated interferon, or albumin or other conjugated interferon), ribavirin, amantadine, another HCV protease inhibitor, or an HCV polymerase, helicase or internal ribosome entry site inhibitor. The invention also relates to methods of treating an HCV infection in a subject by administering to the subject a pharmaceutical composition of the present invention. The present invention further relates to pharmaceutical compositions comprising the compounds of the present invention, or pharmaceutically acceptable salts, esters, or prodrugs thereof, in combination with a pharmaceutically acceptable carrier or excipient.

In one embodiment of the present invention there are disclosed compounds represented by Formulas I or II, or pharmaceutically acceptable salts, esters, or prodrugs thereof:



5

Wherein

A is absent or selected from $-(C=O)-$, $-S(O)_2$, $-C=N-OR_1$ or $-C(=N-CN)$;

10

L_{201} is absent or selected from $-C_1-C_8$ alkylene, $-C_2-C_8$ alkenylene, or $-C_2-C_8$ alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkylene, substituted $-C_2-C_8$ alkenylene, or substituted $-C_2-C_8$ alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkylene, or substituted $-C_3-C_{12}$ cycloalkylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkenylene, or substituted $-C_3-C_{12}$ cycloalkenylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N;

15

M is absent or selected from O, S, SO, SO_2 or NR_1 ; wherein R_1 is selected at each occurrence from the group consisting of:

20

(i) hydrogen;

- (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (iii) heterocycloalkyl or substituted heterocycloalkyl;
- (iv) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;

L_{101} is absent or selected from $-C_1-C_8$ alkylene, $-C_2-C_8$ alkenylene, or $-C_2-C_8$ alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkylene, substituted $-C_2-C_8$ alkenylene, or substituted $-C_2-C_8$ alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkylene, or substituted $-C_3-C_{12}$ cycloalkylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkenylene, or substituted $-C_3-C_{12}$ cycloalkenylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N;

Z_{101} is absent or selected from aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

W_{101} is absent or selected from $-O-$, $-S-$, $-NR_1-$, $-C(O)-$ or $-C(O)NR_1-$;

X and Y taken together with the carbon atoms to which they are attached to form a carbocyclic moiety or a heterocyclic moiety. The carbocyclic or heterocyclic moiety can be selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, or substituted heterocyclic; or X and Y together can form a C_2-C_8 -alkylene group or a C_2-C_8 -heteroalkylene group.

R_{101} and R_{102} are independently selected from the group consisting of:

- (i) hydrogen, halogen, CN, CF₃, N₃, NO₂, OR₁, SR₁, SO₂R₂, -NHS(O)₂-R₂, -NH(SO₂)NR₃R₄, NR₃R₄, CO₂R₁, COR₁, CONR₁R₂, N(R₁)COR₂;
- (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (iii) heterocycloalkyl or substituted heterocycloalkyl;
- (iv) -C₁-C₈ alkyl, -C₂-C₈ alkenyl, or -C₂-C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted -C₁-C₈ alkyl, substituted -C₂-C₈ alkenyl, or substituted -C₂-C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C₃-C₁₂ cycloalkyl, or substituted -C₃-C₁₂ cycloalkyl; -C₃-C₁₂ cycloalkenyl, or substituted -C₃-C₁₂ cycloalkenyl;

R and R' are each independently selected from the group consisting of:

- (i) -C₁-C₈ alkyl, -C₂-C₈ alkenyl, or -C₂-C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted -C₁-C₈ alkyl, substituted -C₂-C₈ alkenyl, or substituted -C₂-C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C₃-C₁₂ cycloalkyl, or substituted -C₃-C₁₂ cycloalkyl; -C₄-C₁₂ alkylcycloalkyl, or substituted -C₄-C₁₂ alkylcycloalkyl; -C₃-C₁₂ cycloalkenyl, or substituted -C₃-C₁₂ cycloalkenyl; -C₄-C₁₂ alkylcycloalkenyl, or substituted -C₄-C₁₂ alkylcycloalkenyl;
- (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (iii) heterocycloalkyl or substituted heterocycloalkyl;
- (iv) hydrogen; deuterium;

or R' is C₁-C₈-alkyl substituted with one or more halogen atoms, preferably one or more fluorine, chlorine or bromine atoms. Preferably, R' is -CHQ₁Q₂, where Q₁ and Q₂ are independently selected from halogen; preferably F, Cl and Br;

G is selected from -OH, -NHS(O)₂-R₂, -NH(SO₂)NR₃R₄, and NR₃R₄;

R₂ is selected from:

- (i) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (ii) heterocycloalkyl; substituted heterocycloalkyl;

- (iii) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N, substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl; heterocyclic; substituted heterocyclic;

R_3 and R_4 are independently selected from:

- (i) hydrogen;
- (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (iii) heterocycloalkyl or substituted heterocycloalkyl;
- (iv) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl; heterocyclic, or substituted heterocyclic;

alternatively, R_3 and R_4 are taken together with the nitrogen they are attached to form a heterocyclic or substituted heterocyclic;

Z is selected from the groups consisting of:

- (i) hydrogen;
- (ii) CN;
- (iii) N_3 ;
- (iv) halogen;
- (v) $-NH-N=CHR_1$;
- (vi) aryl, substituted aryl;
- (vii) heteroaryl, substituted heteroaryl;
- (viii) $-C_3-C_{12}$ cycloalkyl, substituted $-C_3-C_{12}$ cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl;

- (ix) $-C_1-C_6$ alkyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;
- (x) $-C_2-C_6$ alkenyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;
- (xi) $-C_2-C_6$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

W is absent, or selected from alkylene, alkenylene, alkynylene, $-O-$, $-S-$, $-NR_1-$, $-C(O)NR_1-$, or $-C(O)-$;

m is 0, 1, 2 or 3; preferably 1;

m' is 0, 1, 2 or 3; preferably 1; and

s is 1, 2, 3 or 4; preferably 1.

In one subset of the compounds of Formulas I and II:

M is absent or selected from O or NR_1 ;

Z_{101} is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

W_{101} is absent, or selected from $-O-$, $-S-$, $-NH-$, $-N(Me)-$, $-C(O)NH-$, or $-C(O)N(Me)-$;

X and Y taken together with the carbon atoms to which they are attached to form a cyclic moiety which selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocyclic;

R_{101} and R_{102} are independently selected from the group consisting of:

- (i) hydrogen, halogen, CN, CF_3 , NO_2 , OR_1 , SR_1 , $-NHS(O)_2-R_2$, $-NH(SO_2)NR_3R_4$, NR_3R_4 , CO_2R_1 , COR_1 , $CONR_1R_2$, $N(R_1)COR_2$;

- (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
 - (iii) heterocycloalkyl or substituted heterocycloalkyl;
 - (iv) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted
- 5 $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;

R_3 and R_4 are independently selected from:

- (i) hydrogen;
 - (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
 - (iii) heterocycloalkyl or substituted heterocycloalkyl;
 - (iv) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted
- 10 $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;
- 15 heterocyclic, or substituted heterocyclic;

20 W is absent, or selected from alkylene, alkenylene, alkynylene, $-O-$, $-S-$, $-NH-$, $-N(Me)-$, $-C(O)NH-$, or $-C(O)N(Me)-$;

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

$m' = 1 \text{ or } 2$; and

s is 1.

25 In another embodiment, the present invention features pharmaceutical compositions comprising a compound of the invention, or a pharmaceutically acceptable salt, ester or prodrug thereof. In still another embodiment of the present invention there are disclosed pharmaceutical compositions comprising a therapeutically effective amount of a compound

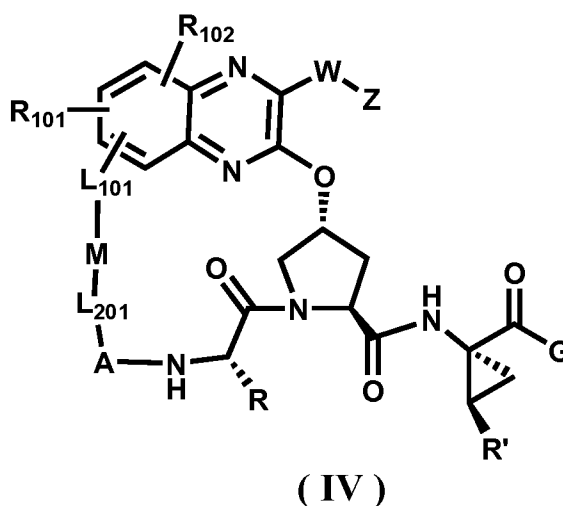
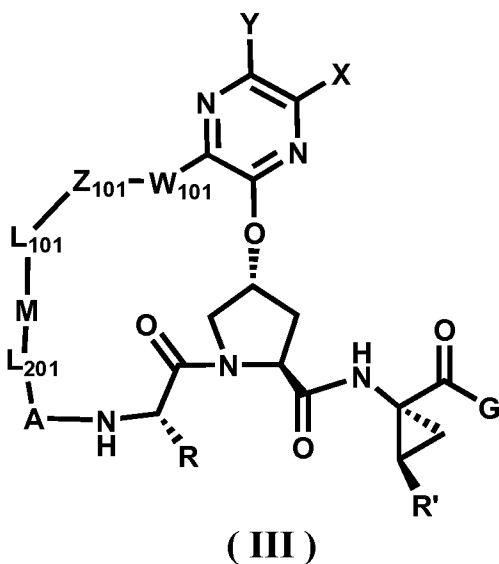
30 of the invention, or a pharmaceutically acceptable salt, ester or prodrug thereof, in

combination with a pharmaceutically acceptable carrier or excipient. In yet another embodiment of the invention are methods of treating a hepatitis C infection in a subject in need of such treatment with said pharmaceutical compositions.

Detailed Description of the Invention

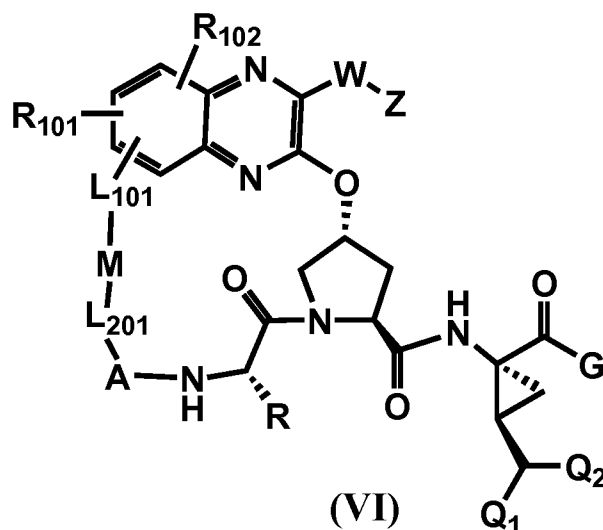
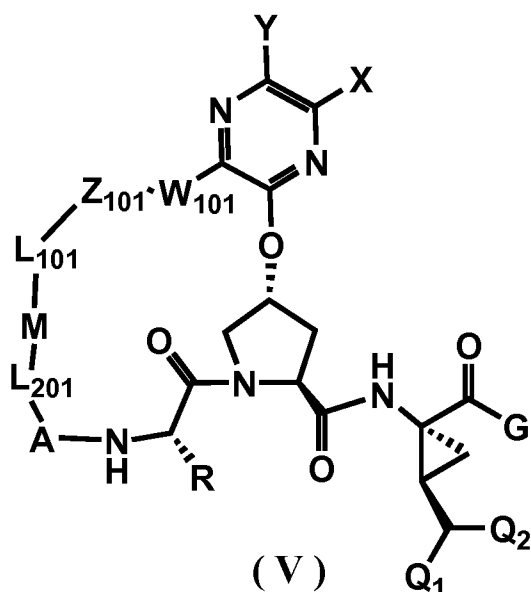
5 A first embodiment of the invention is a compound represented by Formula I or Formula II as described above, or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient.

Other embodiments of the invention are compounds represented by Formula III or IV:



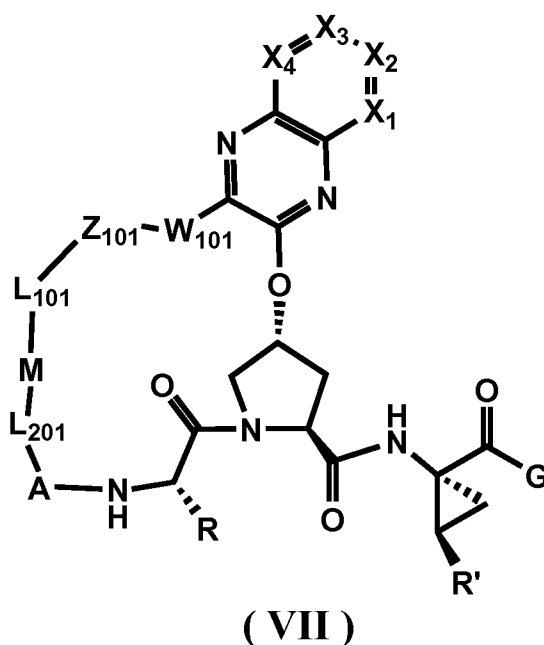
or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where R, R', A, L₂₀₁, M, L₁₀₁, Z₁₀₁, W₁₀₁, X, Y, R₁₀₁, R₁₀₂, W, Z, and G are as previously defined.

Other embodiments of the invention are compounds represented by Formula V or VI:



or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where Q₁ and Q₂ are independently fluorine, chlorine or bromine, and where R, A, L₂₀₁, M, L₁₀₁, Z₁₀₁, W₁₀₁, X, Y, R₁₀₁, R₁₀₂, W, Z, and G are as previously defined. In particularly preferred embodiments, Q₁ and Q₂ are both fluorine.

Another embodiment of the invention is a compound represented by Formula VII:

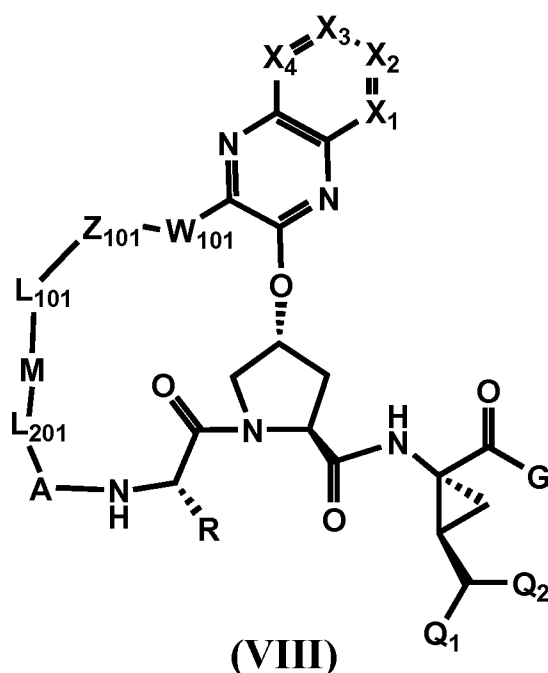


or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where X_1 - X_4 are independently selected from $-CR_5$ and N, wherein R_5 is independently selected from:

- (i) hydrogen; halogen; $-NO_2$; $-CN$; N_3 ; CF_3 ;
- (ii) $-M-R_4$, M is O, S, NH;
- (iii) NR_3R_4 ;
- (iv) $-C_1$ - C_8 alkyl, $-C_2$ - C_8 alkenyl, or $-C_2$ - C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1$ - C_8 alkyl, substituted $-C_2$ - C_8 alkenyl, or substituted $-C_2$ - C_8 alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3$ - C_{12} cycloalkyl, or substituted $-C_3$ - C_{12} cycloalkyl; $-C_3$ - C_{12} cycloalkenyl, or substituted $-C_3$ - C_{12} cycloalkenyl;
- (v) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (vi) heterocycloalkyl or substituted heterocycloalkyl;

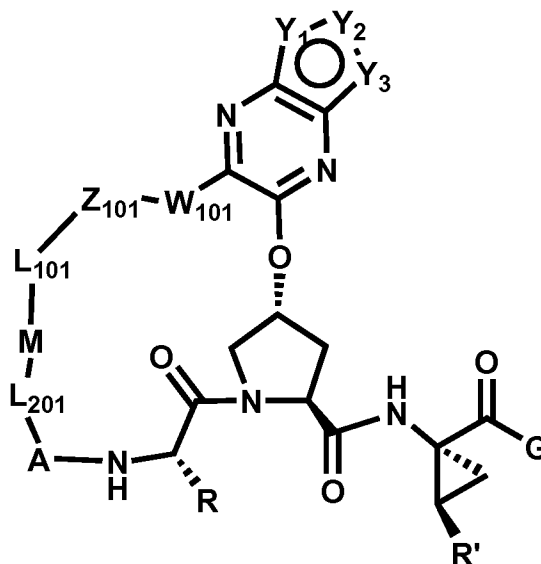
where R_3 , R_4 , R, R' , A, L_{201} , M, L_{101} , Z_{101} , W_{101} and G are as previously defined.

Another embodiment of the invention is a compound represented by Formula VIII:



or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, wherein X_1 - X_4 are as defined for Formula VII, and R, A, Q_1 , Q_2 , L_{201} , M, L_{101} , Z_{101} , W_{101} and G are as previously defined.

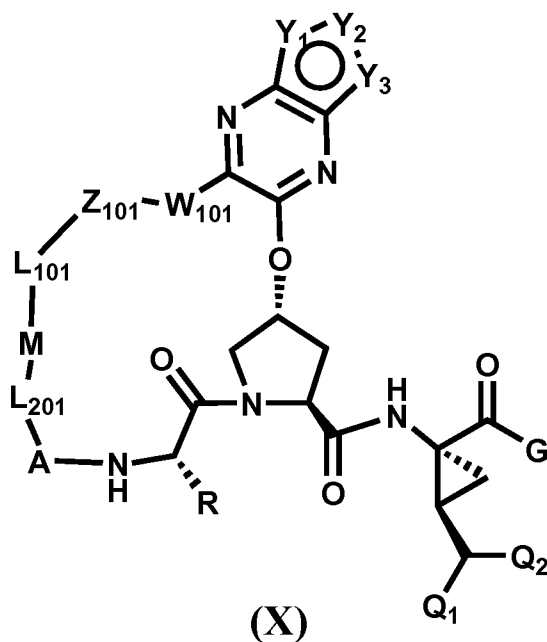
Another embodiment of the invention is a compound represented by Formula IX:



(IX)

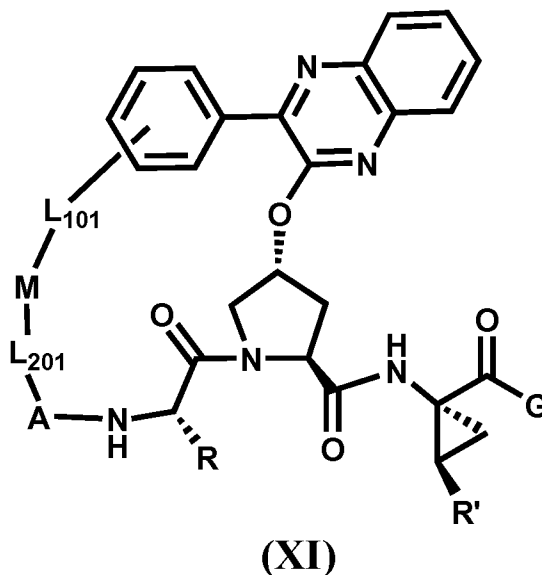
or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where Y_1 - Y_3 are independently selected from CR_5 , N, NR_5 , S and O; where R_5 , R, R' , A, L_{201} , M, L_{101} , Z_{101} , W_{101} and G are as previously defined.

Another embodiment of the invention is a compound represented by Formula X:



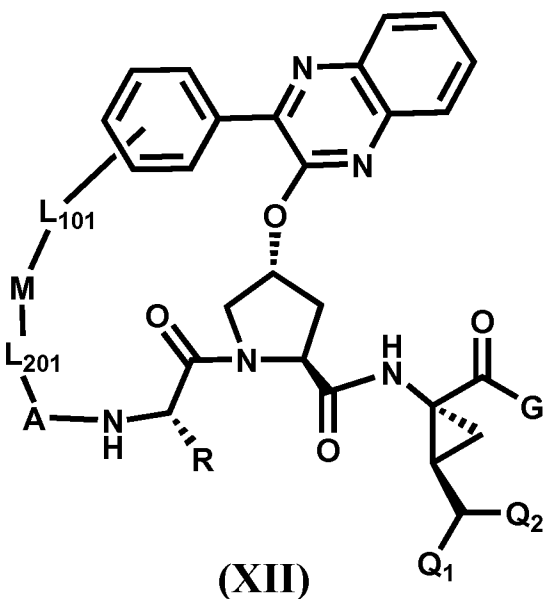
a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where Y₁-Y₃ are as defined for Formula IX, and R, Q₁, Q₂, A, L₂₀₁, M, L₁₀₁, Z₁₀₁, W₁₀₁ and G are as previously defined.

Another embodiment of the invention is a compound represented by Formula XI:



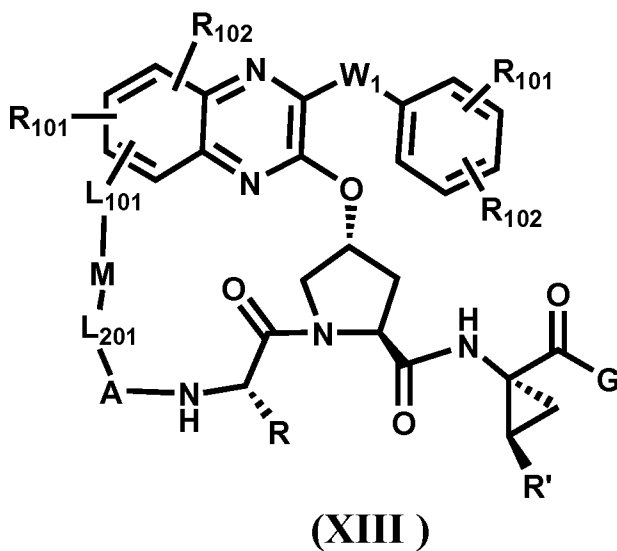
or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where R, R', A, L₂₀₁, M, L₁₀₁ and G are as previously defined.

Another embodiment of the invention is a compound represented by Formula XII:



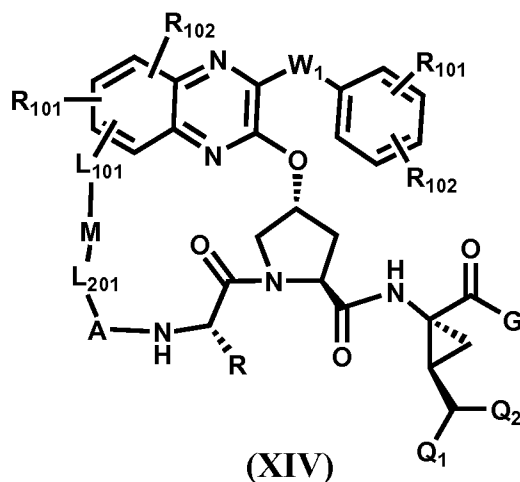
a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where R, Q₁, Q₂, A, L₂₀₁, M, L₁₀₁ and G are as previously defined.

Another embodiment of the invention is a compound represented by Formula XIII:



or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where W₁ is absent or selected from C₁-C₄ alkylene, C₂-C₄ alkenylene, C₂-C₄ alkynylene; where R, R', A, L₂₀₁, M, L₁₀₁, R₁₀₁, R₁₀₂ and G are as previously defined.

Another embodiment of the invention is a compound represented by Formula XIV:



a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in combination with a pharmaceutically acceptable carrier or excipient, where W_1 is as defined for Formula XIII,

5 and R , Q_1 , Q_2 , A , L_{201} , M , L_{101} , R_{101} , R_{102} and G are as previously defined.

Representative compounds of the invention include, but are not limited to, the following compounds (Table 1) according to Formula XV wherein R , M - L , Ar , R' and G are delineated for each example in Table 1.

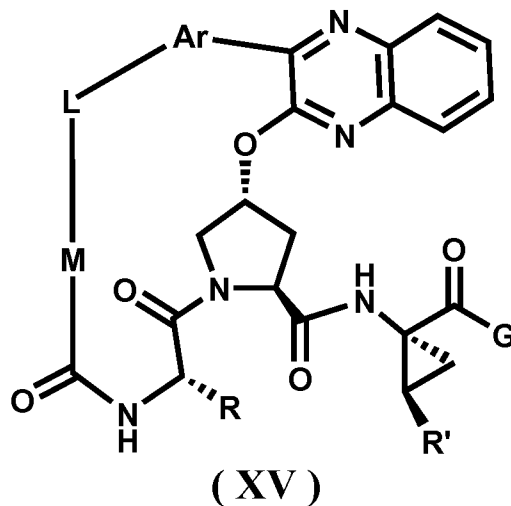
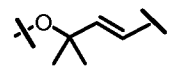
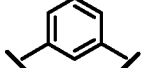
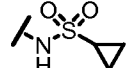
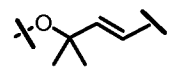
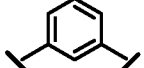
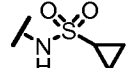
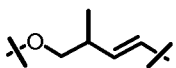
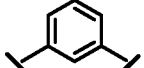
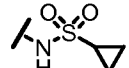
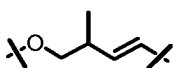
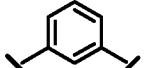
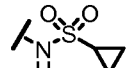
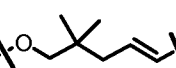
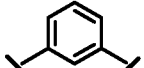
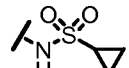
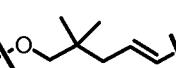
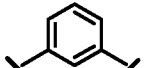
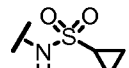
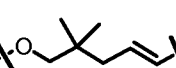
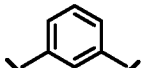
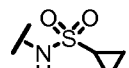
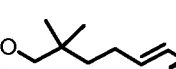
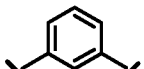
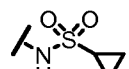
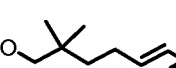
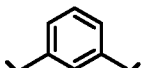
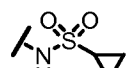
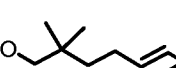
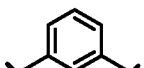
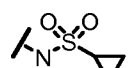
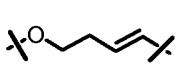
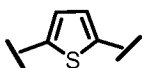
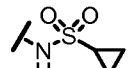
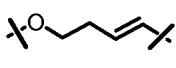
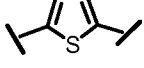
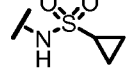
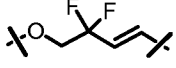
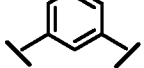
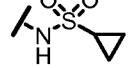
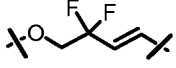
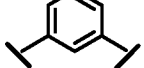
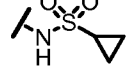
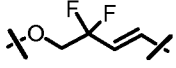
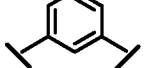
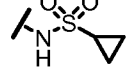
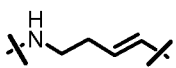
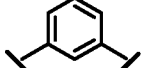
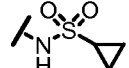
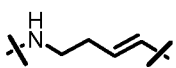
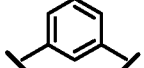
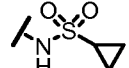
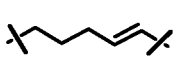
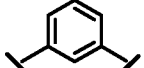
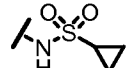
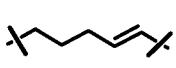
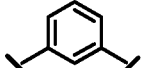
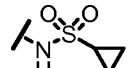
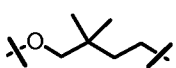
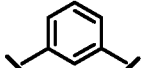
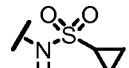
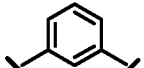
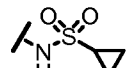
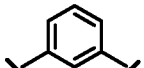
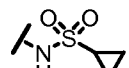
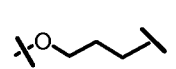
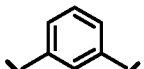
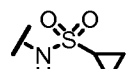
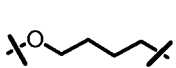
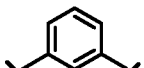
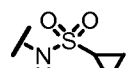
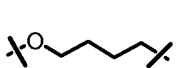
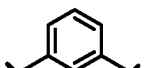
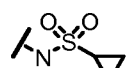
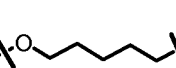
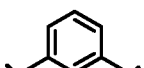
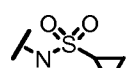
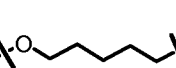
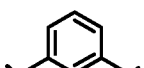
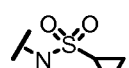
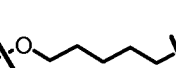
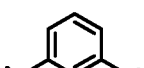
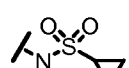
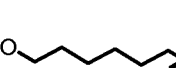
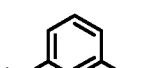
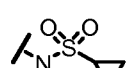
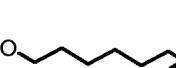
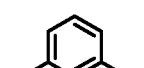
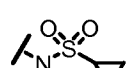


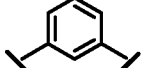
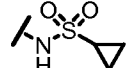
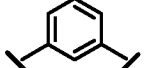
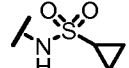
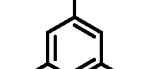
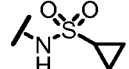
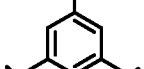
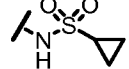
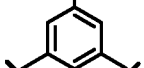
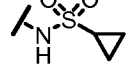
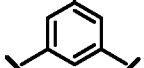
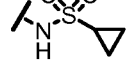
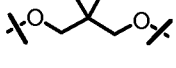
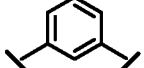
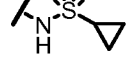
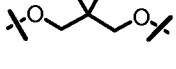
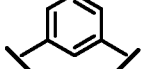
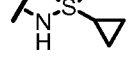
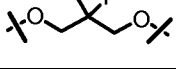
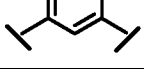
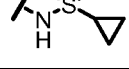
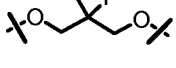
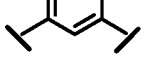
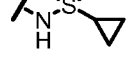
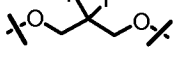
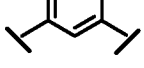
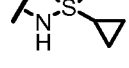
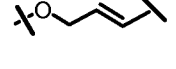
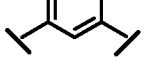
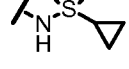
TABLE 1

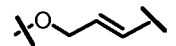
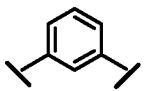
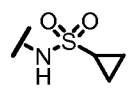
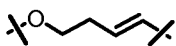
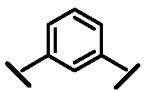
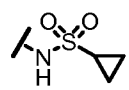
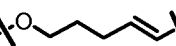
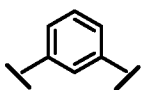
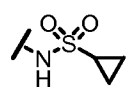
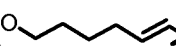
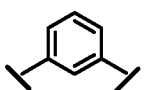
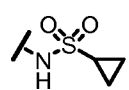
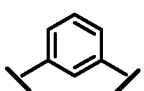
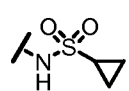
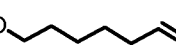
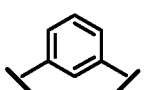
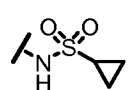
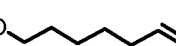
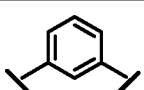
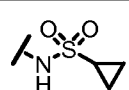
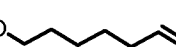
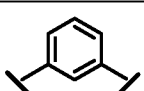
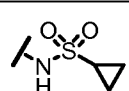
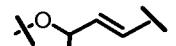
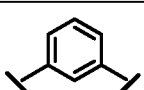
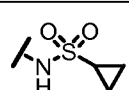
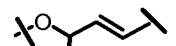
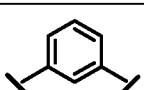
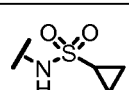
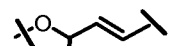
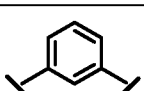
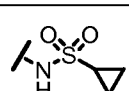
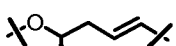
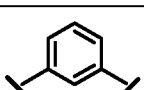
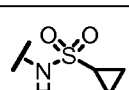
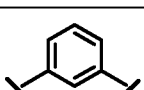
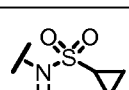
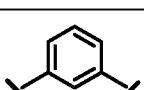
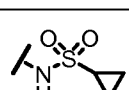
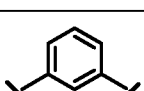
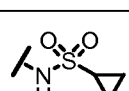
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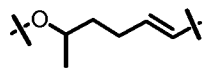
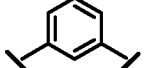
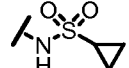
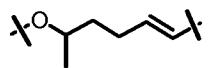
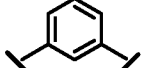
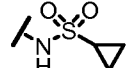
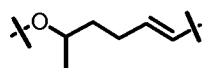
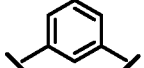
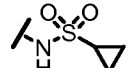
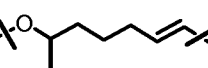
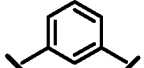
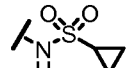
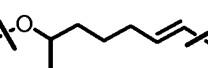
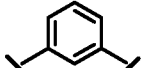
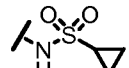
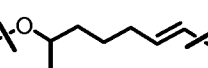
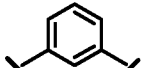
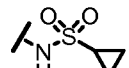
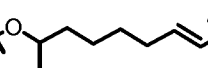
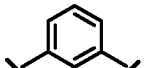
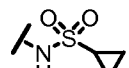
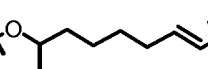
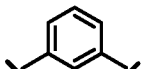
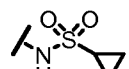
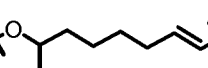
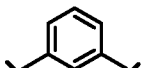
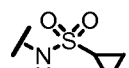
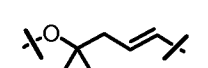
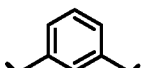
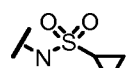
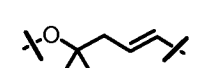
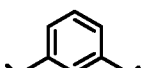
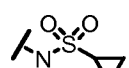
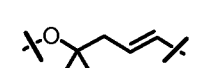
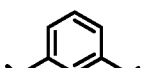
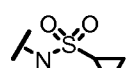
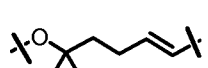
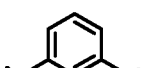
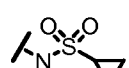
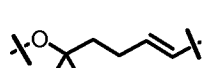
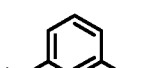
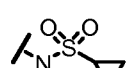
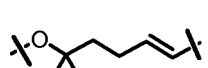
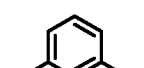
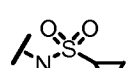
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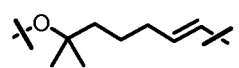
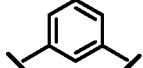
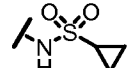
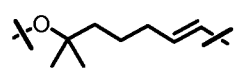
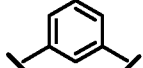
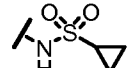
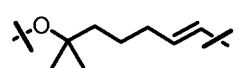
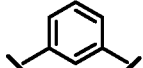
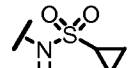
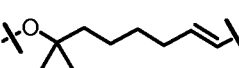
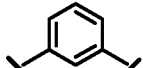
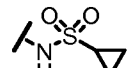
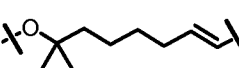
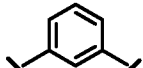
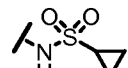
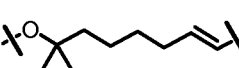
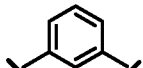
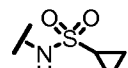
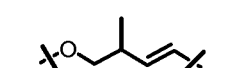
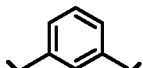
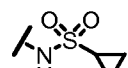
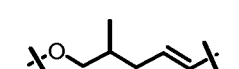
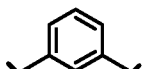
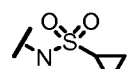
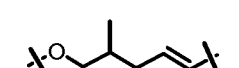
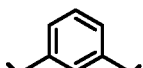
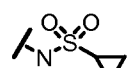
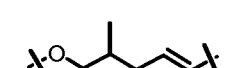
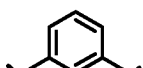
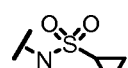
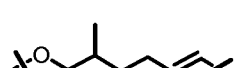
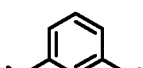
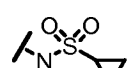
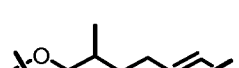
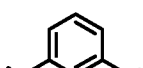
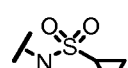
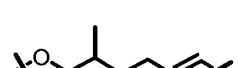
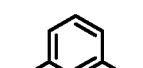
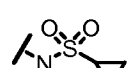
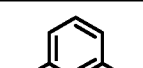
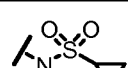
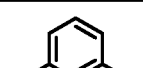
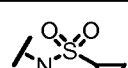
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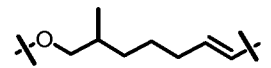
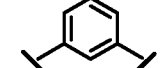
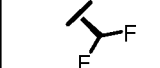
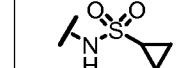
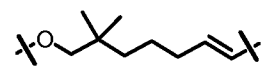
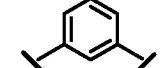
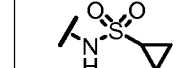
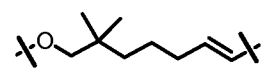
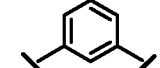
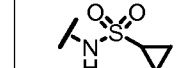
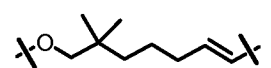
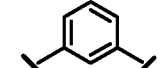
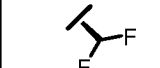
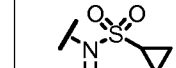
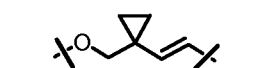
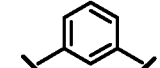
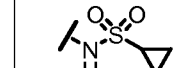
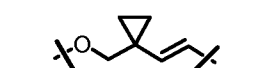
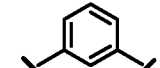
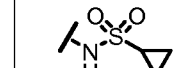
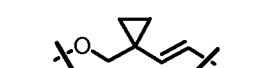
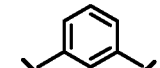
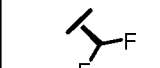
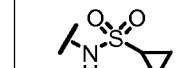
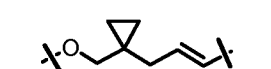
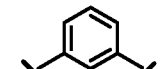
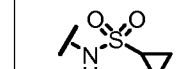
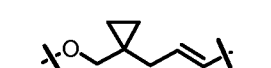
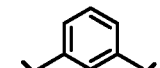
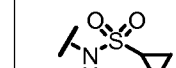
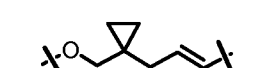
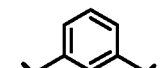
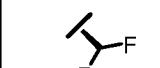
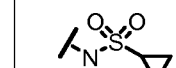
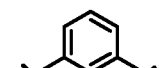
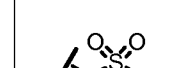
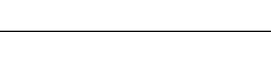
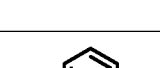
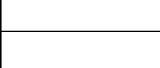
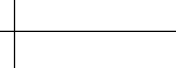
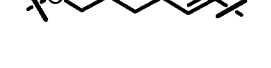
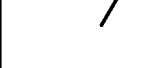
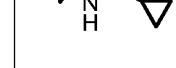
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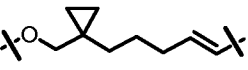
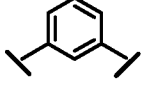
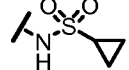
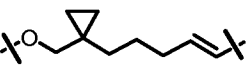
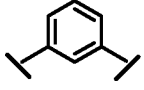
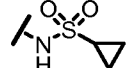
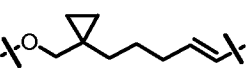
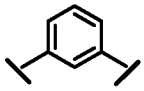
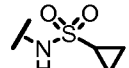
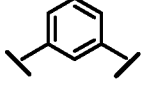
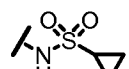
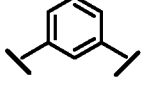
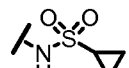
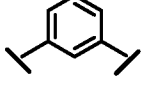
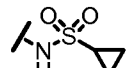
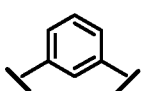
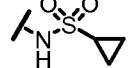
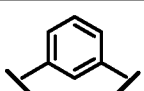
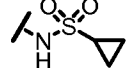
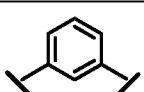
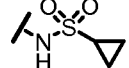
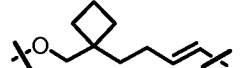
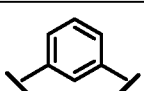
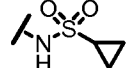
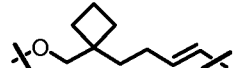
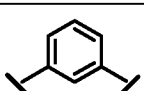
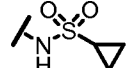
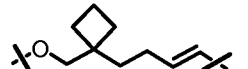
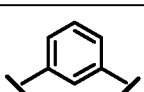
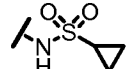
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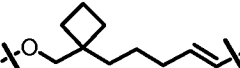
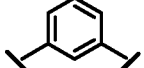
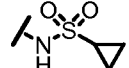
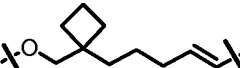
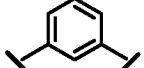
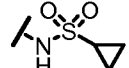
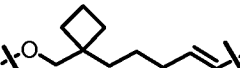
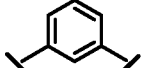
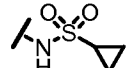
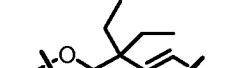
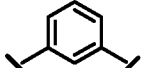
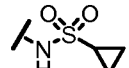
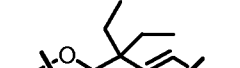
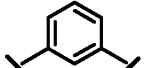
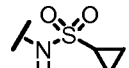
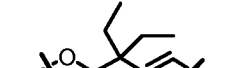
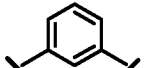
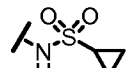
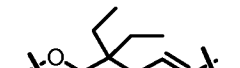
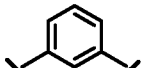
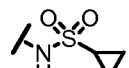
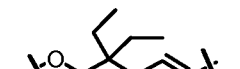
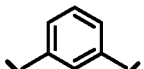
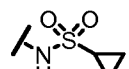
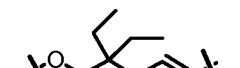
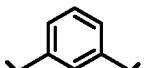
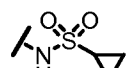
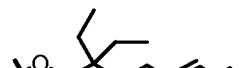
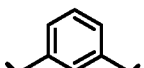
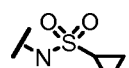
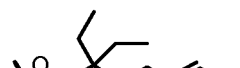
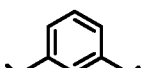
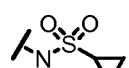
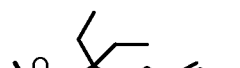
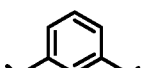
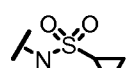
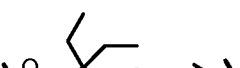
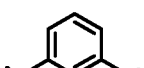
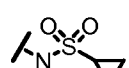
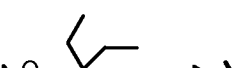
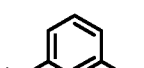
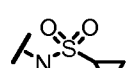
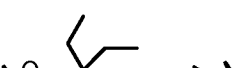
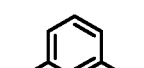
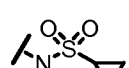
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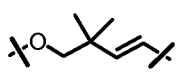
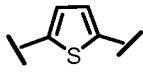
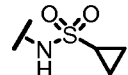
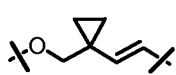
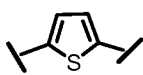
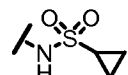
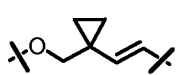
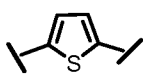
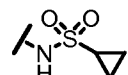
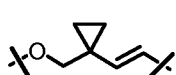
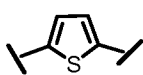
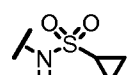
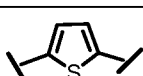
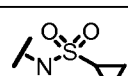
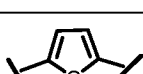
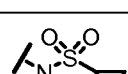
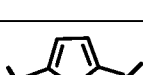
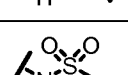
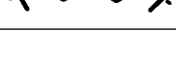
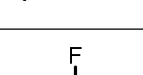
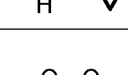
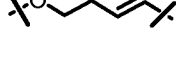
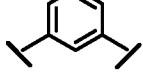
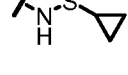
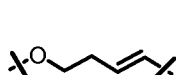
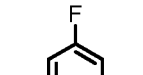
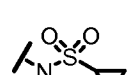
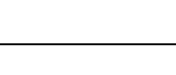
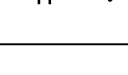
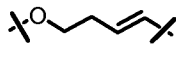
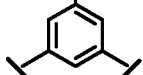
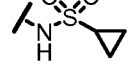
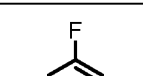
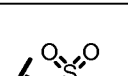
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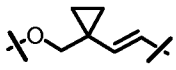
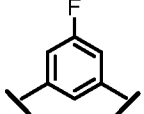
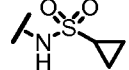
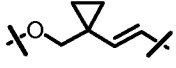
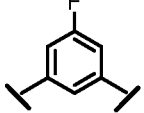
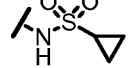
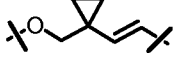
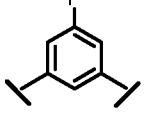
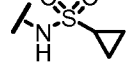
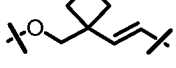
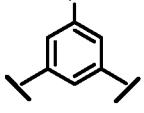
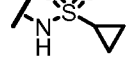
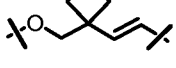
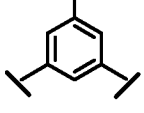
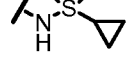
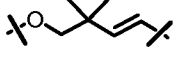
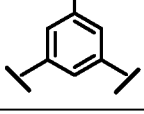
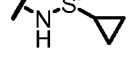
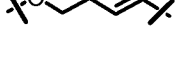
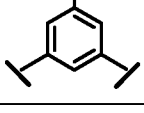
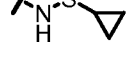
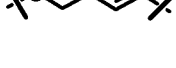
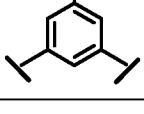
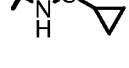
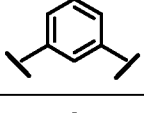
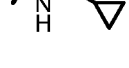
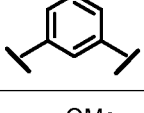
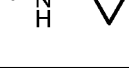
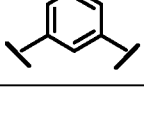
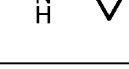
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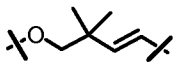
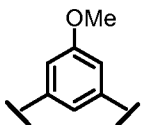
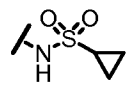
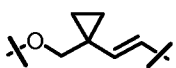
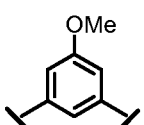
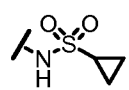
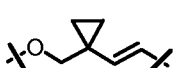
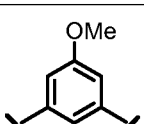
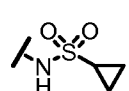
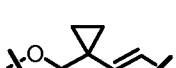
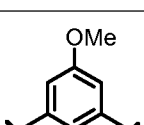
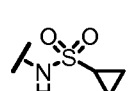
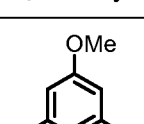
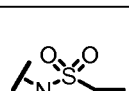
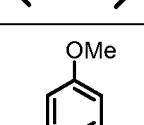
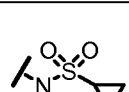
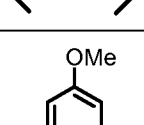
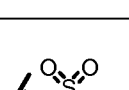
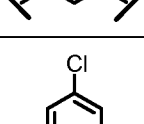
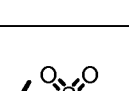
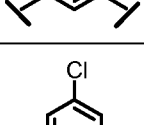
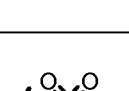
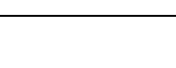
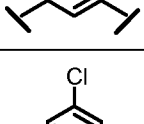
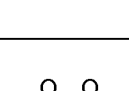
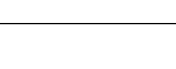
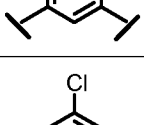
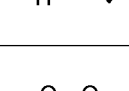
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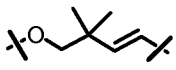
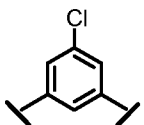
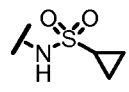
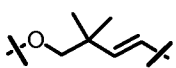
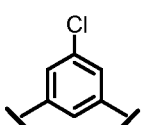
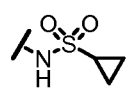
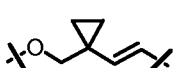
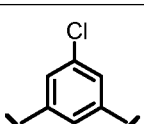
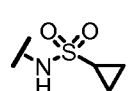
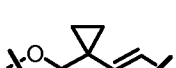
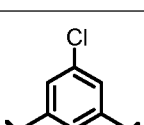
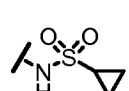
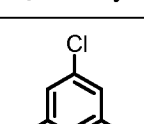
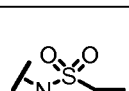
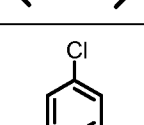
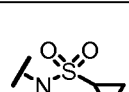
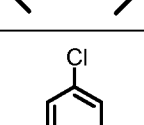
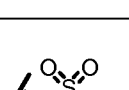
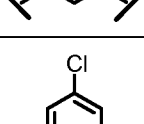
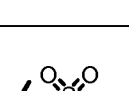
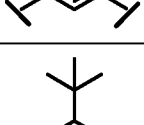
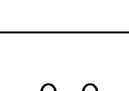
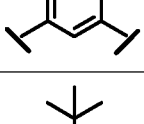
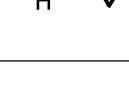
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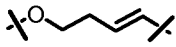
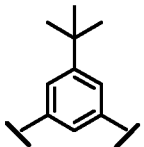
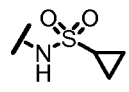
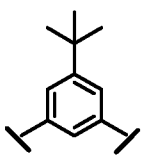
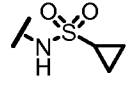
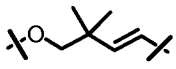
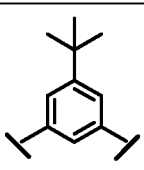
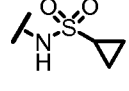
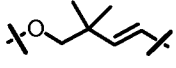
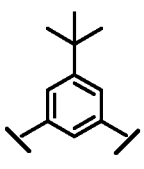
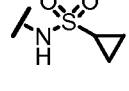
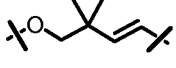
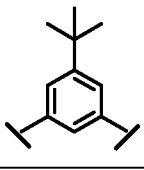
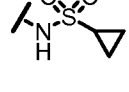
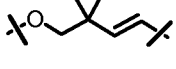
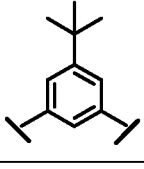
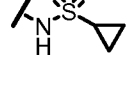
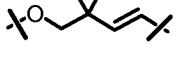
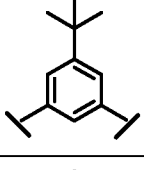
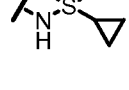
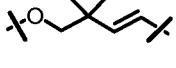
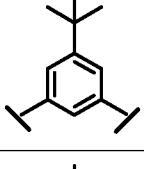
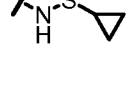
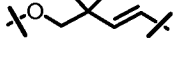
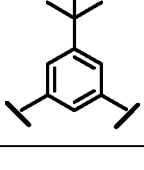
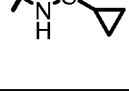
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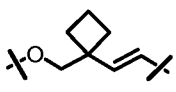
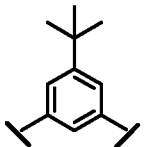
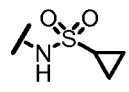
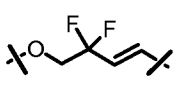
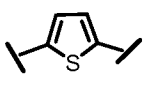
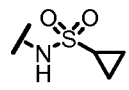
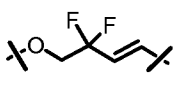
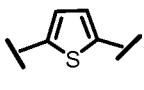
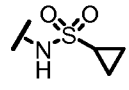
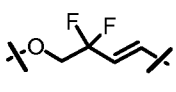
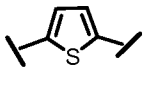
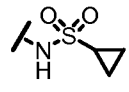
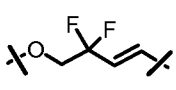
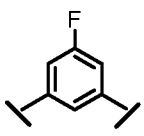
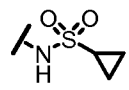
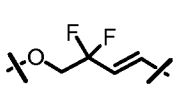
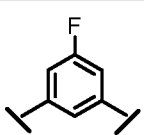
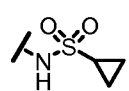
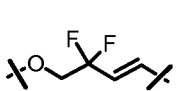
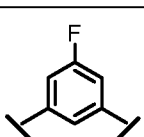
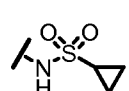
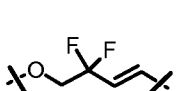
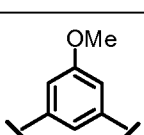
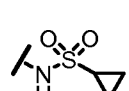
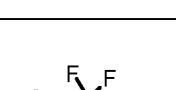
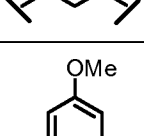
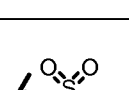
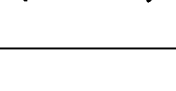
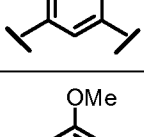
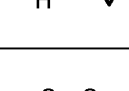
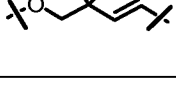
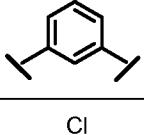
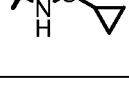
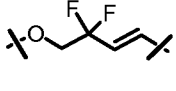
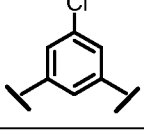
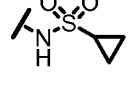
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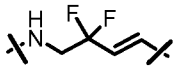
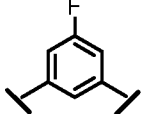
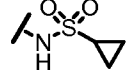
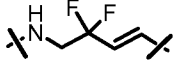
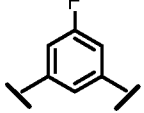
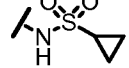
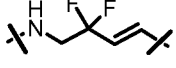
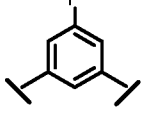
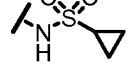
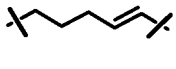
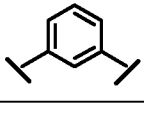
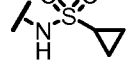
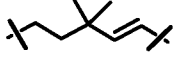
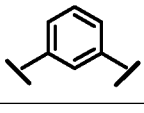
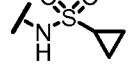
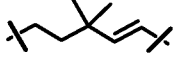
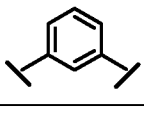
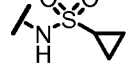
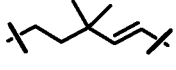
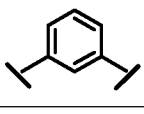
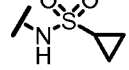
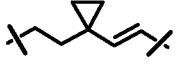
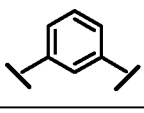
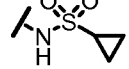
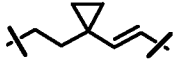
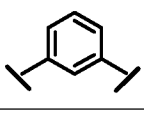
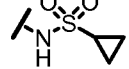
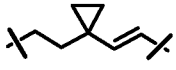
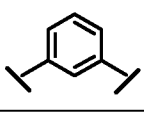
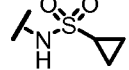
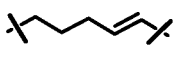
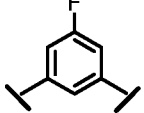
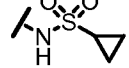
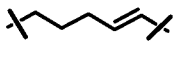
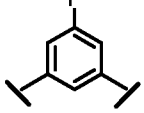
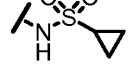
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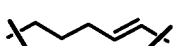
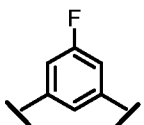
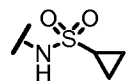
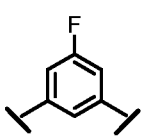
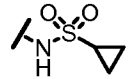
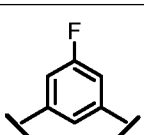
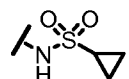
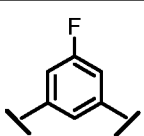
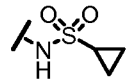
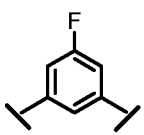
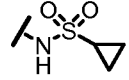
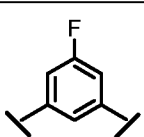
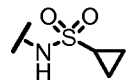
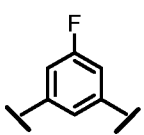
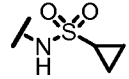
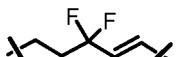
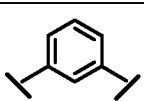
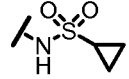
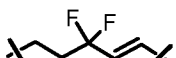
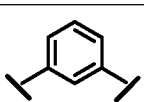
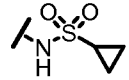
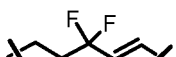
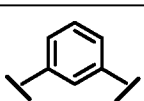
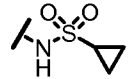
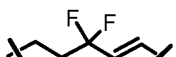
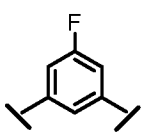
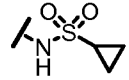
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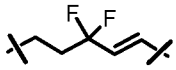
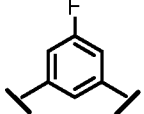
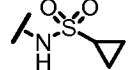
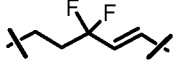
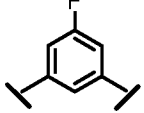
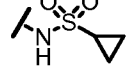
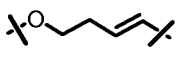
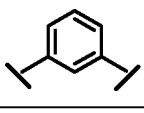
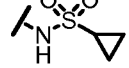
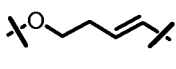
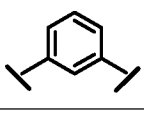
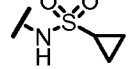
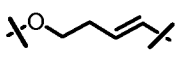
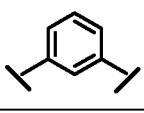
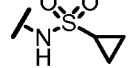
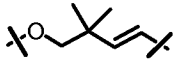
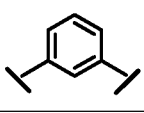
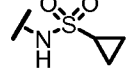
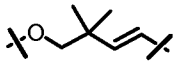
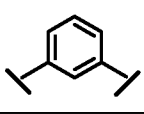
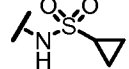
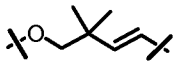
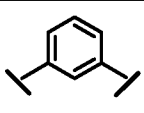
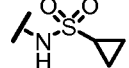
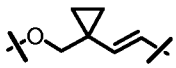
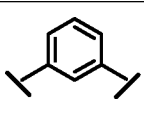
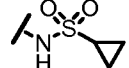
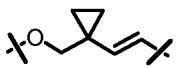
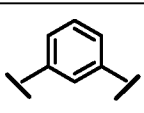
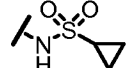
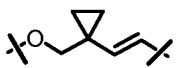
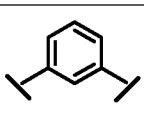
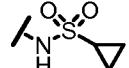
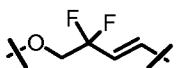
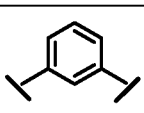
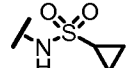
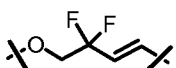
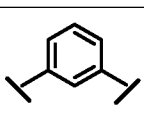
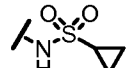
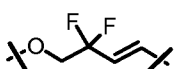
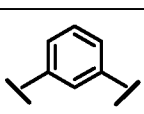
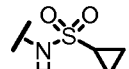
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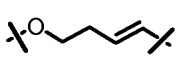
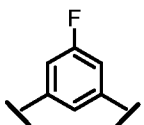
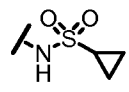
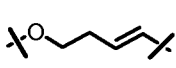
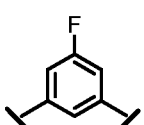
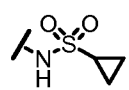
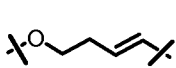
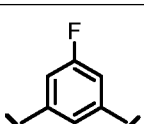
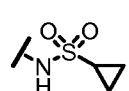
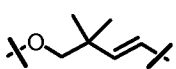
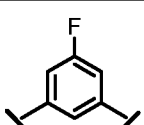
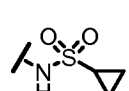
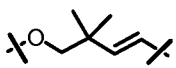
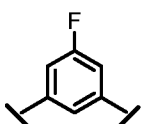
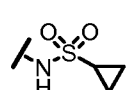
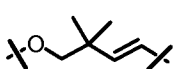
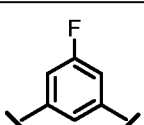
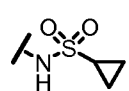
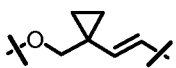
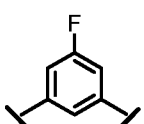
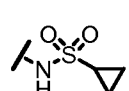
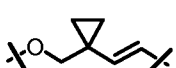
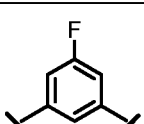
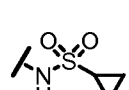
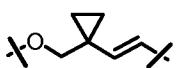
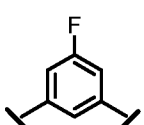
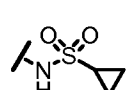
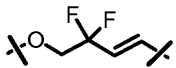
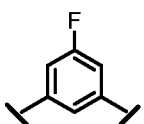
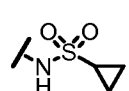
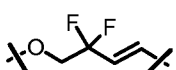
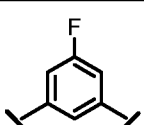
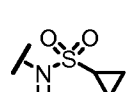
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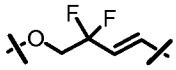
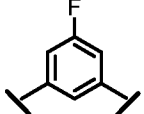
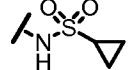
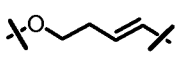
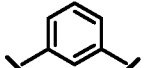
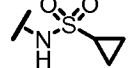
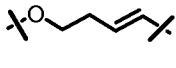
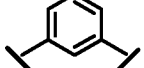
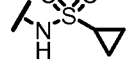
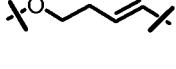
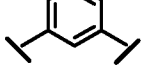
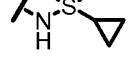
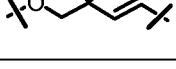
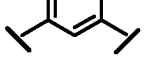
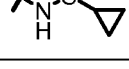
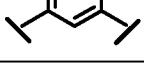
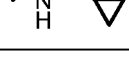
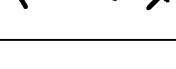
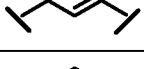
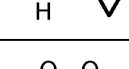
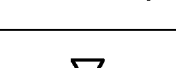
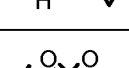
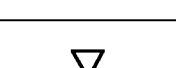
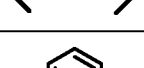
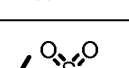
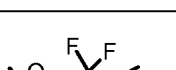
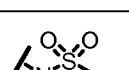
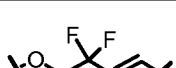
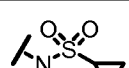
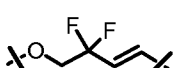
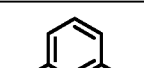
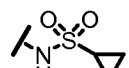
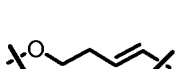
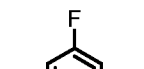
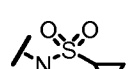
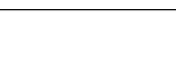
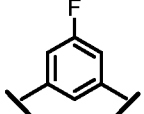
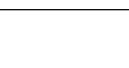
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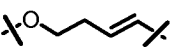
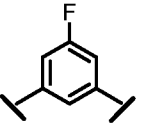
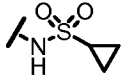
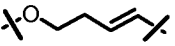
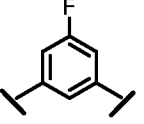
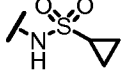
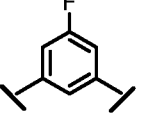
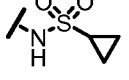
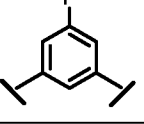
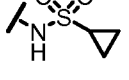
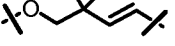
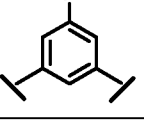
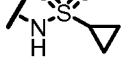
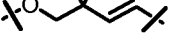
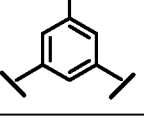
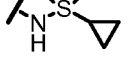
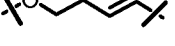
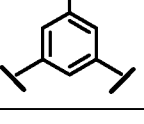
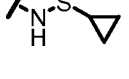
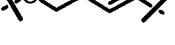
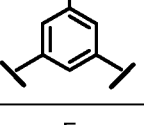
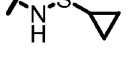
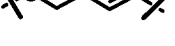
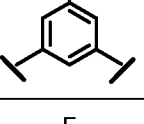
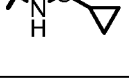
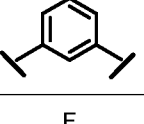
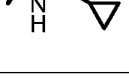
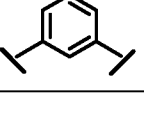
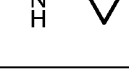
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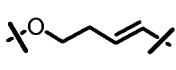
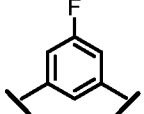
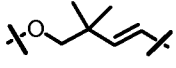
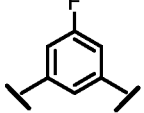
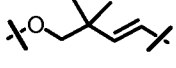
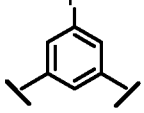
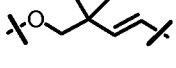
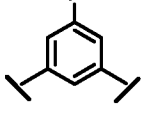
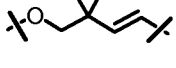
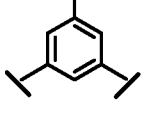
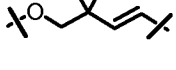
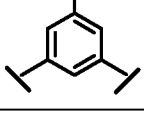
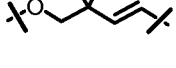
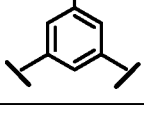
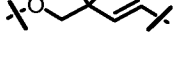
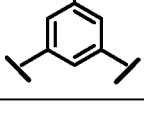
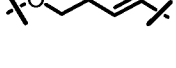
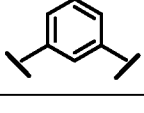
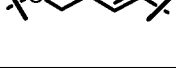
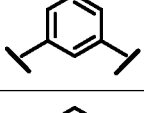
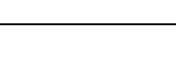
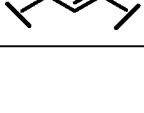
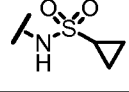
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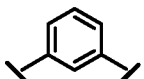
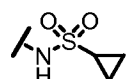
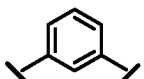
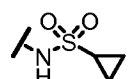
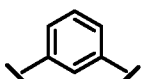
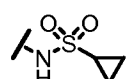
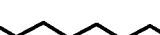
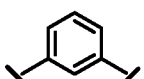
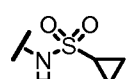
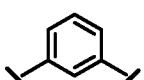
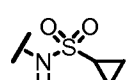
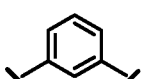
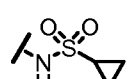
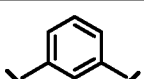
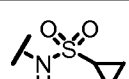
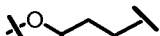
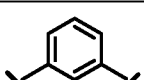
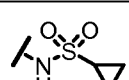
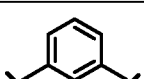
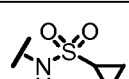
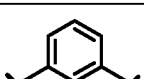
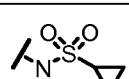
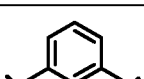
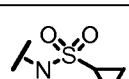
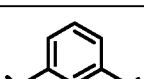
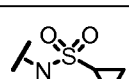
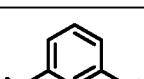
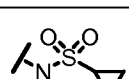
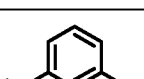
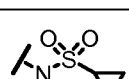
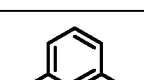
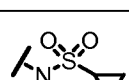
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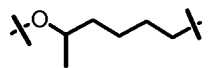
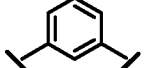
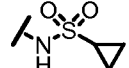
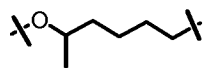
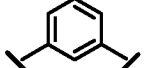
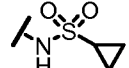
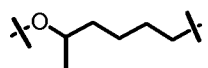
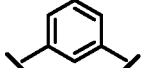
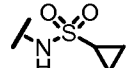
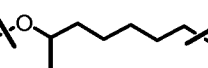
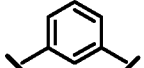
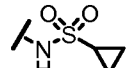
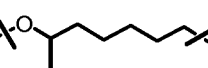
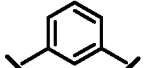
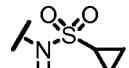
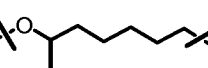
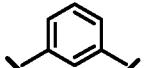
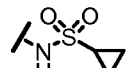
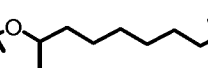
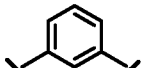
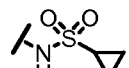
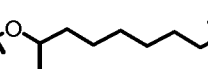
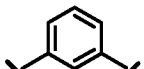
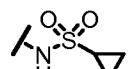
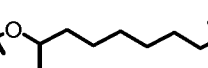
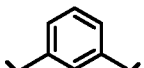
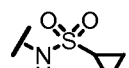
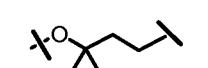
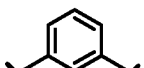
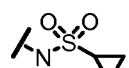
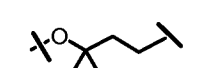
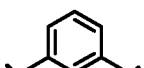
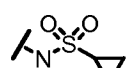
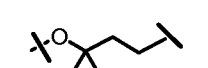
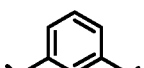
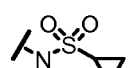
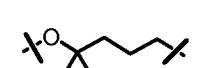
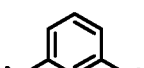
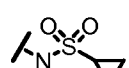
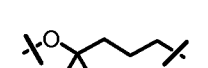
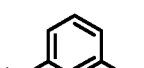
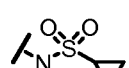
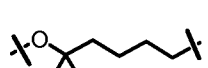
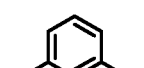
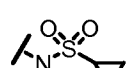
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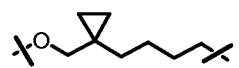
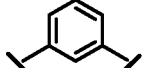
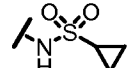
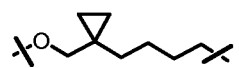
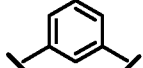
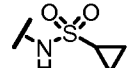
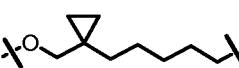
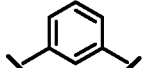
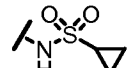
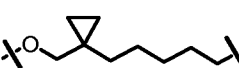
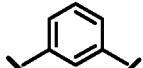
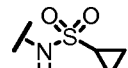
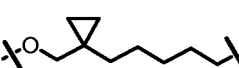
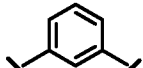
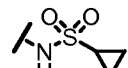
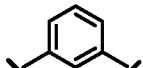
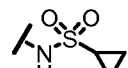
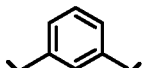
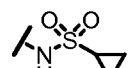
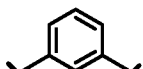
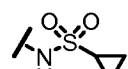
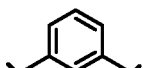
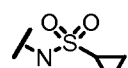
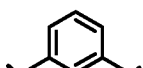
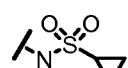
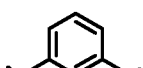
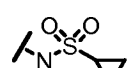
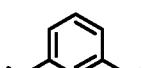
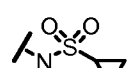
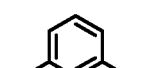
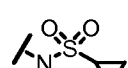
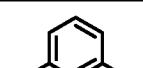
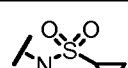
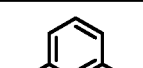
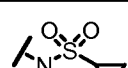
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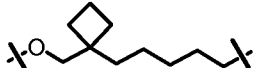
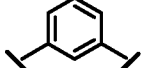
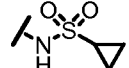
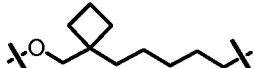
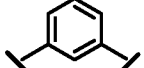
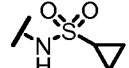
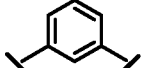
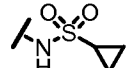
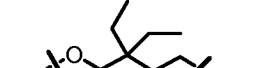
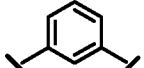
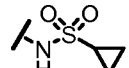
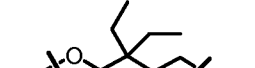
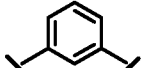
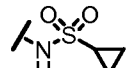
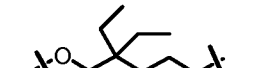
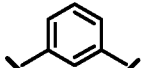
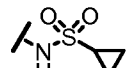
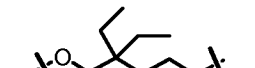
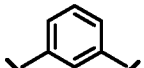
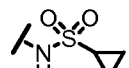
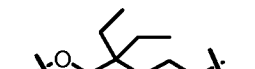
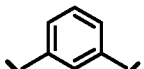
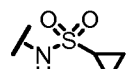
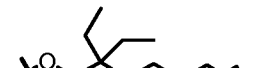
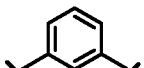
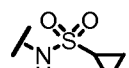
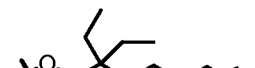
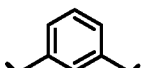
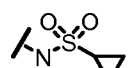
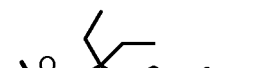
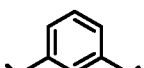
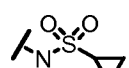
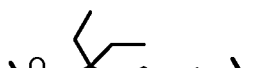
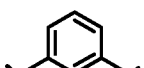
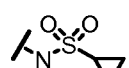
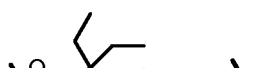
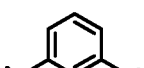
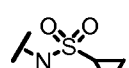
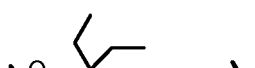
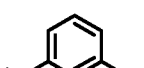
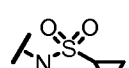
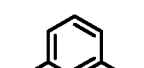
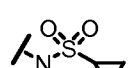
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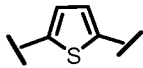
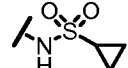
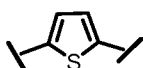
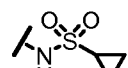
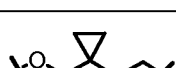
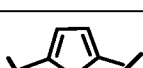
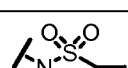
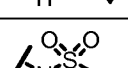
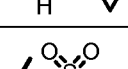
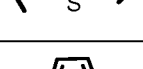
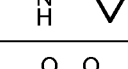
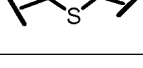
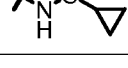
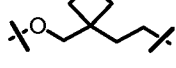
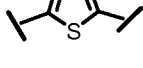
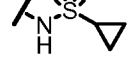
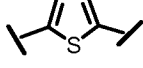
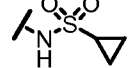
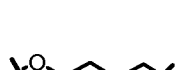
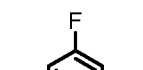
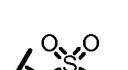
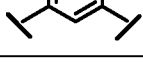
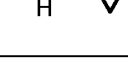
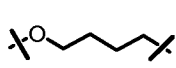
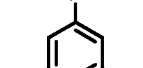
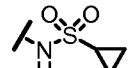
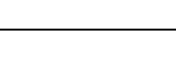
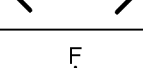
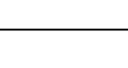
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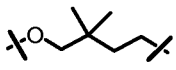
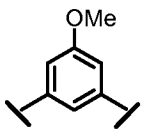
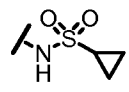
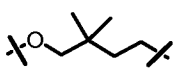
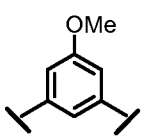
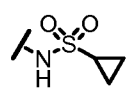
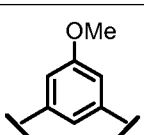
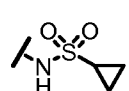
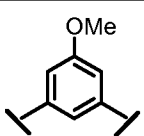
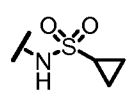
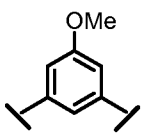
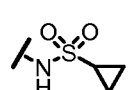
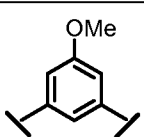
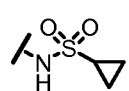
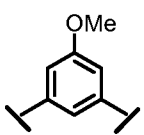
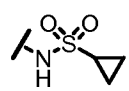
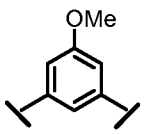
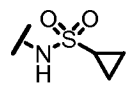
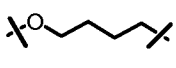
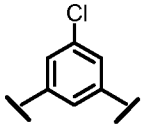
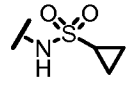
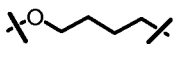
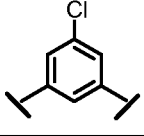
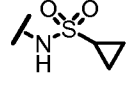
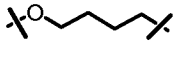
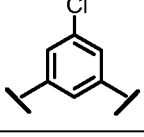
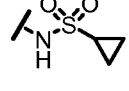
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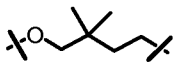
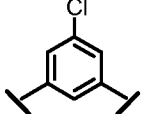
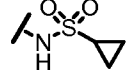
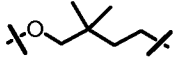
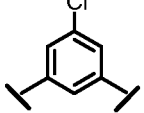
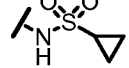
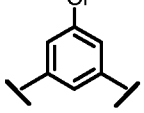
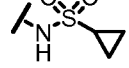
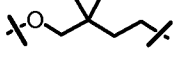
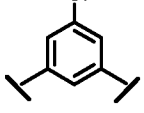
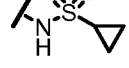
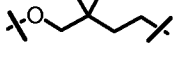
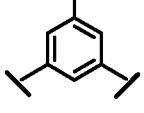
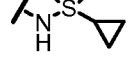
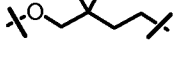
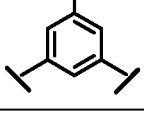
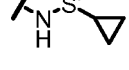
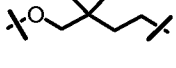
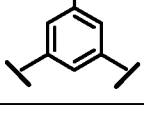
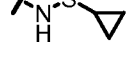
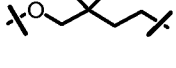
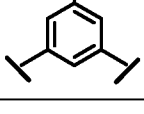
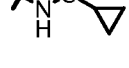
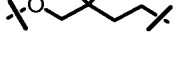
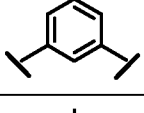
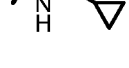
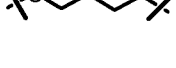
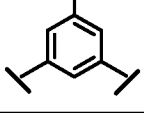
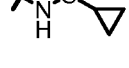
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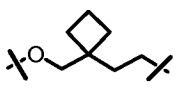
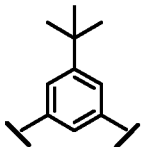
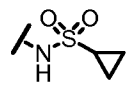
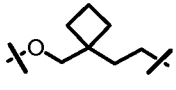
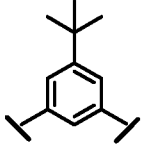
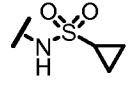
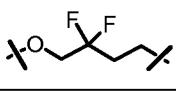
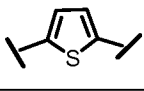
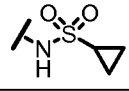
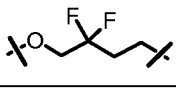
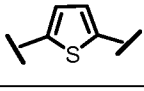
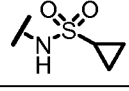
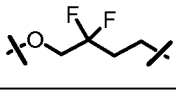
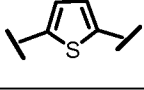
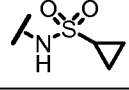
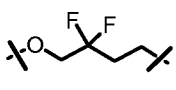
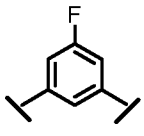
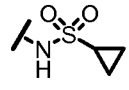
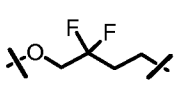
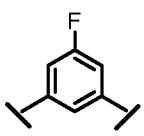
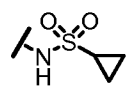
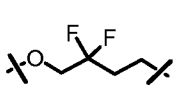
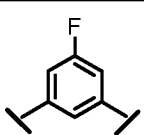
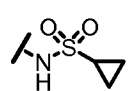
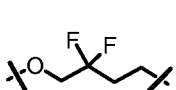
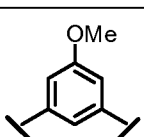
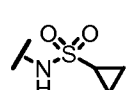
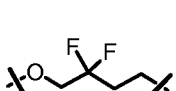
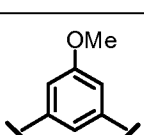
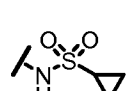
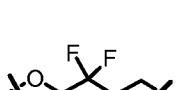
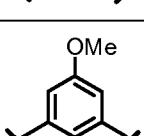
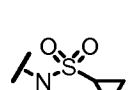
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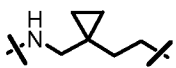
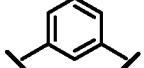
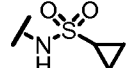
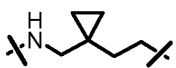
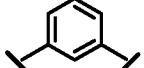
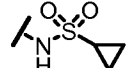
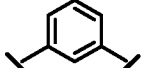
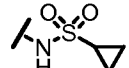
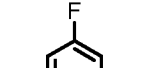
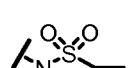
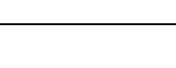
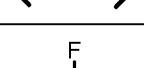
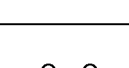
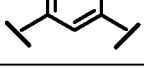
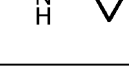
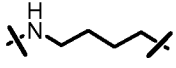
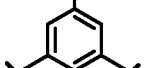
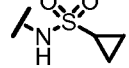
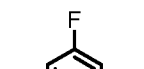
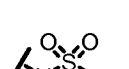
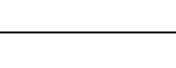
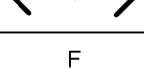
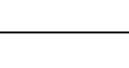
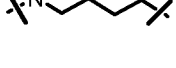
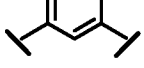
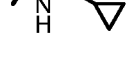
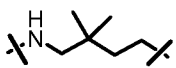
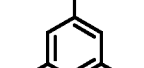
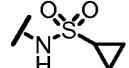
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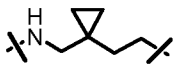
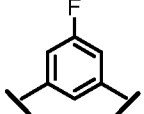
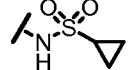
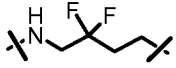
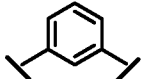
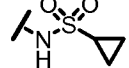
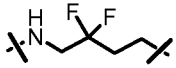
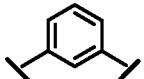
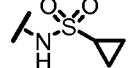
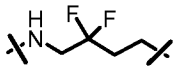
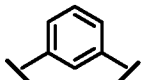
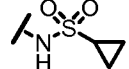
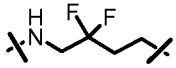
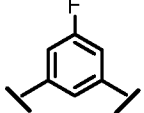
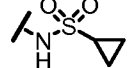
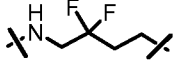
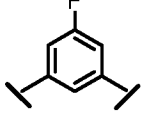
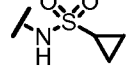
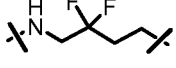
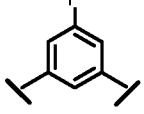
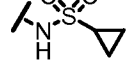
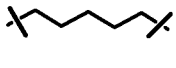
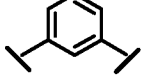
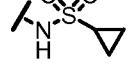
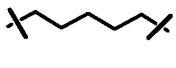
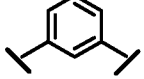
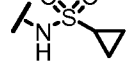
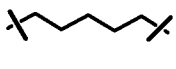
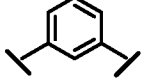
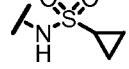
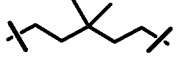
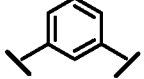
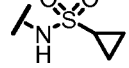
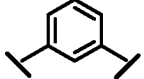
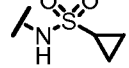
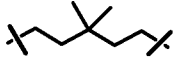
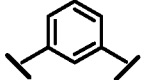
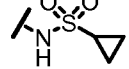
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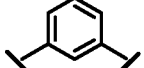
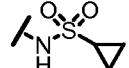
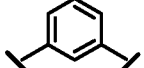
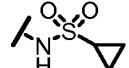
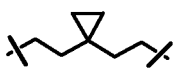
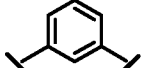
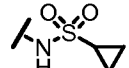
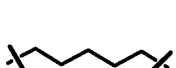
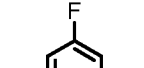
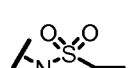
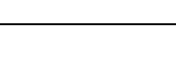
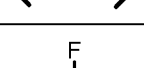
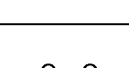
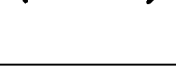
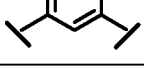
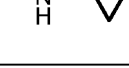
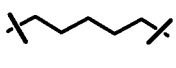
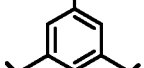
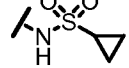
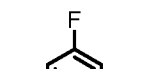
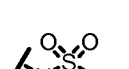
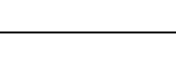
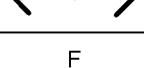
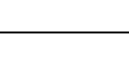
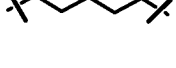
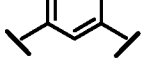
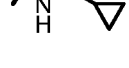
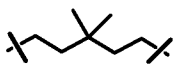
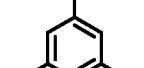
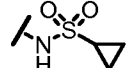
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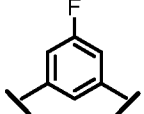
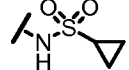
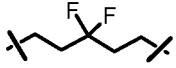
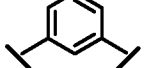
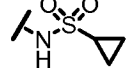
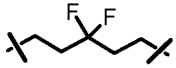
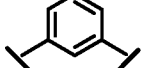
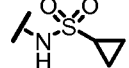
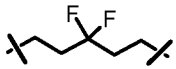
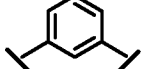
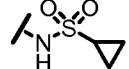
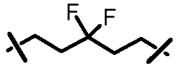
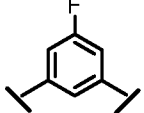
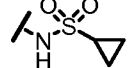
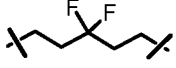
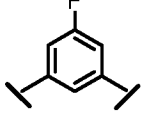
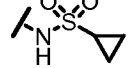
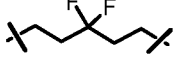
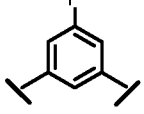
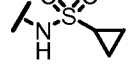
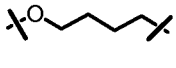
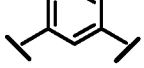
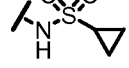
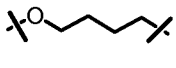
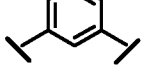
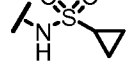
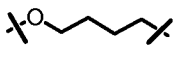
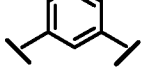
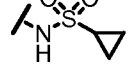
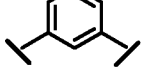
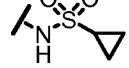
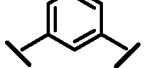
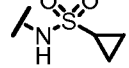
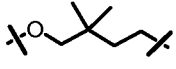
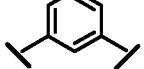
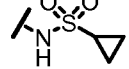
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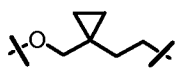
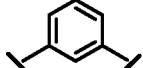
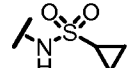
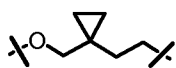
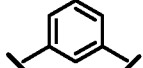
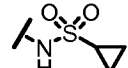
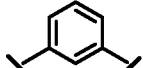
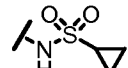
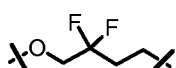
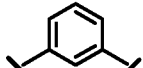
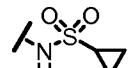
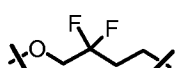
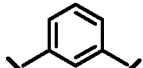
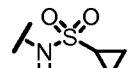
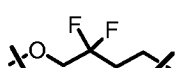
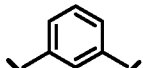
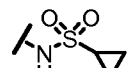
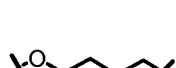
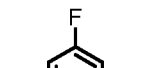
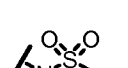
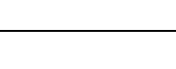
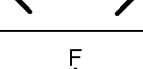
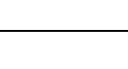
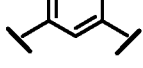
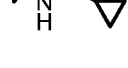
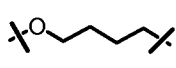
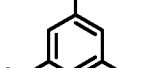
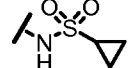
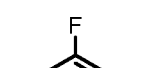
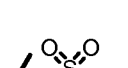
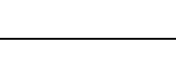
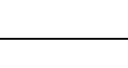
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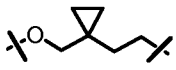
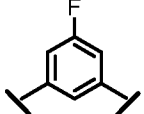
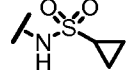
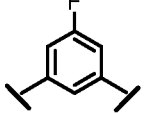
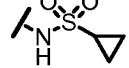
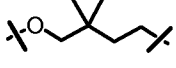
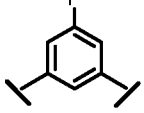
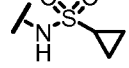
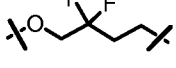
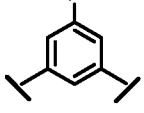
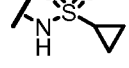
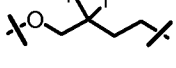
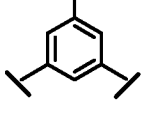
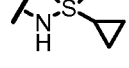
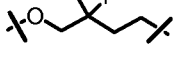
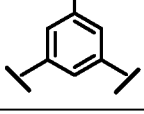
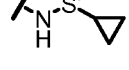
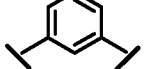
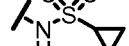
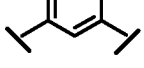
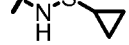
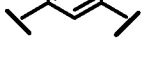
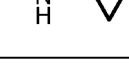
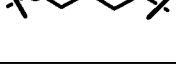
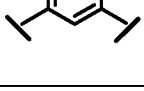
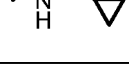
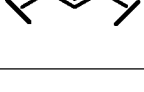
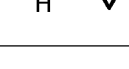
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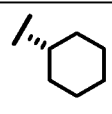
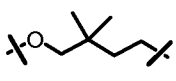
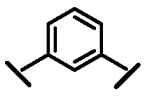
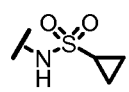
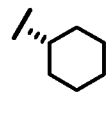
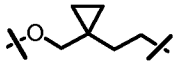
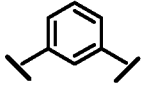
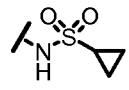
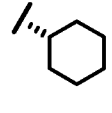
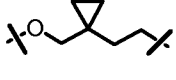
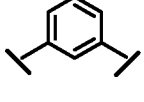
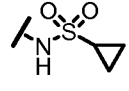
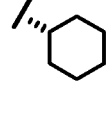
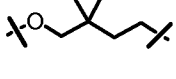
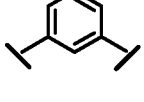
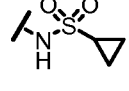
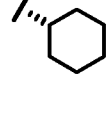
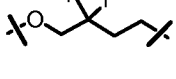
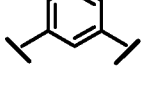
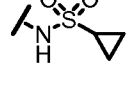
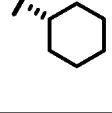
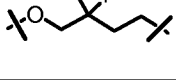
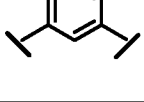
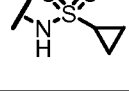
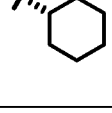
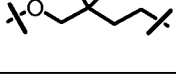
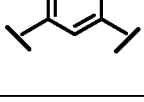
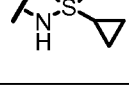
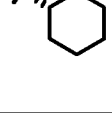
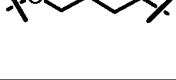
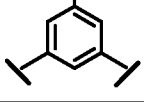
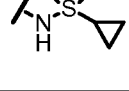
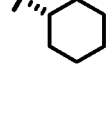
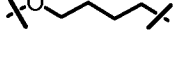
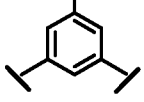
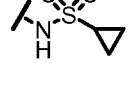
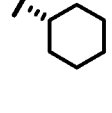
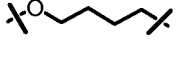
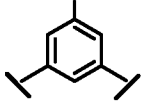
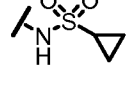
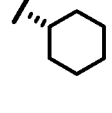
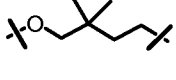
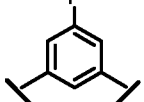
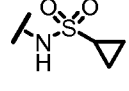
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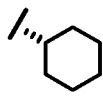
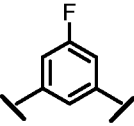
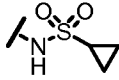
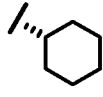
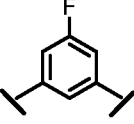
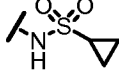
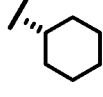
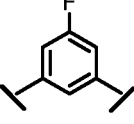
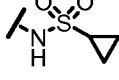
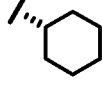
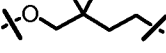
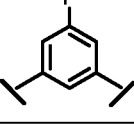
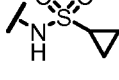
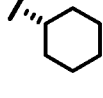
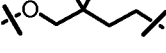
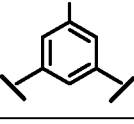
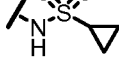
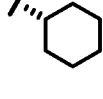
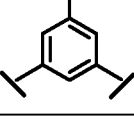
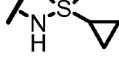
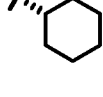
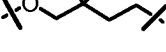
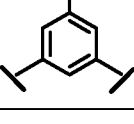
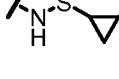
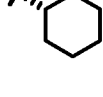
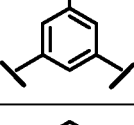
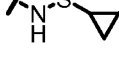
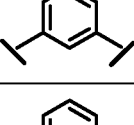
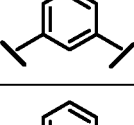
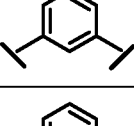
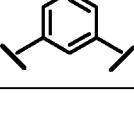
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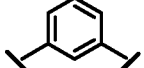
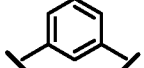
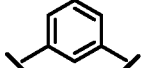
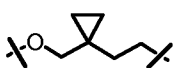
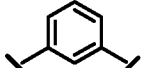
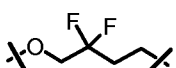
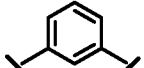
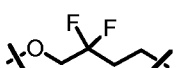
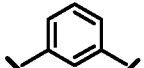
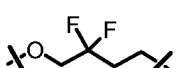
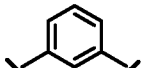
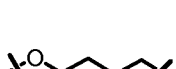
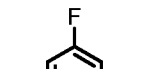
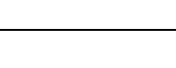
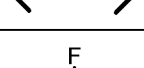
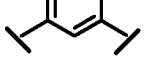
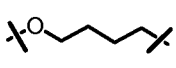
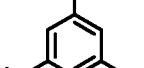
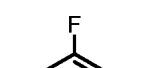
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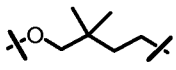
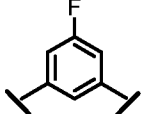
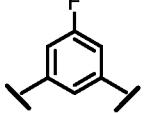
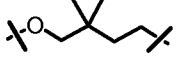
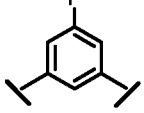
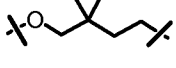
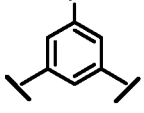
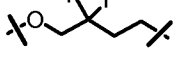
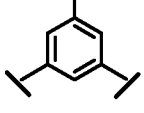
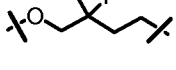
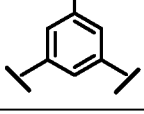
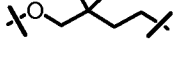
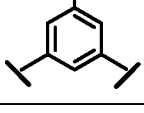
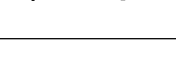
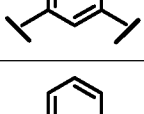
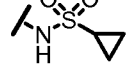
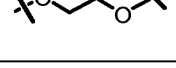
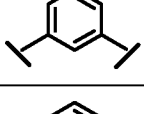
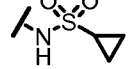
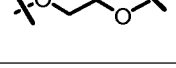
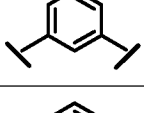
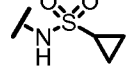
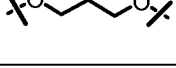
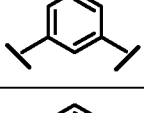
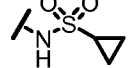
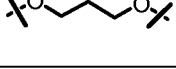
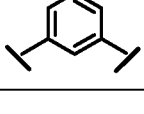
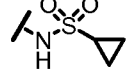
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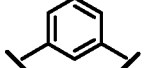
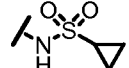
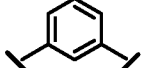
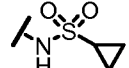
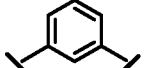
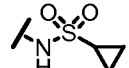
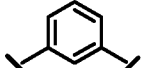
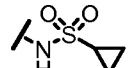
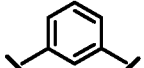
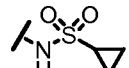
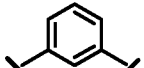
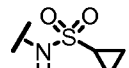
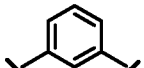
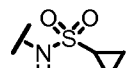
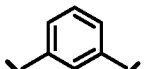
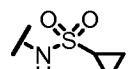
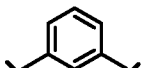
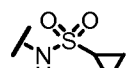
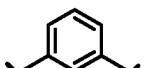
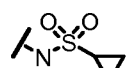
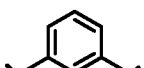
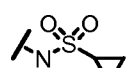
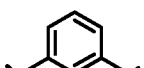
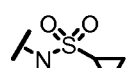
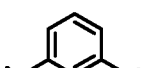
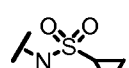
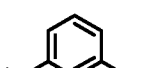
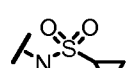
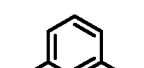
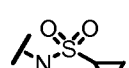
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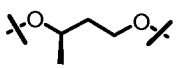
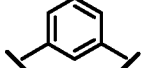
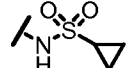
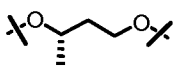
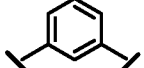
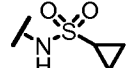
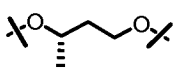
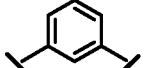
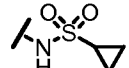
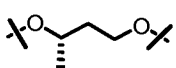
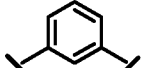
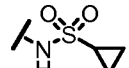
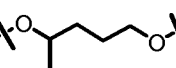
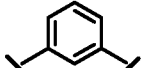
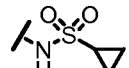
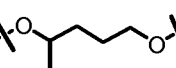
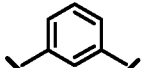
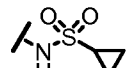
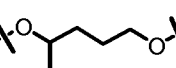
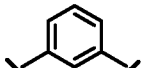
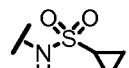
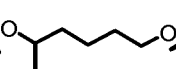
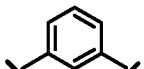
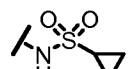
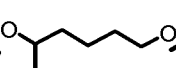
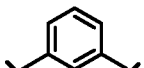
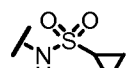
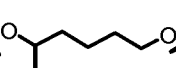
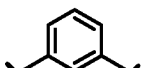
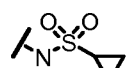
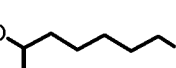
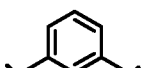
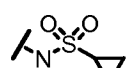
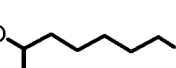
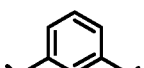
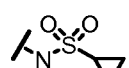
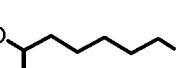
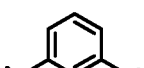
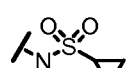
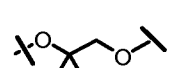
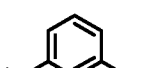
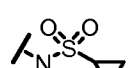
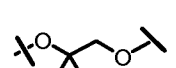
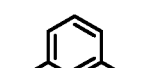
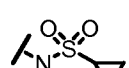
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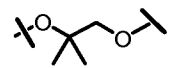
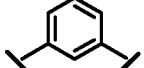
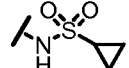
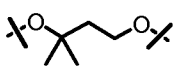
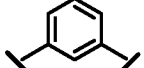
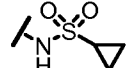
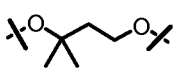
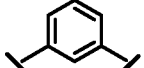
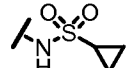
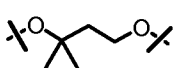
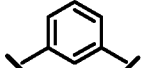
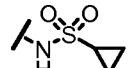
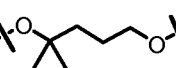
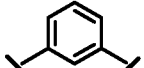
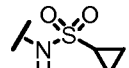
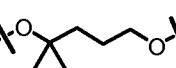
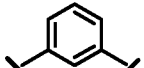
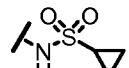
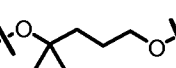
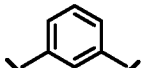
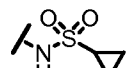
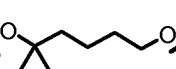
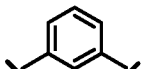
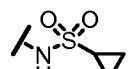
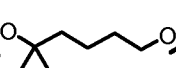
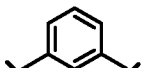
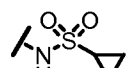
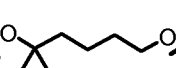
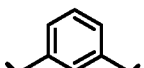
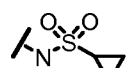
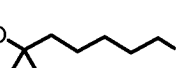
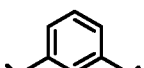
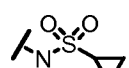
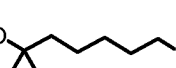
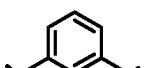
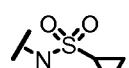
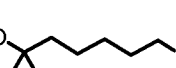
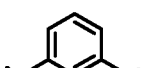
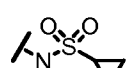
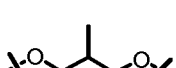
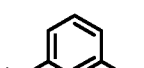
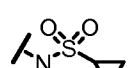
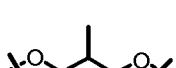
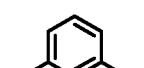
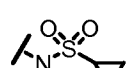
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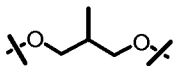
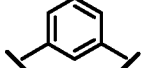
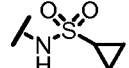
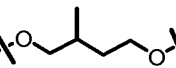
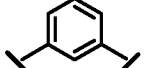
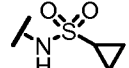
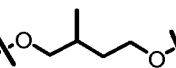
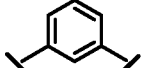
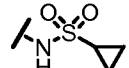
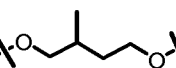
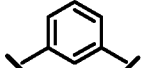
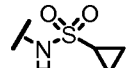
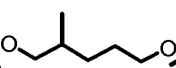
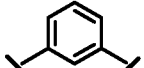
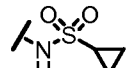
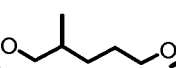
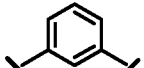
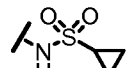
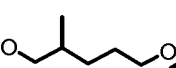
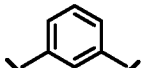
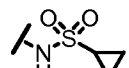
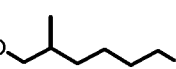
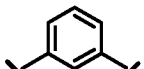
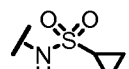
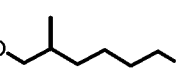
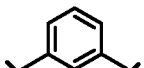
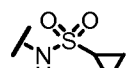
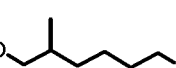
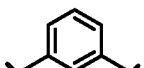
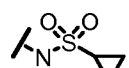
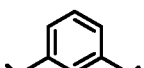
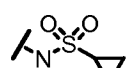
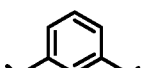
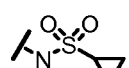
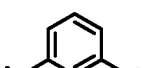
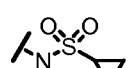
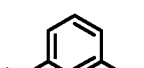
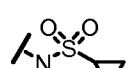
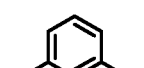
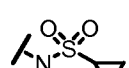
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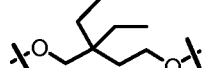
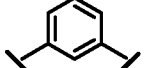
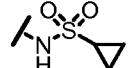
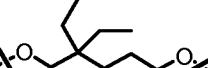
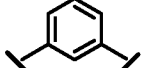
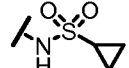
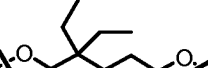
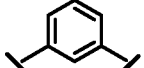
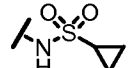
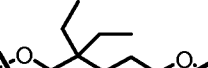
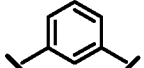
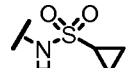
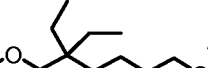
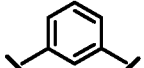
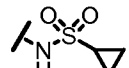
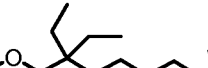
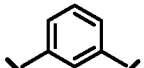
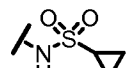
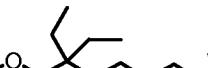
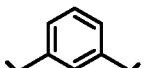
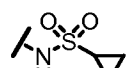
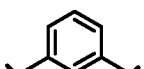
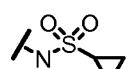
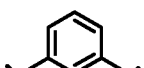
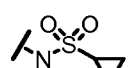
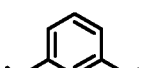
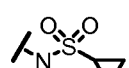
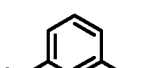
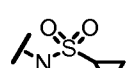
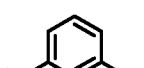
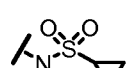
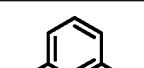
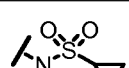
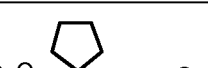
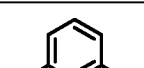
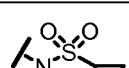
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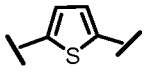
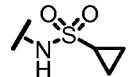
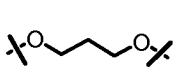
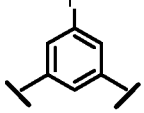
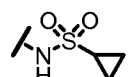
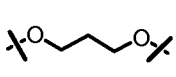
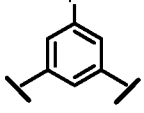
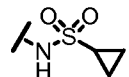
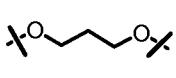
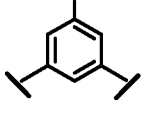
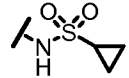
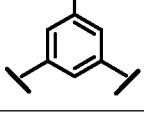
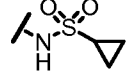
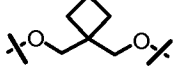
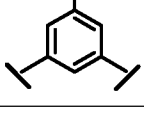
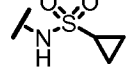
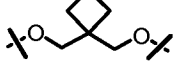
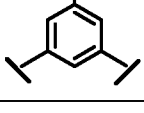
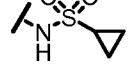
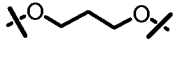
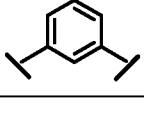
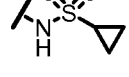
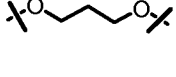
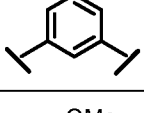
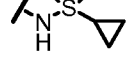
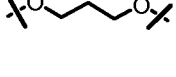
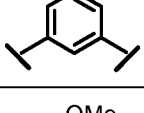
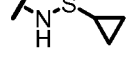
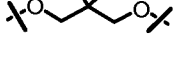
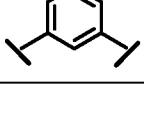
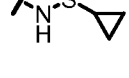
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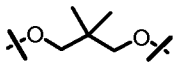
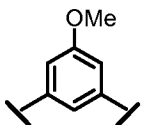
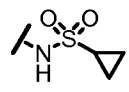
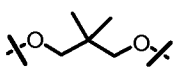
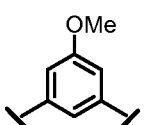
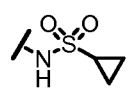
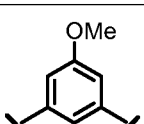
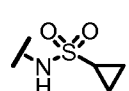
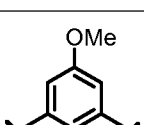
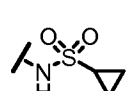
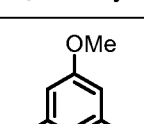
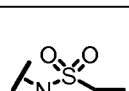
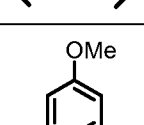
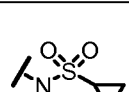
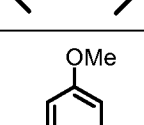
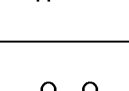
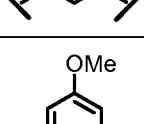
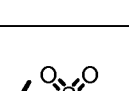
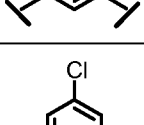
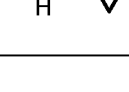
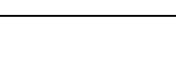
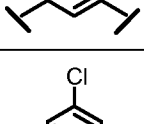
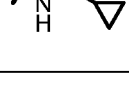
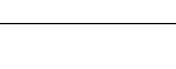
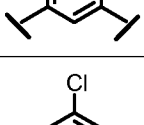
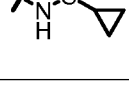
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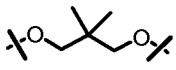
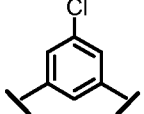
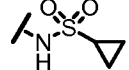
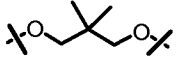
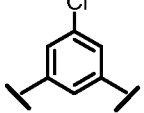
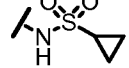
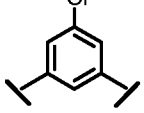
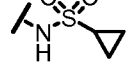
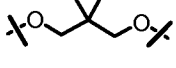
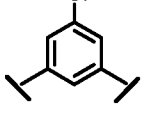
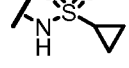
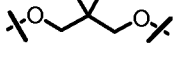
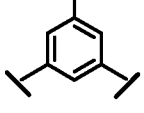
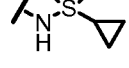
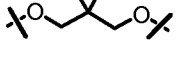
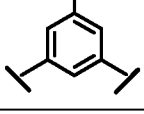
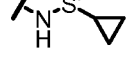
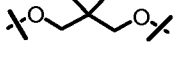
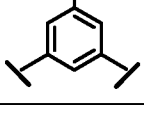
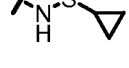
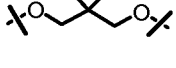
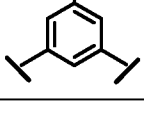
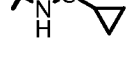
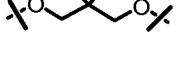
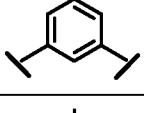
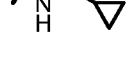
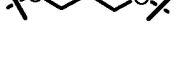
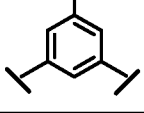
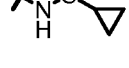
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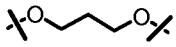
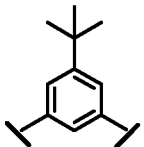
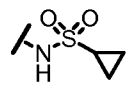
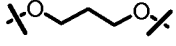
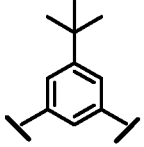
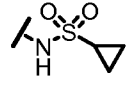
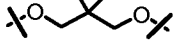
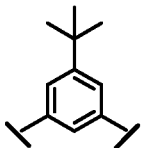
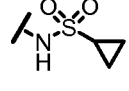
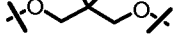
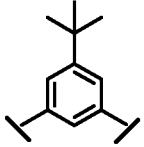
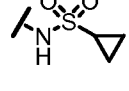
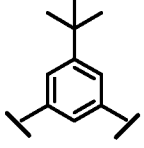
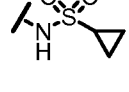
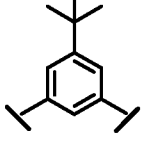
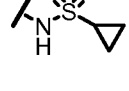
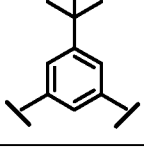
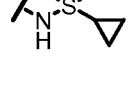
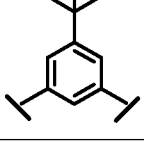
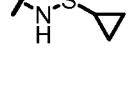
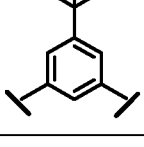
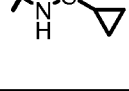
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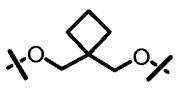
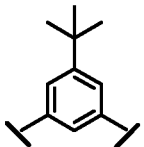
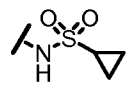
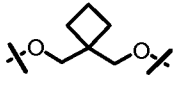
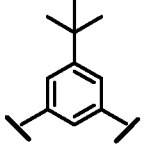
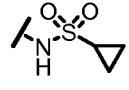
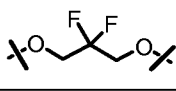
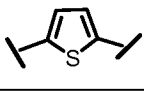
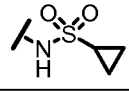
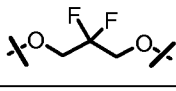
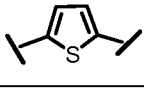
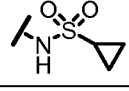
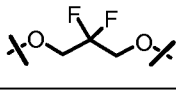
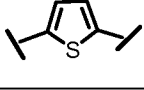
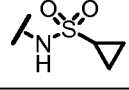
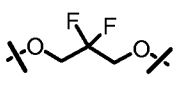
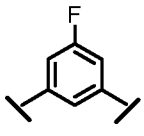
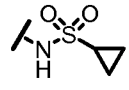
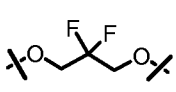
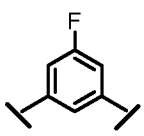
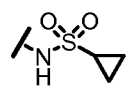
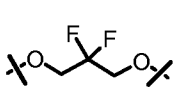
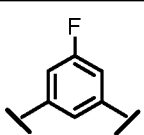
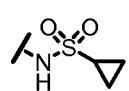
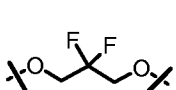
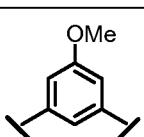
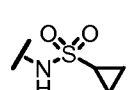
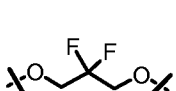
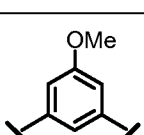
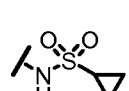
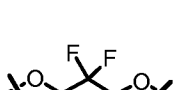
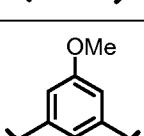
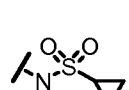
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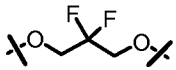
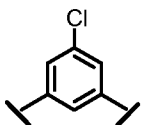
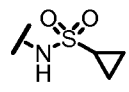
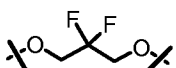
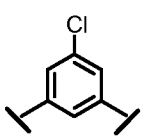
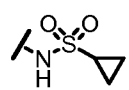
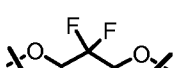
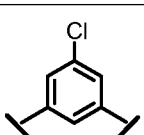
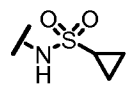
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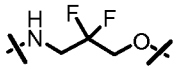
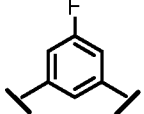
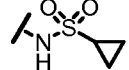
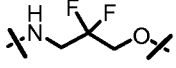
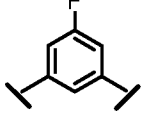
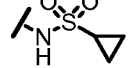
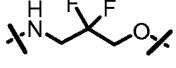
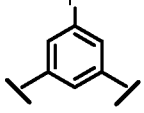
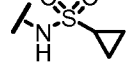
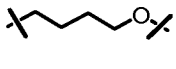
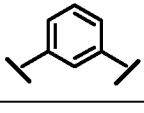
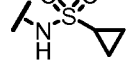
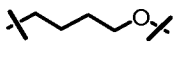
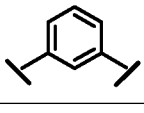
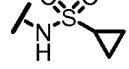
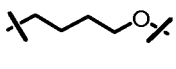
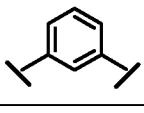
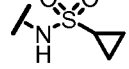
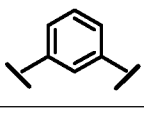
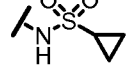
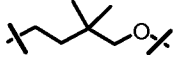
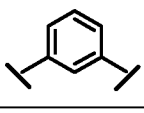
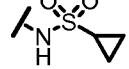
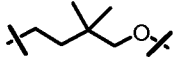
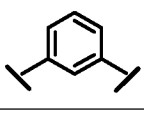
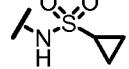
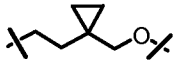
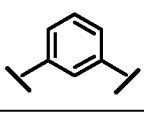
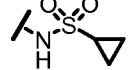
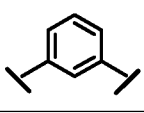
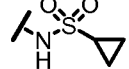
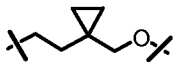
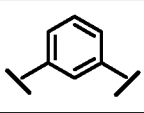
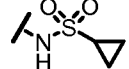
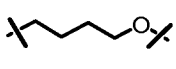
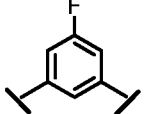
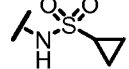
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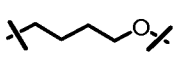
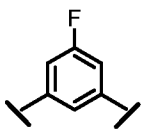
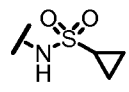
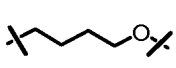
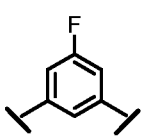
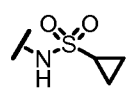
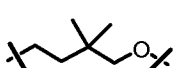
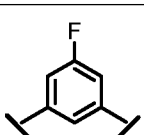
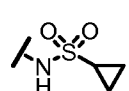
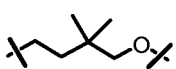
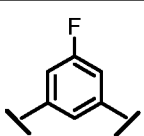
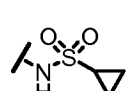
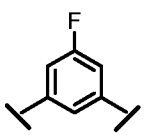
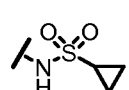
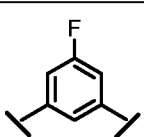
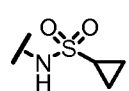
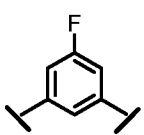
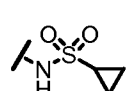
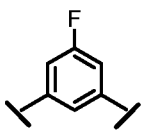
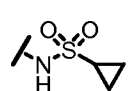
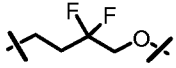
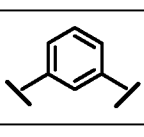
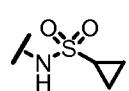
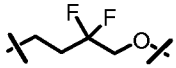
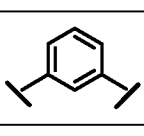
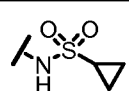
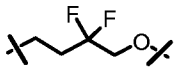
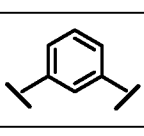
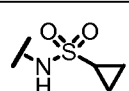
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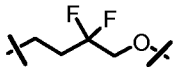
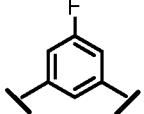
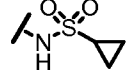
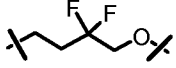
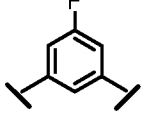
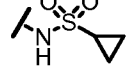
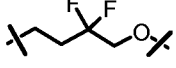
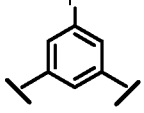
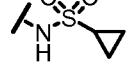
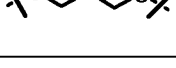
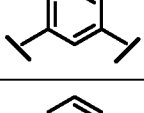
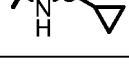
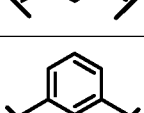
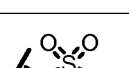
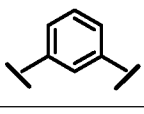
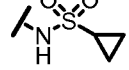
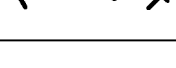
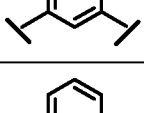
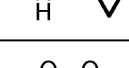
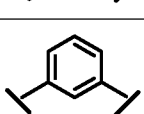
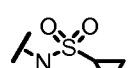
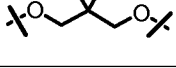
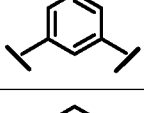
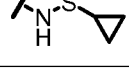
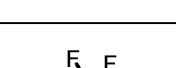
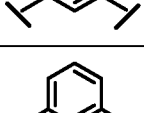
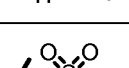
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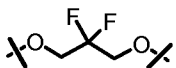
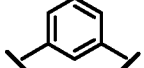
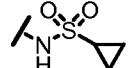
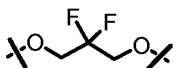
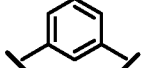
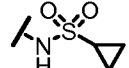
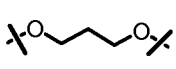
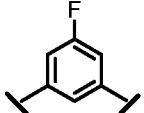
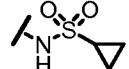
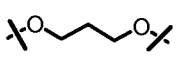
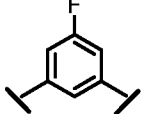
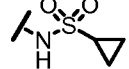
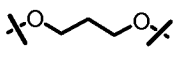
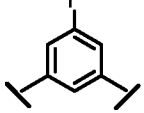
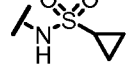
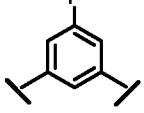
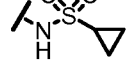
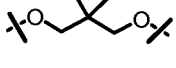
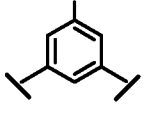
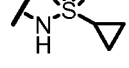
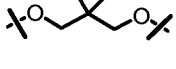
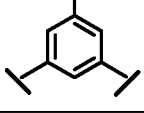
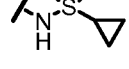
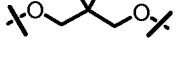
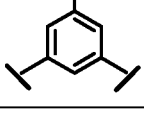
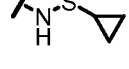
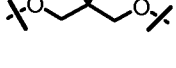
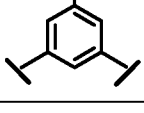
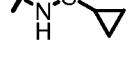
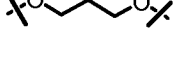
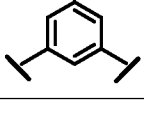
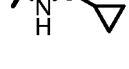
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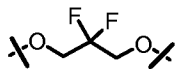
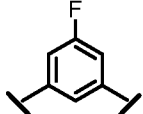
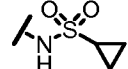
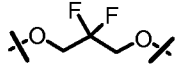
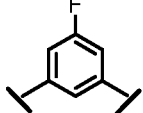
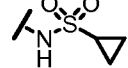
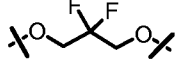
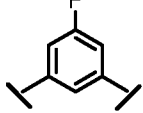
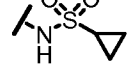
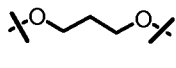
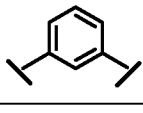
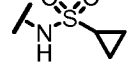
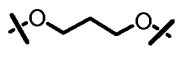
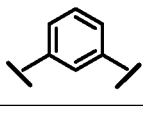
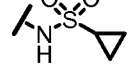
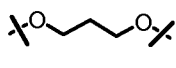
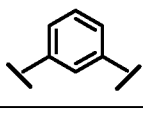
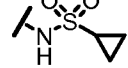
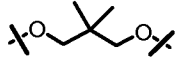
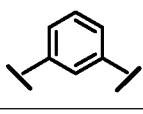
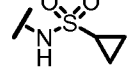
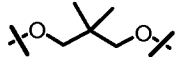
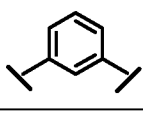
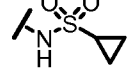
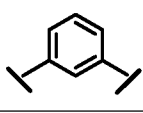
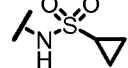
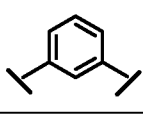
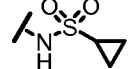
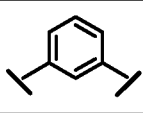
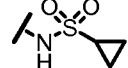
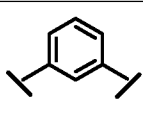
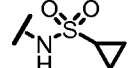
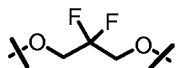
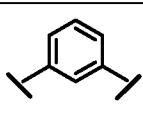
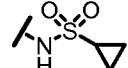
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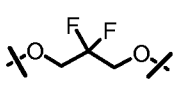
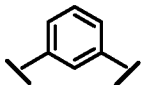
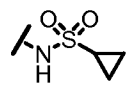
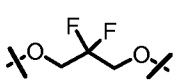
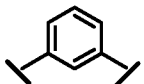
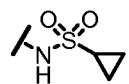
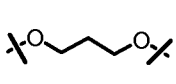
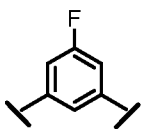
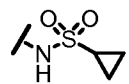
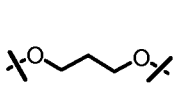
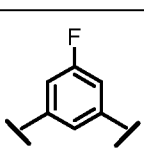
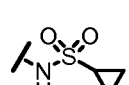
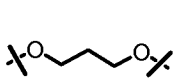
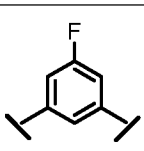
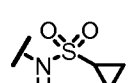
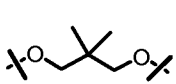
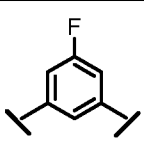
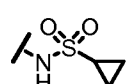
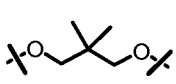
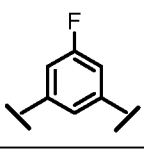
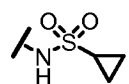
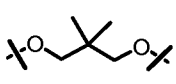
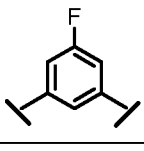
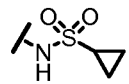
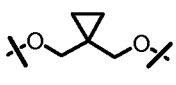
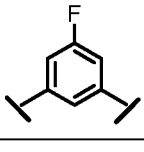
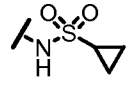
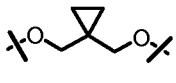
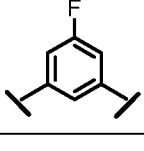
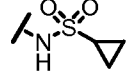
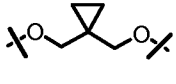
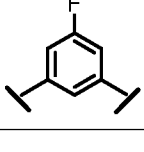
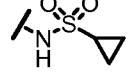
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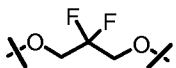
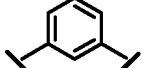
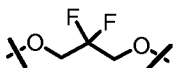
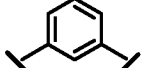
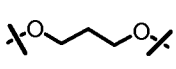
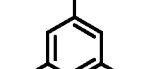
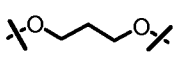
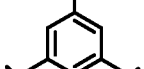
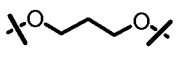
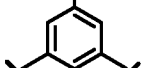
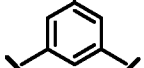
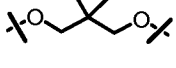
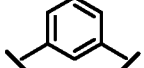
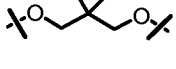
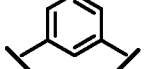
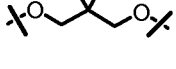
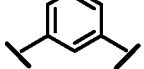
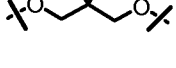
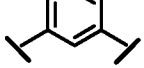
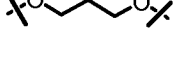
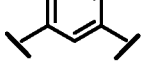
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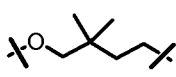
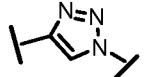
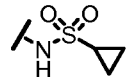
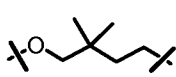
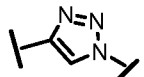
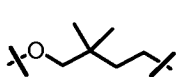
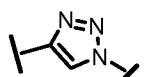
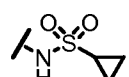
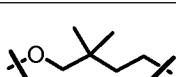
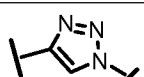
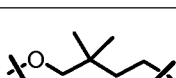
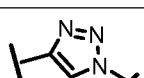
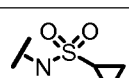
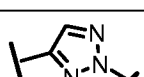
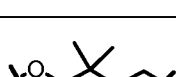
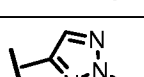
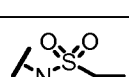
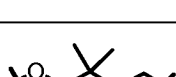
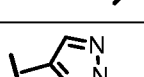
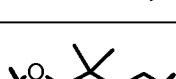
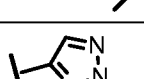
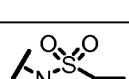
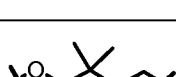
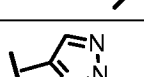
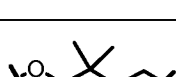
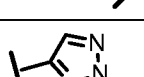
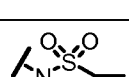
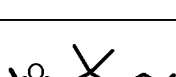
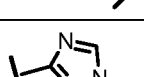
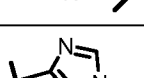
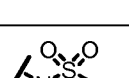
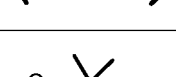
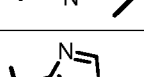
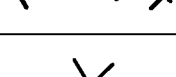
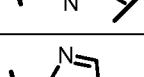
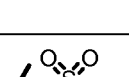
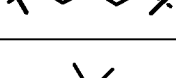
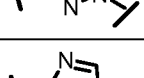
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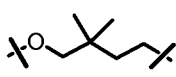
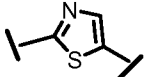
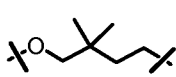
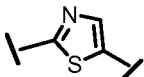
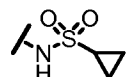
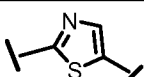
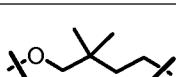
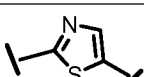
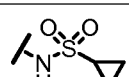
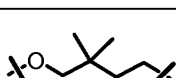
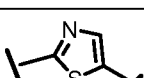
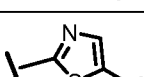
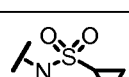
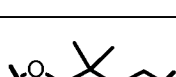
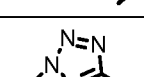
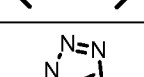
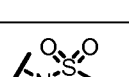
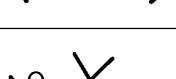
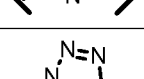
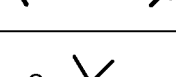
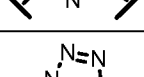
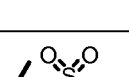
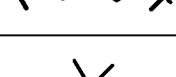
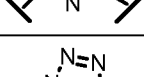
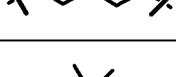
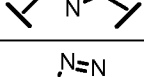
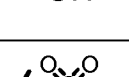
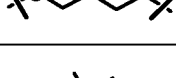
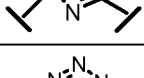
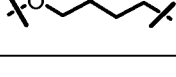
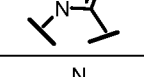
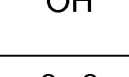
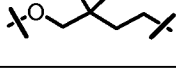
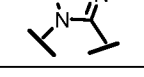
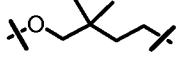
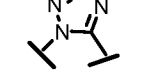
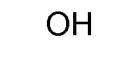
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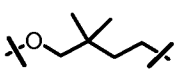
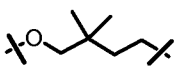
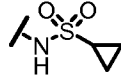
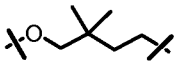
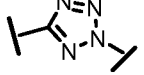
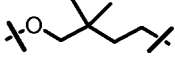
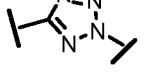
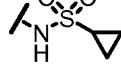
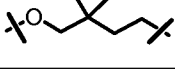
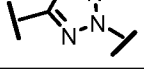
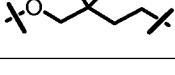
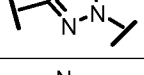
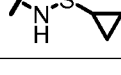
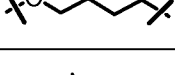
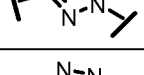
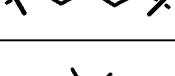
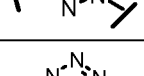
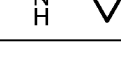
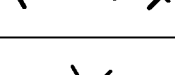
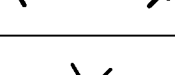
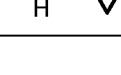
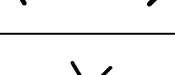
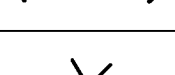
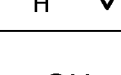
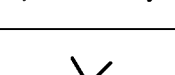
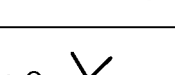
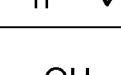
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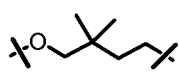
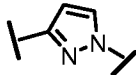
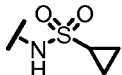
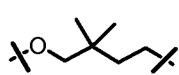
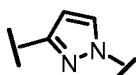
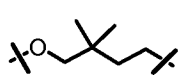
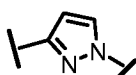
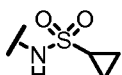
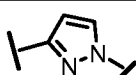
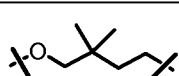
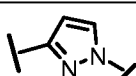
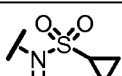
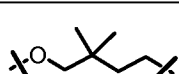
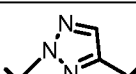
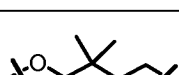
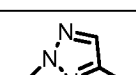
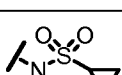
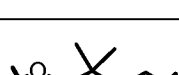
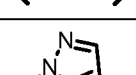
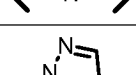
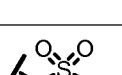
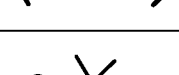
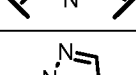
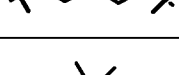
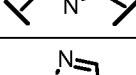
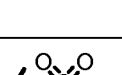
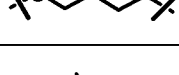
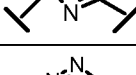
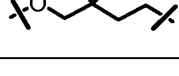
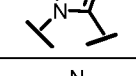
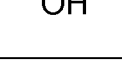
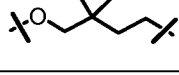
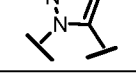
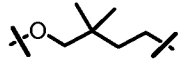
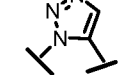
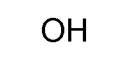
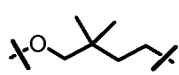
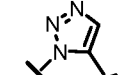
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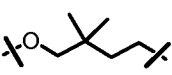
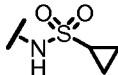
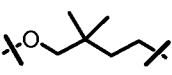
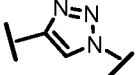
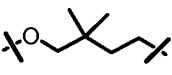
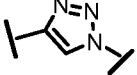
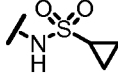
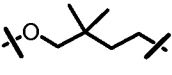
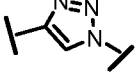
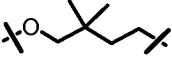
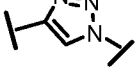
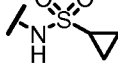
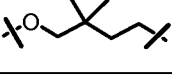
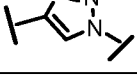
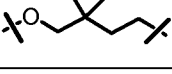
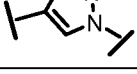
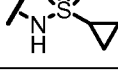
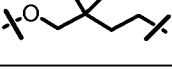
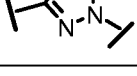
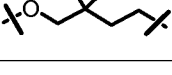
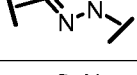
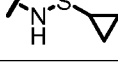
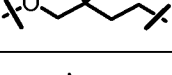
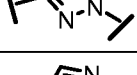
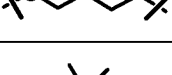
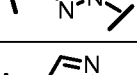
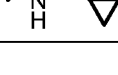
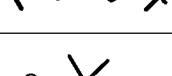
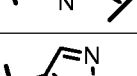
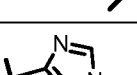
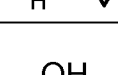
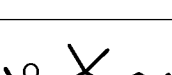
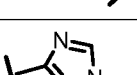
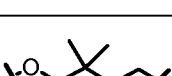
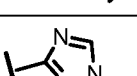
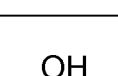
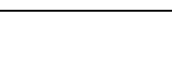
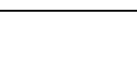
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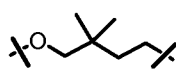
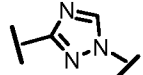
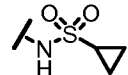
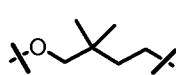
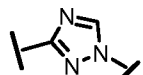
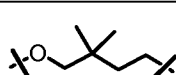
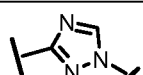
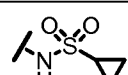
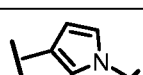
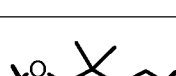
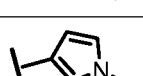
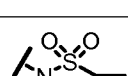
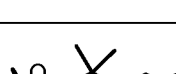
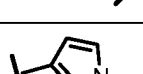
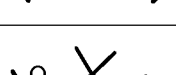
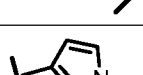
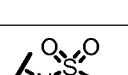
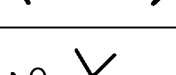
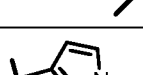
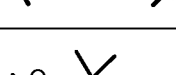
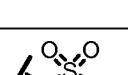
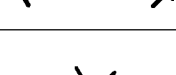
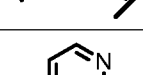
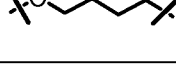
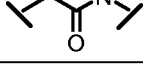
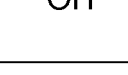
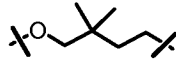
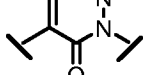
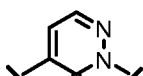
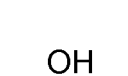
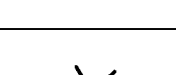
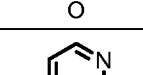
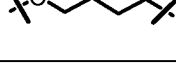
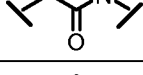
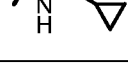
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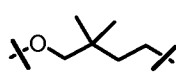
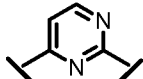
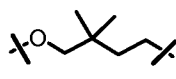
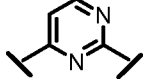
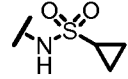
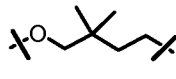
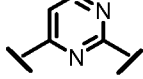
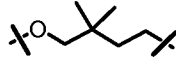
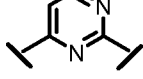
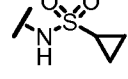
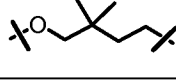
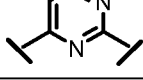
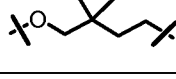
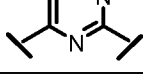
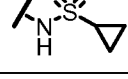
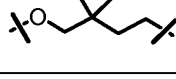
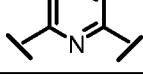
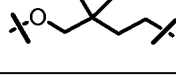
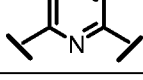
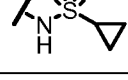
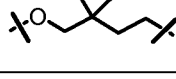
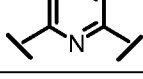
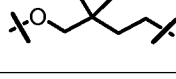
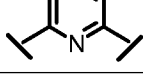
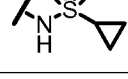
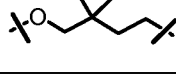
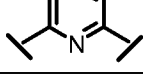
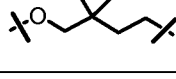
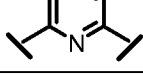
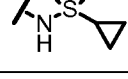
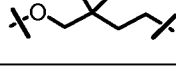
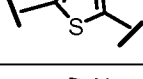
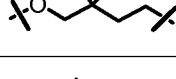
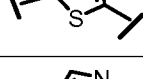
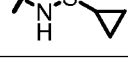
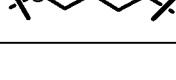
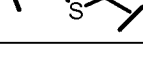
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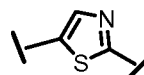
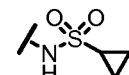
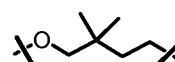
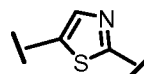
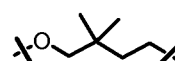
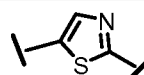
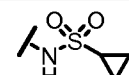
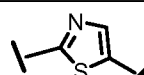
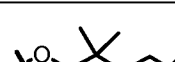
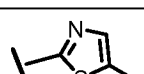
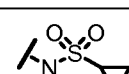
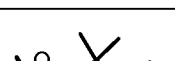
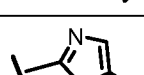
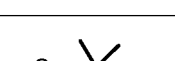
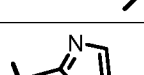
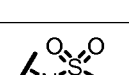
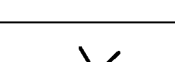
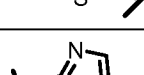
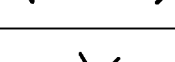
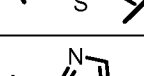
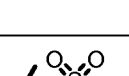
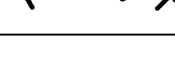
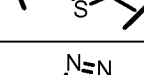
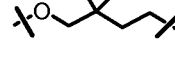
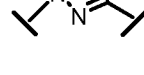
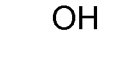
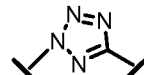
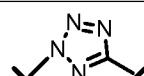
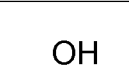
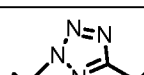
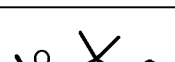
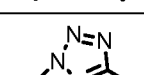
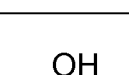
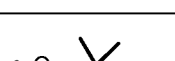
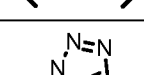
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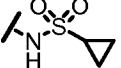
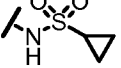
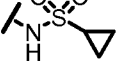
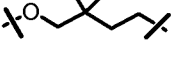
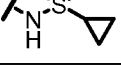
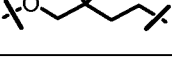
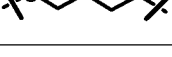
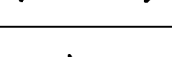
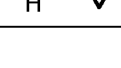
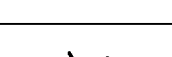
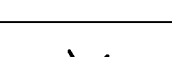
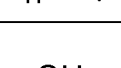
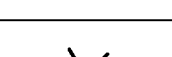
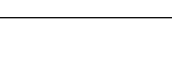
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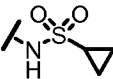
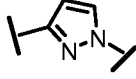
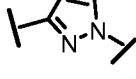
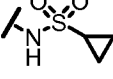
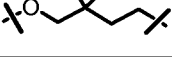
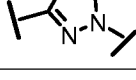
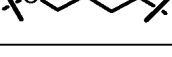
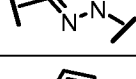
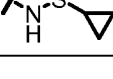
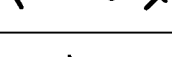
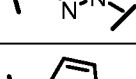
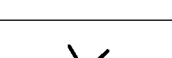
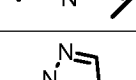
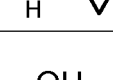
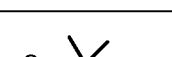
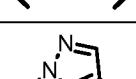
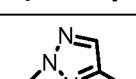
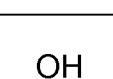
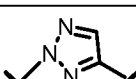
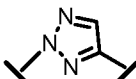
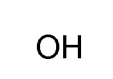
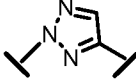
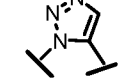
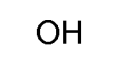
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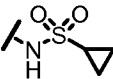
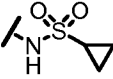
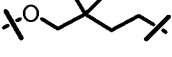
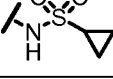
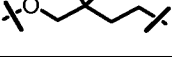
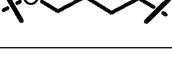
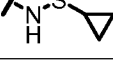
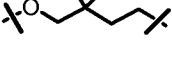
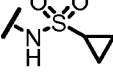
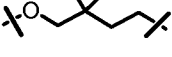
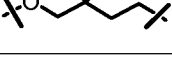
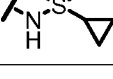
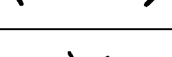
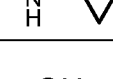
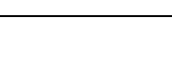
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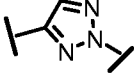
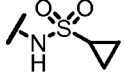
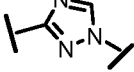
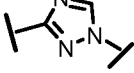
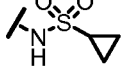
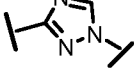
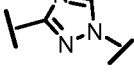
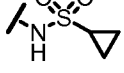
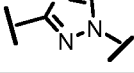
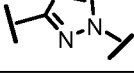
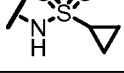
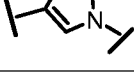
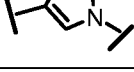
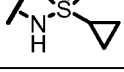
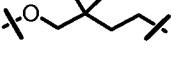
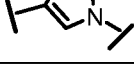
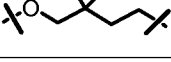
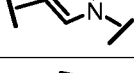
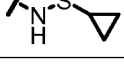
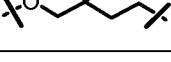
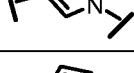
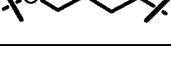
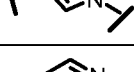
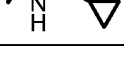
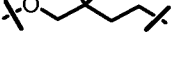
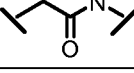
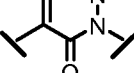
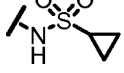
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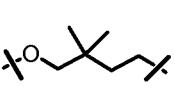
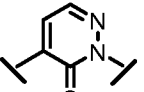
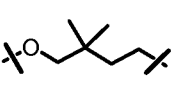
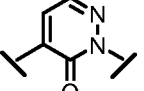
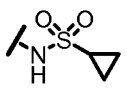
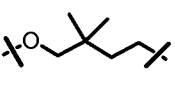
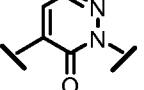
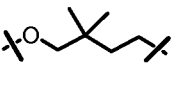
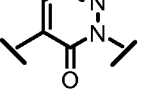
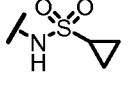
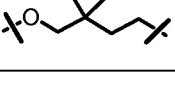
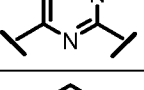
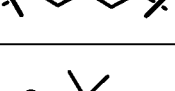
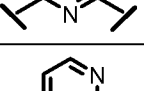
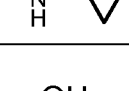
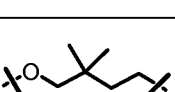
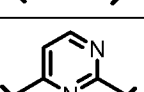
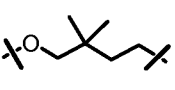
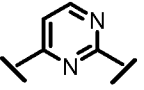
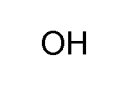
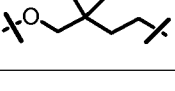
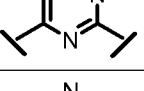
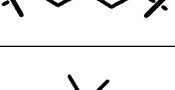
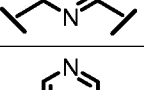
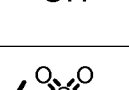
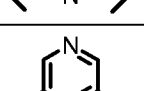
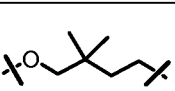
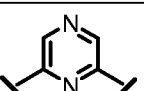
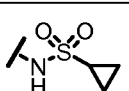
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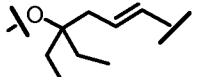
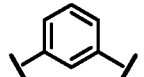
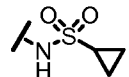
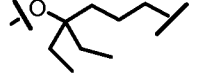
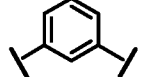
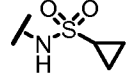
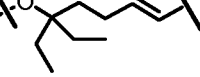
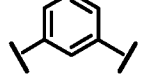
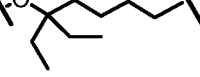
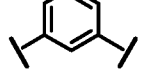
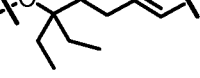
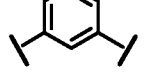
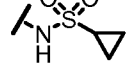
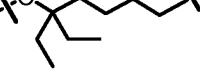
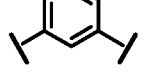
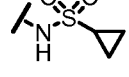
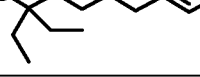
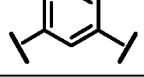
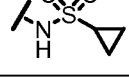
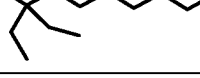
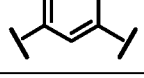
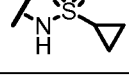
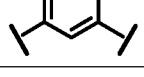
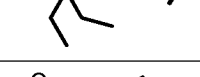
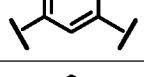
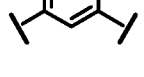
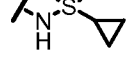
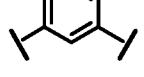
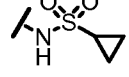
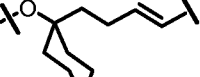
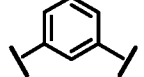
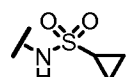
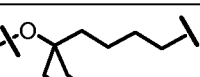
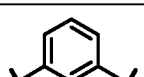
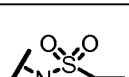
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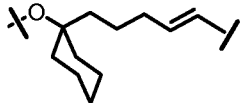
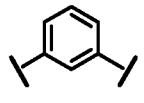
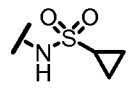
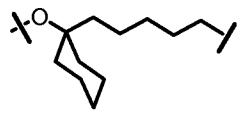
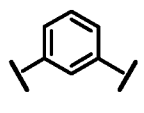
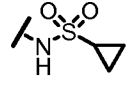
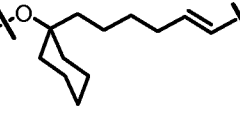
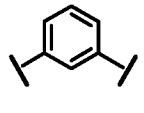
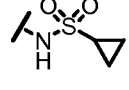
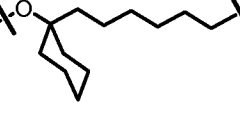
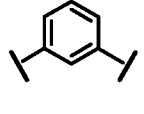
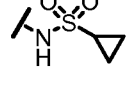
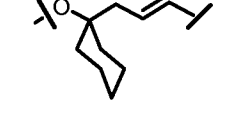
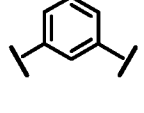
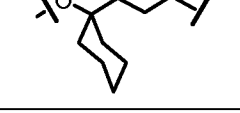
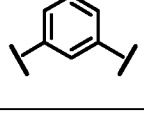
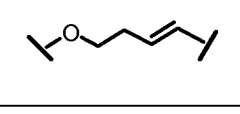
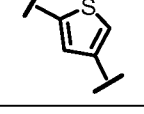
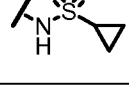
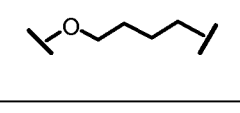
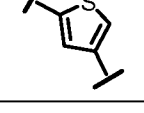
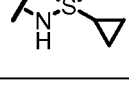
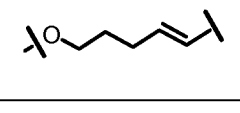
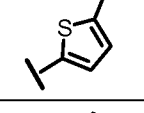
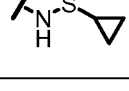
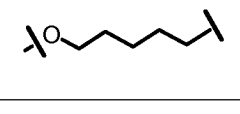
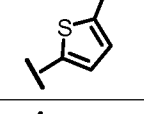
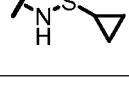
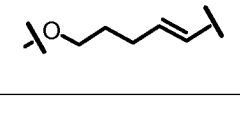
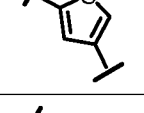
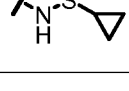
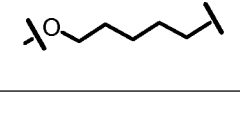
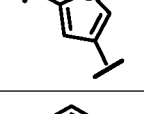
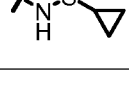
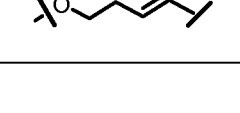
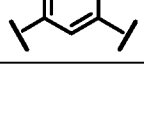
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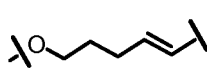
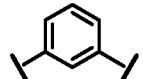
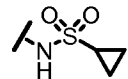
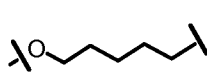
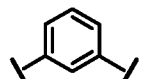
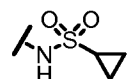
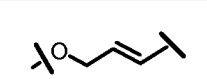
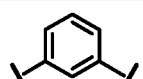
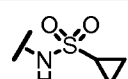
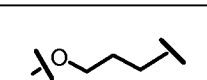
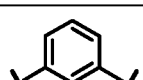
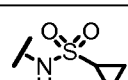
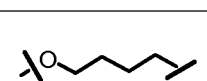
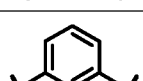
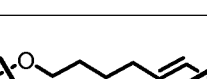
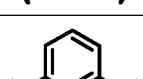
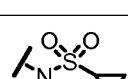
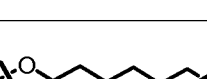
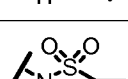
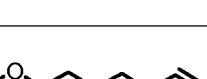
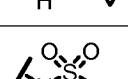
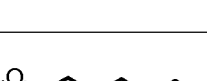
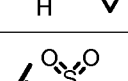
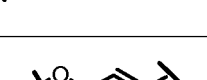
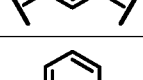
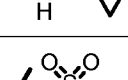
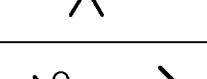
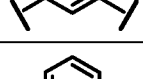
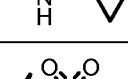
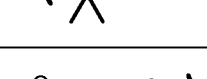
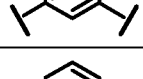
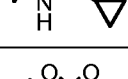
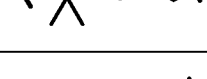
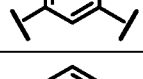
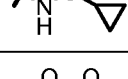
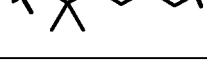
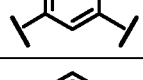
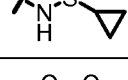
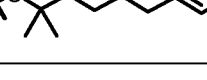
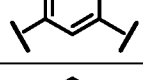
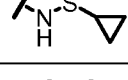
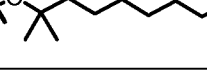
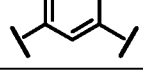
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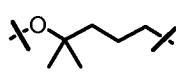
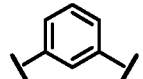
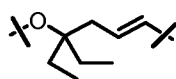
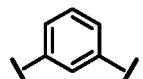
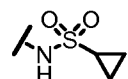
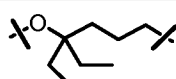
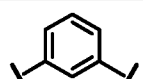
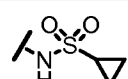
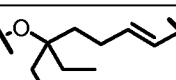
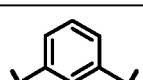
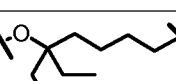
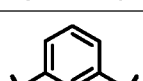
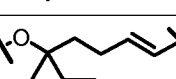
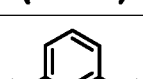
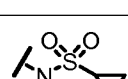
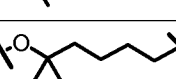
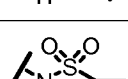
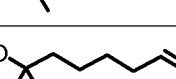
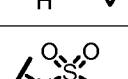
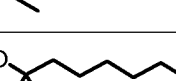
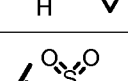
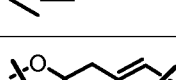
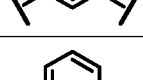
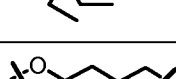
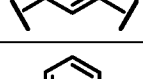
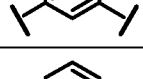
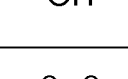
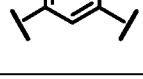
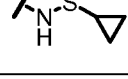
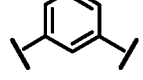
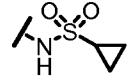
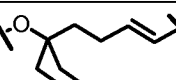
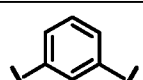
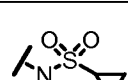
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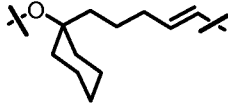
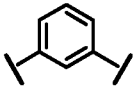
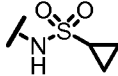
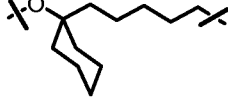
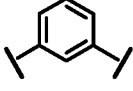
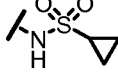
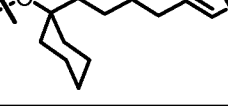
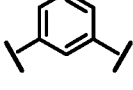
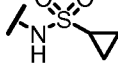
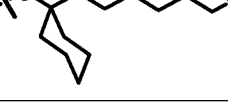
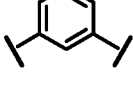
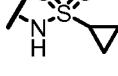
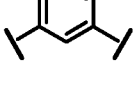
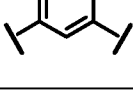
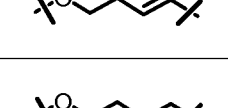
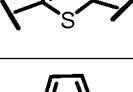
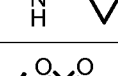
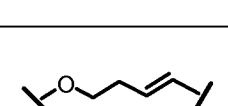
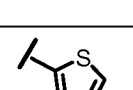
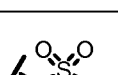
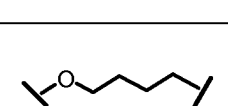
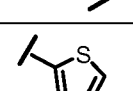
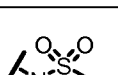
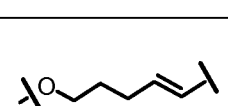
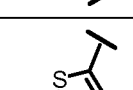
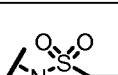
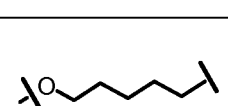
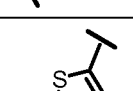
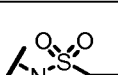
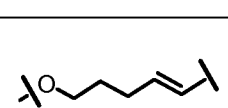
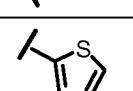
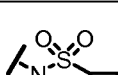
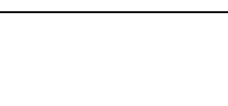
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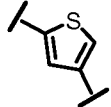
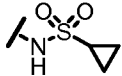
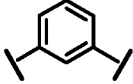
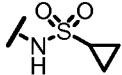
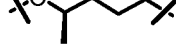
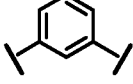
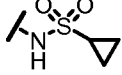
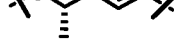
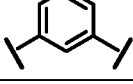
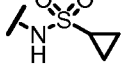
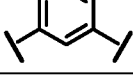
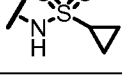
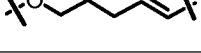
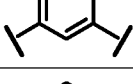
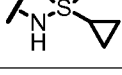
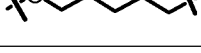
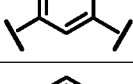
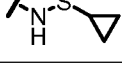
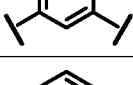
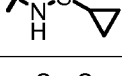
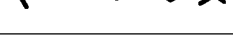
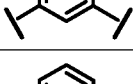
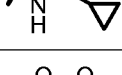
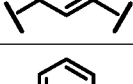
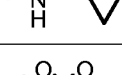
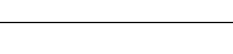
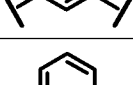
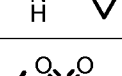
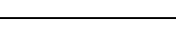
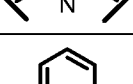
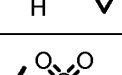
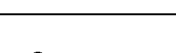
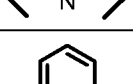
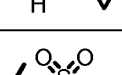
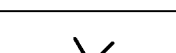
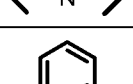
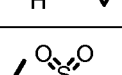
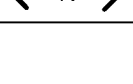
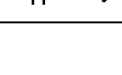
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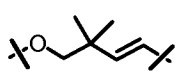
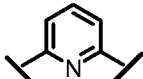
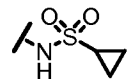
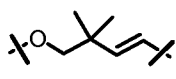
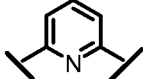
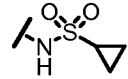
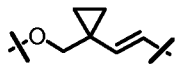
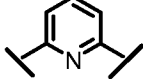
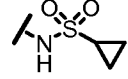
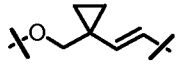
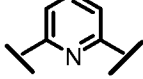
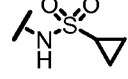
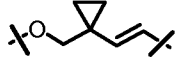
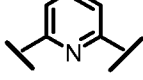
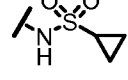
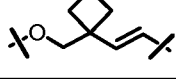
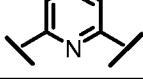
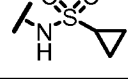
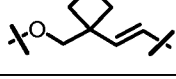
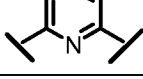
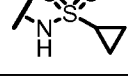
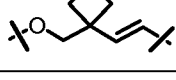
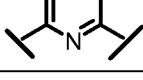
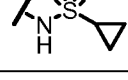
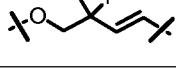
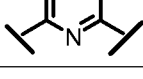
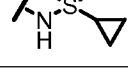
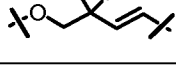
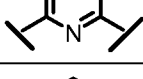
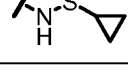
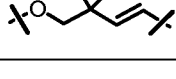
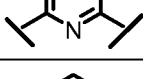
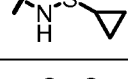
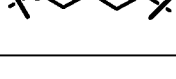
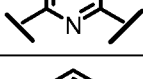
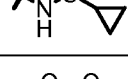
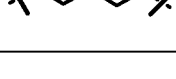
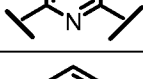
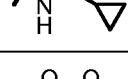
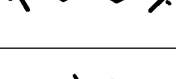
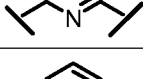
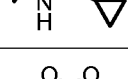
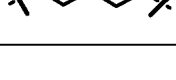
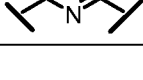
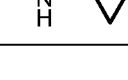
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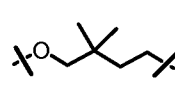
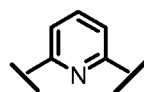
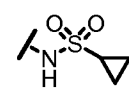
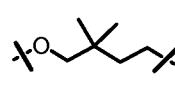
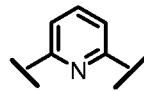
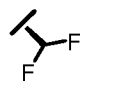
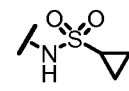
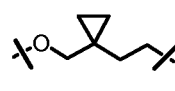
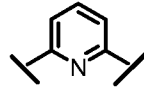
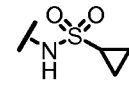
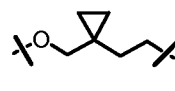
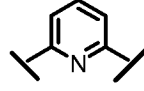
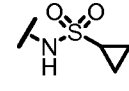
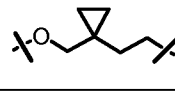
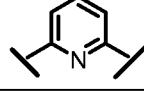
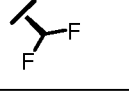
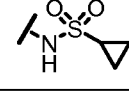
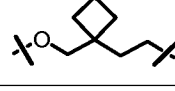
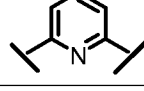
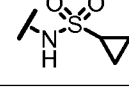
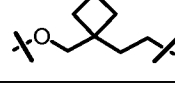
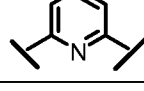
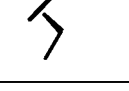
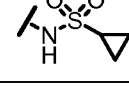
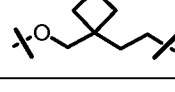
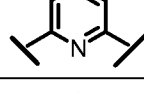
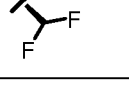
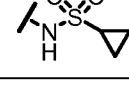
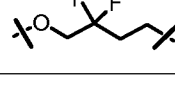
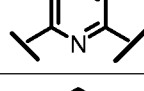
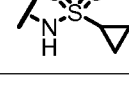
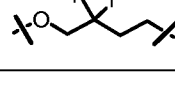
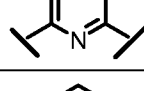
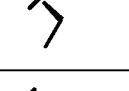
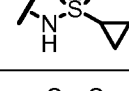
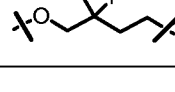
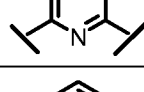
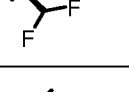
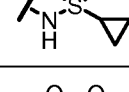
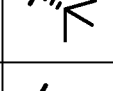
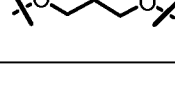
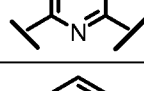
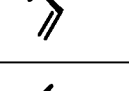
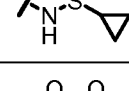
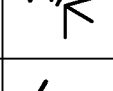
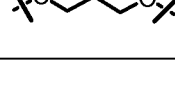
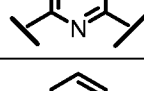
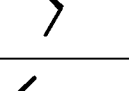
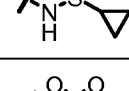
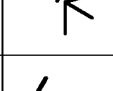
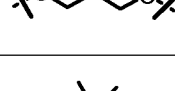
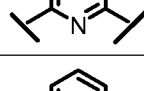
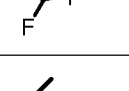
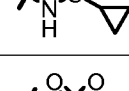
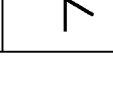
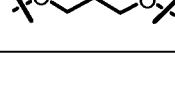
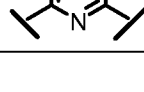
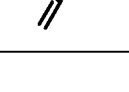
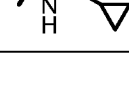
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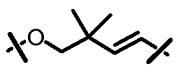
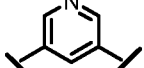
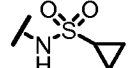
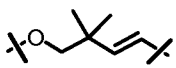
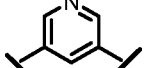
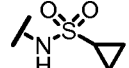
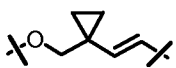
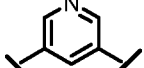
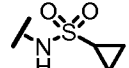
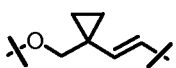
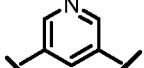
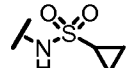
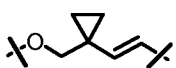
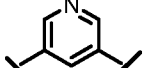
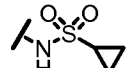
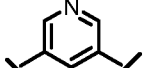
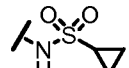
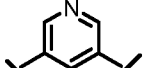
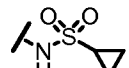
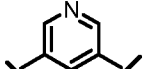
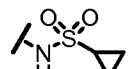
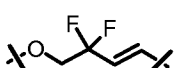
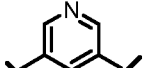
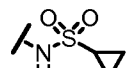
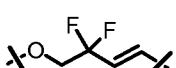
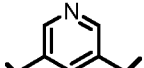
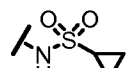
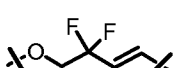
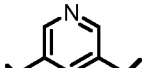
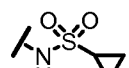
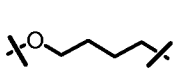
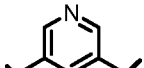
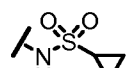
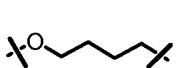
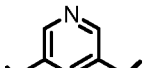
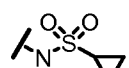
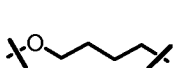
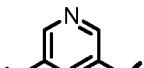
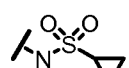
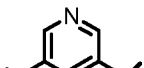
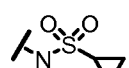
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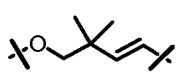
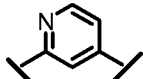
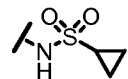
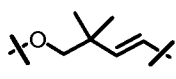
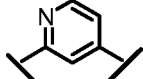
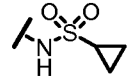
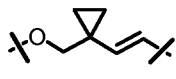
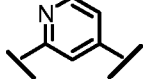
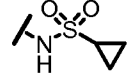
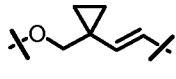
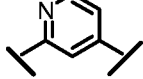
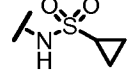
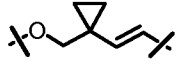
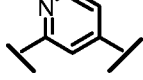
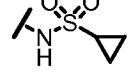
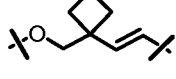
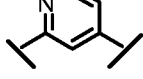
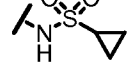
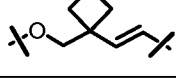
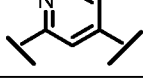
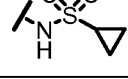
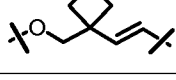
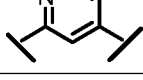
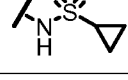
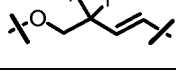
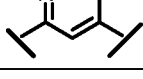
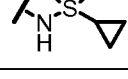
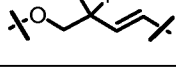
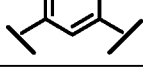
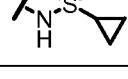
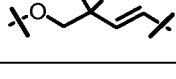
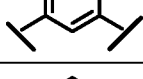
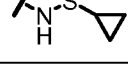
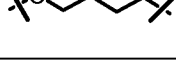
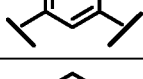
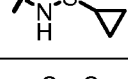
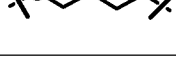
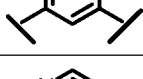
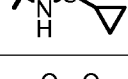
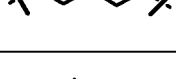
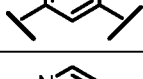
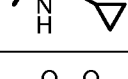
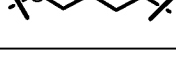
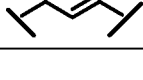
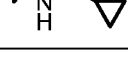
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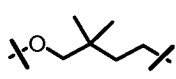
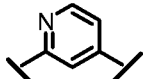
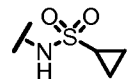
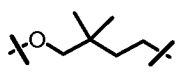
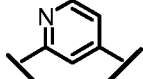
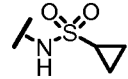
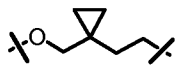
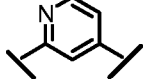
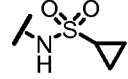
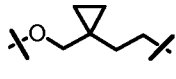
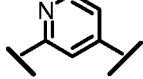
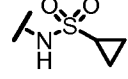
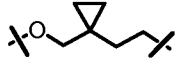
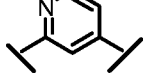
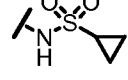
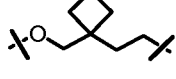
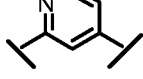
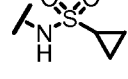
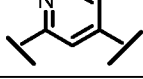
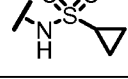
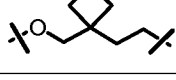
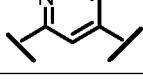
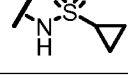
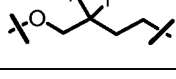
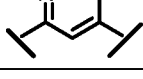
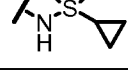
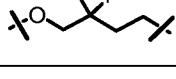
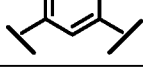
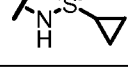
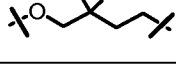
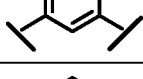
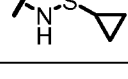
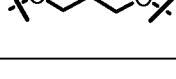
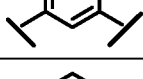
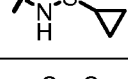
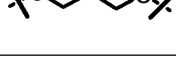
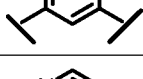
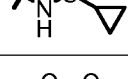
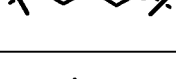
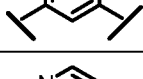
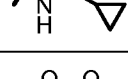
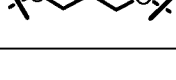
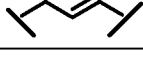
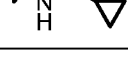
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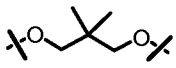
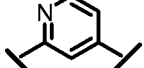
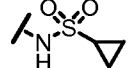
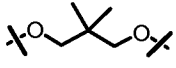
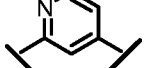
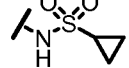
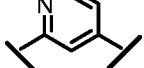
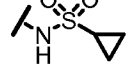
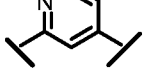
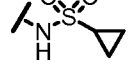
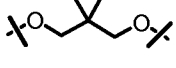
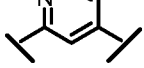
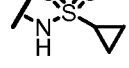
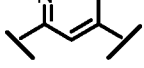
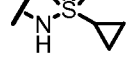
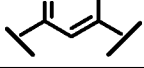
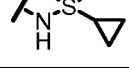
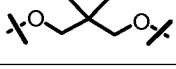
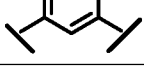
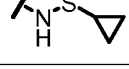
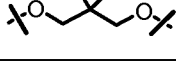
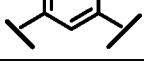
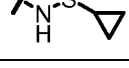
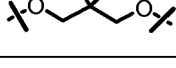
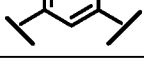
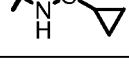
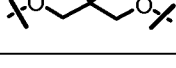
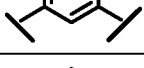
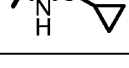
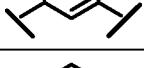
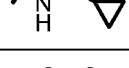
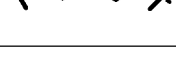
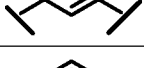
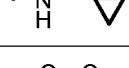
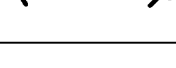
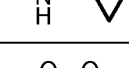
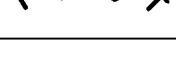
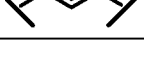
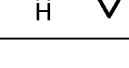
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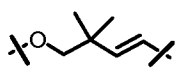
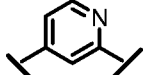
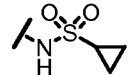
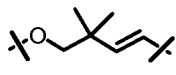
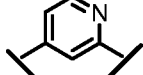
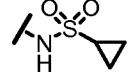
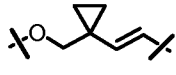
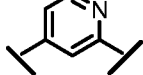
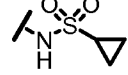
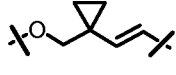
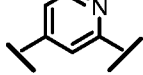
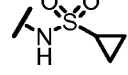
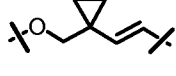
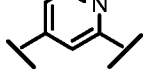
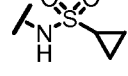
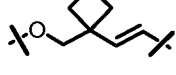
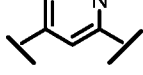
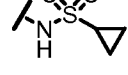
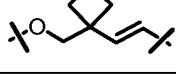
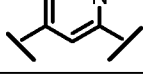
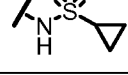
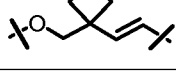
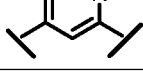
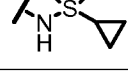
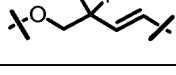
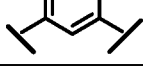
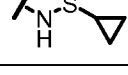
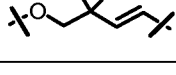
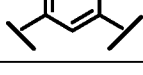
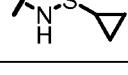
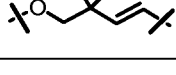
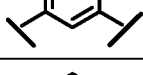
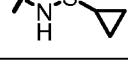
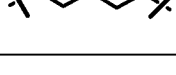
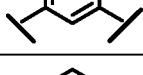
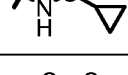
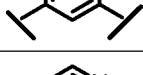
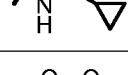
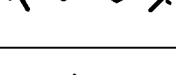
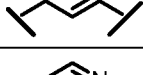
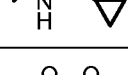
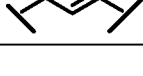
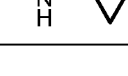
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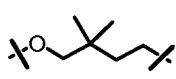
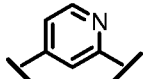
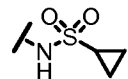
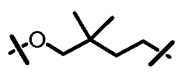
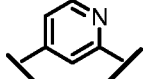
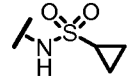
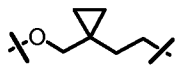
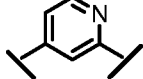
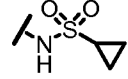
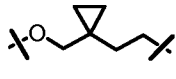
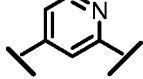
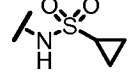
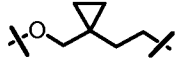
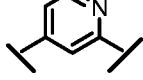
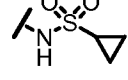
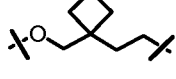
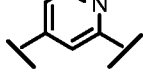
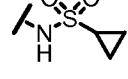
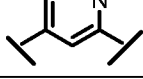
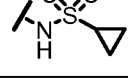
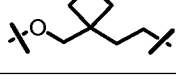
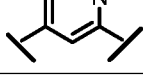
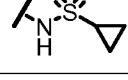
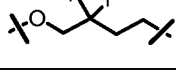
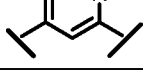
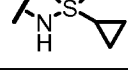
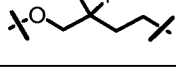
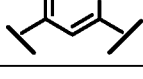
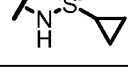
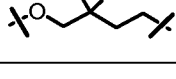
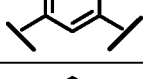
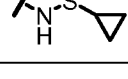
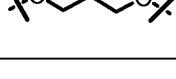
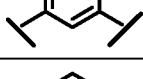
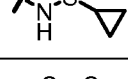
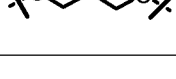
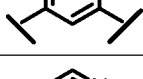
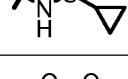
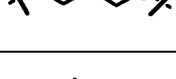
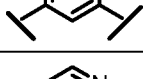
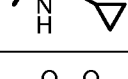
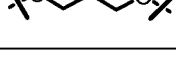
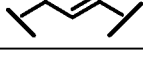
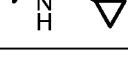
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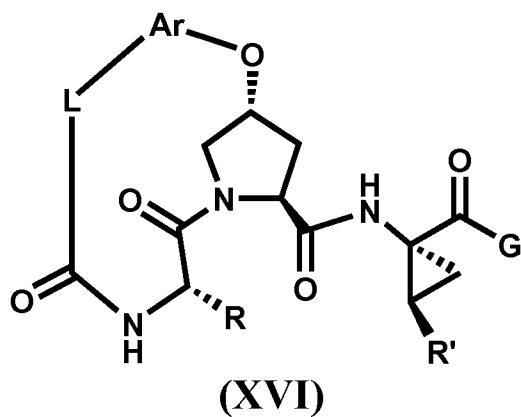
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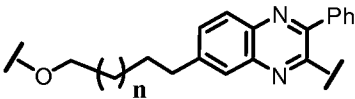
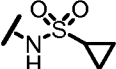
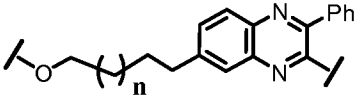
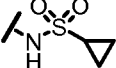
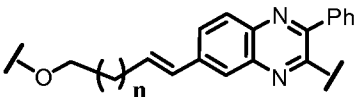
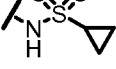
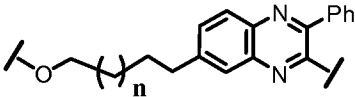
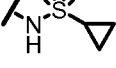
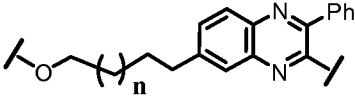
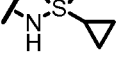
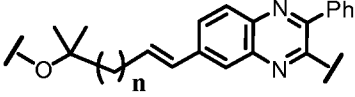
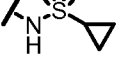
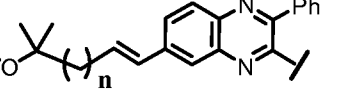
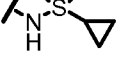
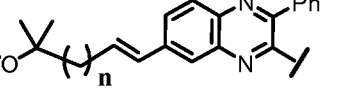
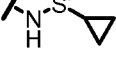
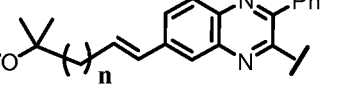
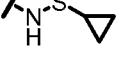
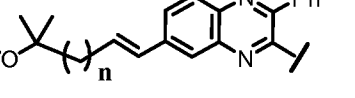
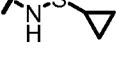
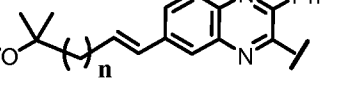
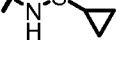
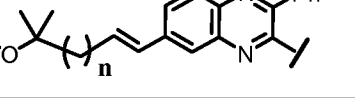
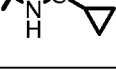
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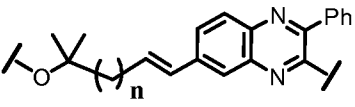
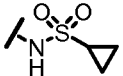
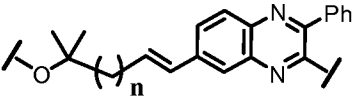
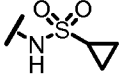
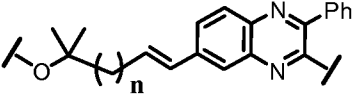
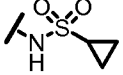
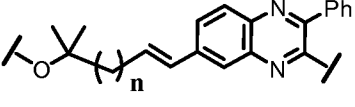
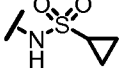
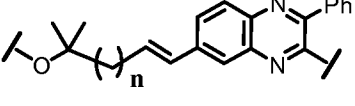
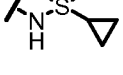
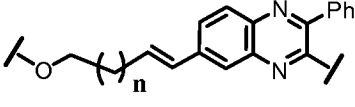
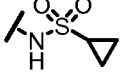
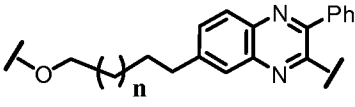
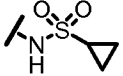
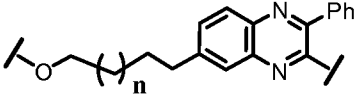
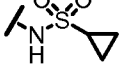
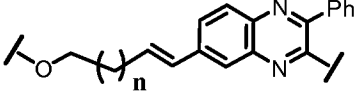
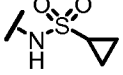
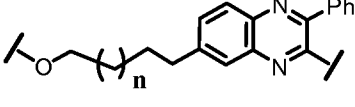
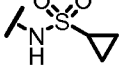
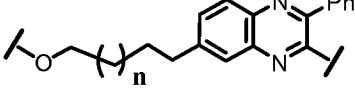
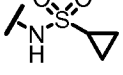
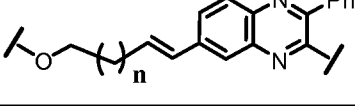
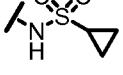
Representative compounds of the invention also include, but are not limited to, the following compounds (Table 2) according to Formula XVI wherein R, L-Ar, n, R' and G are delineated for each example in Table 2.

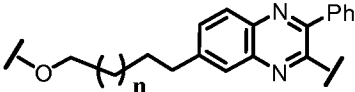
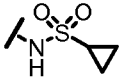
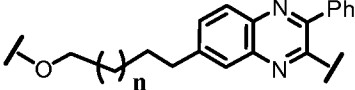
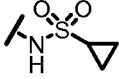
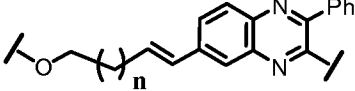
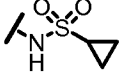
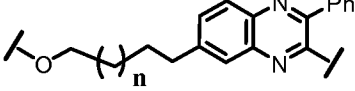
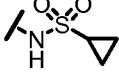
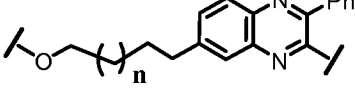
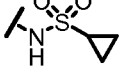
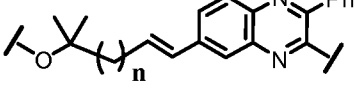
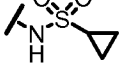
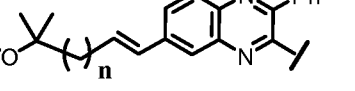
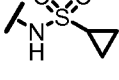
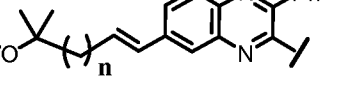
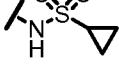
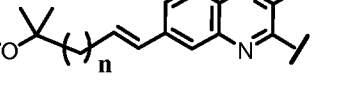
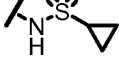
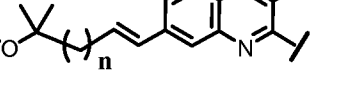
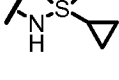
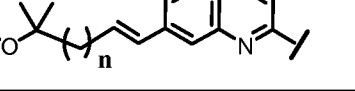
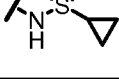
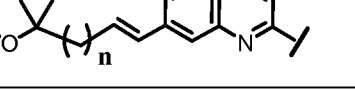
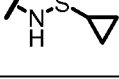
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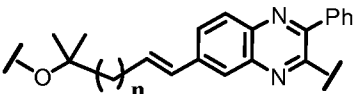
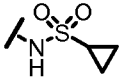
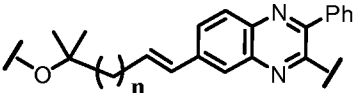
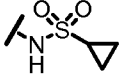
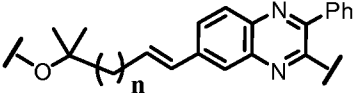
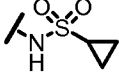
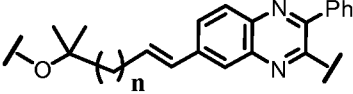
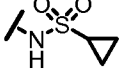
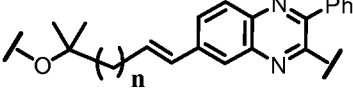
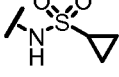
**TABLE 2**

Example#	R	L-Ar	n	R'	G
1507.			4		
1508.			4		
1509.			4		
1510.			3		
1511.			3		
1512.			3		
1513.			2		

1514.			2		
1515.			2		
1516.			1		
1517.			1		
1518.			1		
1519.			4		
1520.			4		
1521.			4		
1522.			3		
1523.			3		
1524.			3		
1525.			2		

1526.			2		
1527.			2		
1528.			1		
1529.			1		
1530.			1		
1531.			4		
1532.			4		
1533.			4		
1534.			3		
1535.			3		
1536.			3		
1537.			2		

1538.			2		
1539.			2		
1540.			1		
1541.			1		
1542.			1		
1543.			4		
1544.			4		
1545.			4		
1546.			3		
1547.			3		
1548.			3		
1549.			2		

1550.			2		
1551.			2		
1552.			1		
1553.			1		
1554.			1		

Representative compounds of the invention also include, but are not limited to, the following compounds (Table 3) according to Formula XVII wherein R, L-Ar, n and G are

5 delineated for each example in Table 3.

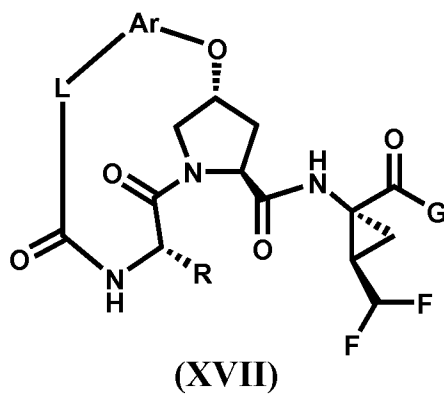
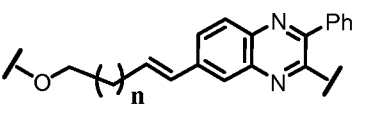
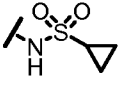
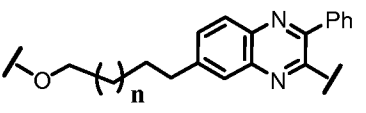
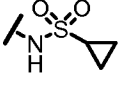
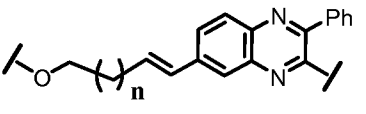
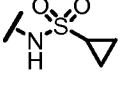
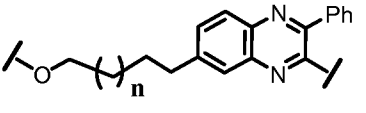
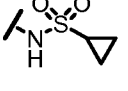
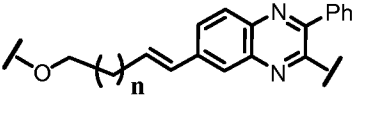
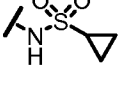
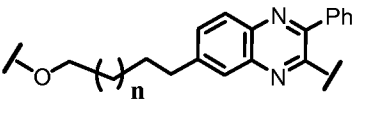
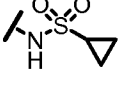
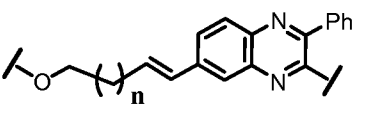
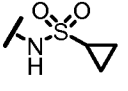
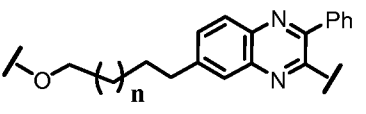
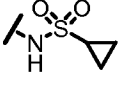
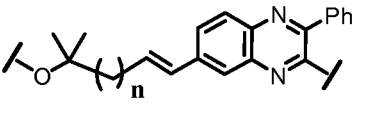
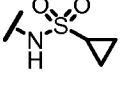
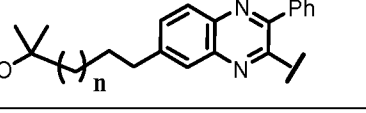
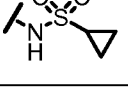
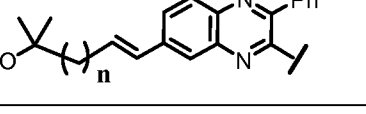
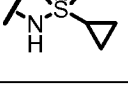
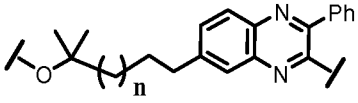
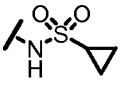
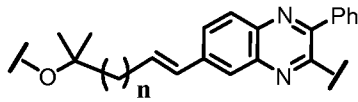
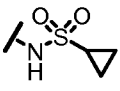
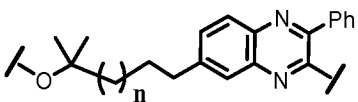
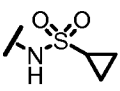
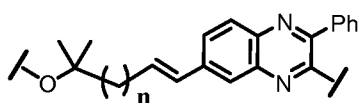
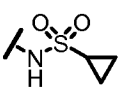
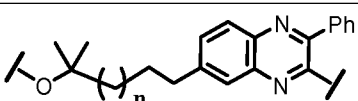
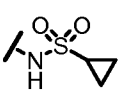
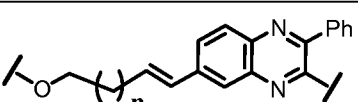
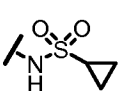
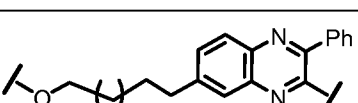
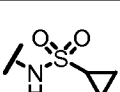
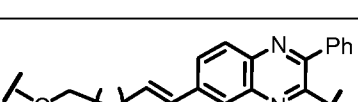
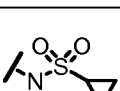
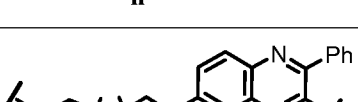
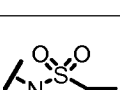
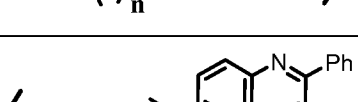
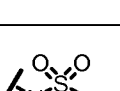
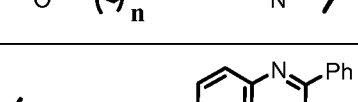
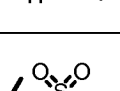
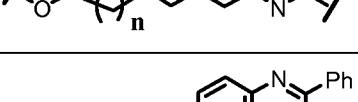
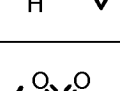
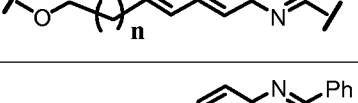
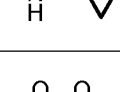
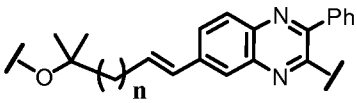
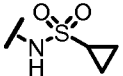
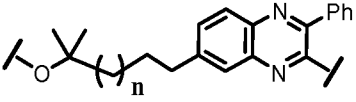
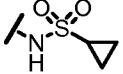
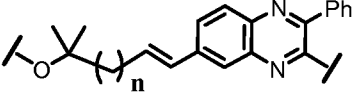
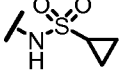
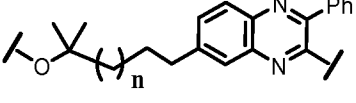
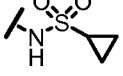
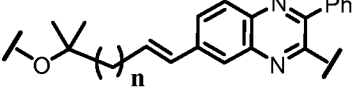
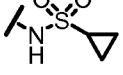
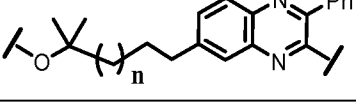
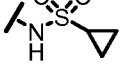
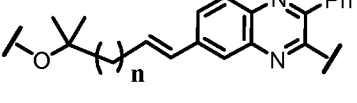
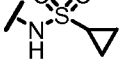
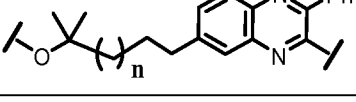
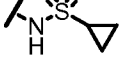


TABLE 3

Example #	R	L-Ar	n	G
1555.			4	
1556.			4	
1557.			3	
1558.			3	
1559.			2	
1560.			2	
1561.			1	
1562.			1	
1563.			4	
1564.			4	
1565.			3	

1566.			3	
1567.			2	
1568.			2	
1569.			1	
1570.			1	
1571.			4	
1572.			4	
1573.			3	
1574.			3	
1575.			2	
1576.			2	
1577.			1	
1578.			1	

1579.			4	
1580.			4	
1581.			3	
1582.			3	
1583.			2	
1584.			2	
1585.			1	
1586.			1	

The present invention also features pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, ester or prodrug thereof.

Compounds of the present invention can be administered as the sole active pharmaceutical agent, or used in combination with one or more agents to treat or prevent hepatitis C infections or the symptoms associated with HCV infection. Other agents to be administered in combination with a compound or combination of compounds of the invention include therapies for disease caused by HCV infection that suppresses HCV viral replication by direct or indirect mechanisms. These include agents such as host immune modulators (for example, interferon-alpha, pegylated interferon-alpha, interferon-beta,

interferon-gamma, CpG oligonucleotides and the like), or antiviral compounds that inhibit host cellular functions such as inosine monophosphate dehydrogenase (for example, ribavirin and the like). Also included are cytokines that modulate immune function. Also included are vaccines comprising HCV antigens or antigen adjuvant combinations directed against HCV.

5 Also included are agents that interact with host cellular components to block viral protein synthesis by inhibiting the internal ribosome entry site (IRES) initiated translation step of HCV viral replication or to block viral particle maturation and release with agents targeted toward the viroporin family of membrane proteins such as, for example, HCV P7 and the like. Other agents to be administered in combination with a compound of the present
10 invention include any agent or combination of agents that inhibit the replication of HCV by targeting proteins of the viral genome involved in the viral replication. These agents include but are not limited to other inhibitors of HCV RNA dependent RNA polymerase such as, for example, nucleoside type polymerase inhibitors described in WO01 90121(A2), or U.S. Pat. No. 6,348,587B1 or WO0160315 or WO0132153 or non-nucleoside inhibitors such as, for
15 example, benzimidazole polymerase inhibitors described in EP 1162196A1 or WO0204425 or inhibitors of HCV protease such as, for example, peptidomimetic type inhibitors such as BILN2061 and the like or inhibitors of HCV helicase.

Other agents to be administered in combination with a compound of the present invention include any agent or combination of agents that inhibit the replication of other
20 viruses for co-infected individuals. These agent include but are not limited to therapies for disease caused by hepatitis B (HBV) infection such as, for example, adefovir, lamivudine, and tenofovir or therapies for disease caused by human immunodeficiency virus (HIV) infection such as, for example, protease inhibitors: ritonavir, lopinavir, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, tipranavir, TMC-114, fosamprenavir; reverse
25 transcriptase inhibitors: zidovudine, lamivudine, didanosine, stavudine, tenofovir, zalcitabine, abacavir, efavirenz, nevirapine, delavirdine, TMC-125; integrase inhibitors: L-870812, S-1360, or entry inhibitors: enfuvirtide (T-20), T-1249.

Accordingly, one aspect of the invention is directed to a method for treating or preventing an infection caused by an RNA-containing virus comprising co-administering to a
30 patient in need of such treatment one or more agents selected from the group consisting of a host immune modulator and a second antiviral agent, or a combination thereof, with a

therapeutically effective amount of a compound or combination of compounds of the invention, or a pharmaceutically acceptable salt, stereoisomer, tautomer, prodrug, salt of a prodrug, or combination thereof. Examples of the host immune modulator are, but not limited to, interferon-alpha, pegylated-interferon-alpha, interferon-beta, interferon-gamma, a cytokine, a vaccine, and a vaccine comprising an antigen and an adjuvant, and said second antiviral agent inhibits replication of HCV either by inhibiting host cellular functions associated with viral replication or by targeting proteins of the viral genome.

Further aspect of the invention is directed to a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment an agent or combination of agents that treat or alleviate symptoms of HCV infection including cirrhosis and inflammation of the liver, with a therapeutically effective amount of a compound or combination of compounds of the invention, or a pharmaceutically acceptable salt, stereoisomer, tautomer, prodrug, salt of a prodrug, or combination thereof. Yet another aspect of the invention provides a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment one or more agents that treat patients for disease caused by hepatitis B (HBV) infection, with a therapeutically effective amount of a compound or a combination of compounds of the invention, or a pharmaceutically acceptable salt, stereoisomer, tautomer, prodrug, salt of a prodrug, or combination thereof. An agent that treats patients for disease caused by hepatitis B (HBV) infection may be for example, but not limited thereto, L- deoxythymidine, adefovir, lamivudine or tenfovir, or any combination thereof. Example of the RNA-containing virus includes, but not limited to, hepatitis C virus (HCV).

Another aspect of the invention provides a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment one or more agents that treat patients for disease caused by human immunodeficiency virus (HIV) infection, with a therapeutically effective amount of a compound or a combination of compounds of the invention, or a pharmaceutically acceptable salt, stereoisomer, tautomer, prodrug, salt of a prodrug, or combination thereof. The agent that treats patients for disease caused by human immunodeficiency virus (HIV) infection may include, but is not limited thereto, ritonavir, lopinavir, indinavir, nelfmavir,

saquinavir, amprenavir, atazanavir, tipranavir, TMC-114, fosamprenavir, zidovudine, lamivudine, didanosine, stavudine, tenofovir, zalcitabine, abacavir, efavirenz, nevirapine, delavirdine, TMC-125, L-870812, S-1360, enfuvirtide (T-20) or T-1249, or any combination thereof. Example of the RNA-containing virus includes, but not limited to, hepatitis C virus (HCV). In addition, the present invention provides the use of a compound or a combination of compounds of the invention, or a therapeutically acceptable salt form, stereoisomer, or tautomer, prodrug, salt of a prodrug, or combination thereof, and one or more agents selected from the group consisting of a host immune modulator and a second antiviral agent, or a combination thereof, to prepare a medicament for the treatment of an infection caused by an RNA-containing virus in a patient, particularly hepatitis C virus. Examples of the host immune modulator are, but not limited to, interferon-alpha, pegylated- interferon-alpha, interferon-beta, interferon-gamma, a cytokine, a vaccine, and a vaccine comprising an antigen and an adjuvant, and said second antiviral agent inhibits replication of HCV either by inhibiting host cellular functions associated with viral replication or by targeting proteins of the viral genome.

When used in the above or other treatments, combination of compound or compounds of the invention, together with one or more agents as defined herein above, can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt form, prodrug, salt of a prodrug, or combination thereof. Alternatively, such combination of therapeutic agents can be administered as a pharmaceutical composition containing a therapeutically effective amount of the compound or combination of compounds of interest, or their pharmaceutically acceptable salt form, prodrugs, or salts of the prodrug, in combination with one or more agents as defined hereinabove, and a pharmaceutically acceptable carrier. Such pharmaceutical compositions can be used for inhibiting the replication of an RNA-containing virus, particularly Hepatitis C virus (HCV), by contacting said virus with said pharmaceutical composition. In addition, such compositions are useful for the treatment or prevention of an infection caused by an RNA-containing virus, particularly Hepatitis C virus (HCV).

Hence, further aspect of the invention is directed to a method of treating or preventing infection caused by an RNA-containing virus, particularly a hepatitis C virus (HCV), comprising administering to a patient in need of such treatment a pharmaceutical

composition comprising a compound or combination of compounds of the invention or a pharmaceutically acceptable salt, stereoisomer, or tautomer, prodrug, salt of a prodrug, or combination thereof, one or more agents as defined hereinabove, and a pharmaceutically acceptable carrier.

5 When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or within a predetermined period of time, or the therapeutic agents can be given as a single unit dosage form.

 Antiviral agents contemplated for use in such combination therapy include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of a
10 virus in a mammal, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a mammal. Such agents can be selected from another anti-HCV agent; an HIV inhibitor; an HAV inhibitor; and an HBV inhibitor.

 Other anti-HCV agents include those agents that are effective for diminishing or
15 preventing the progression of hepatitis C related symptoms or disease. Such agents include but are not limited to immunomodulatory agents, inhibitors of HCV NS3 protease, other inhibitors of HCV polymerase, inhibitors of another target in the HCV life cycle and other anti-HCV agents, including but not limited to ribavirin, amantadine, levovirin and viremagine.

20 Immunomodulatory agents include those agents (compounds or biologicals) that are effective to enhance or potentiate the immune system response in a mammal.

 Immunomodulatory agents include, but are not limited to, inosine monophosphate dehydrogenase inhibitors such as VX-497 (merimepodib, Vertex Pharmaceuticals), class I interferons, class II interferons, consensus interferons, asialo-interferons pegylated
25 interferons and conjugated interferons, including but not limited to interferons conjugated with other proteins including but not limited to human albumin. Class I interferons are a group of interferons that all bind to receptor type I, including both naturally and synthetically produced class I interferons, while class II interferons all bind to receptor type II. Examples of class I interferons include, but are not limited to, [alpha]-, [beta]-, [delta]-, [omega]-, and
30 [tau]-interferons, while examples of class II interferons include, but are not limited to, [gamma]-interferons.

Inhibitors of HCV NS3 protease include agents (compounds or biologicals) that are effective to inhibit the function of HCV NS3 protease in a mammal. Inhibitors of HCV NS3 protease include, but are not limited to, those compounds described in WO 99/07733, WO 99/07734, WO 00/09558, WO 00/09543, WO 00/59929, WO 03/064416, WO 03/064455, 5 WO 03/064456, WO 2004/030670, WO 2004/037855, WO 2004/039833, WO 2004/101602, WO 2004/101605, WO 2004/103996, WO 2005/028501, WO 2005/070955, WO 2006/000085, WO 2006/007700 and WO 2006/007708 (all by Boehringer Ingelheim), WO 02/060926, WO 03/053349, WO03/099274, WO 03/099316, WO 2004/032827, WO 2004/043339, WO 2004/094452, WO 2005/046712, WO 2005/051410, WO 2005/054430 10 (all by BMS), WO 2004/072243, WO 2004/093798, WO 2004/113365, WO 2005/010029 (all by Enanta), WO 2005/037214 (Intermune) and WO 2005/051980 (Schering), and the candidates identified as VX-950, ITMN-191 and SCH 503034.

Inhibitors of HCV polymerase include agents (compounds or biologicals) that are effective to inhibit the function of an HCV polymerase. Such inhibitors include, but are not 15 limited to, non-nucleoside and nucleoside inhibitors of HCV NS5B polymerase. Examples of inhibitors of HCV polymerase include but are not limited to those compounds described in: WO 02/04425, WO 03/007945, WO 03/010140, WO 03/010141, WO 2004/064925, WO 2004/065367, WO 2005/080388 and WO 2006/007693 (all by Boehringer Ingelheim), WO 2005/049622 (Japan Tobacco), WO 2005/014543 (Japan Tobacco), WO 2005/012288 20 (Genelabs), WO 2004/087714 (IRBM), WO 03/101993 (Neogenesis), WO 03/026587 (BMS), WO 03/000254 (Japan Tobacco), and WO 01/47883 (Japan Tobacco), and the clinical candidates XTL-2125, HCV 796, R-1626 and NM 283.

Inhibitors of another target in the HCV life cycle include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of HCV other than 25 by inhibiting the function of the HCV NS3 protease. Such agents may interfere with either host or HCV viral mechanisms necessary for the formation and/or replication of HCV. Inhibitors of another target in the HCV life cycle include, but are not limited to, entry inhibitors, agents that inhibit a target selected from a helicase, a NS2/3 protease and an internal ribosome entry site (IRES) and agents that interfere with the function of other viral 30 targets including but not limited to an NS5A protein and an NS4B protein.

It can occur that a patient may be co-infected with hepatitis C virus and one or more

other viruses, including but not limited to human immunodeficiency virus (HIV), hepatitis A virus (HAV) and hepatitis B virus (HBV). Thus also contemplated is combination therapy to treat such co-infections by co-administering a compound according to the present invention with at least one of an HIV inhibitor, an HAV inhibitor and an HBV inhibitor.

5 According to yet another embodiment, the pharmaceutical compositions of the present invention may further comprise inhibitor(s) of other targets in the HCV life cycle, including, but not limited to, helicase, polymerase, metalloprotease, and internal ribosome entry site (IRES).

10 According to another embodiment, the pharmaceutical compositions of the present invention may further comprise another anti-viral, anti-bacterial, anti-fungal or anti-cancer agent, or an immune modulator, or another therapeutic agent.

15 According to still another embodiment, the present invention includes methods of treating viral infection such as, but not limited to, hepatitis C infections in a subject in need of such treatment by administering to said subject an effective amount of a compound of the present invention or a pharmaceutically acceptable salt, ester, or prodrug thereof.

 According to a further embodiment, the present invention includes methods of treating hepatitis C infections in a subject in need of such treatment by administering to said subject an anti-HCV virally effective amount or an inhibitory amount of a pharmaceutical composition of the present invention.

20 An additional embodiment of the present invention includes methods of treating biological samples by contacting the biological samples with the compounds of the present invention.

 Yet a further aspect of the present invention is a process of making any of the compounds delineated herein employing any of the synthetic means delineated herein.

25 The cytochrome P450 monooxygenase inhibitor used in this invention is expected to inhibit metabolism of the compounds of the invention. Therefore, the cytochrome P450 monooxygenase inhibitor would be in an amount effective to inhibit metabolism of the protease inhibitor. Accordingly, the CYP inhibitor is administered in an amount such that the bioavailability of the protease inhibitor is increased in comparison to the bioavailability in
30 the absence of the CYP inhibitor.

In one embodiment, the invention provides methods for improving the pharmacokinetics of compounds of the invention. The advantages of improving the pharmacokinetics of drugs are recognized in the art (US 2004/0091527; US 2004/0152625; US 2004/0091527). Accordingly, one embodiment of this invention provides a method for administering an inhibitor of CYP3A4 and a compound of the invention. Another embodiment of this invention provides a method for administering a compound of the invention and an inhibitor of isozyme 3A4 ("CYP3A4"), isozyme 2C19 ("CYP2C19"), isozyme 2D6 ("CYP2D6"), isozyme 1A2 ("CYP1A2"), isozyme 2C9 ("CYP2C9"), or isozyme 2E1 ("CYP2E1"). In a preferred embodiment, the CYP inhibitor preferably inhibits CYP3A4. Any CYP inhibitor that improves the pharmacokinetics of the relevant NS3/4A protease may be used in a method of this invention. These CYP inhibitors include, but are not limited to, ritonavir (WO 94/14436), ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, clomethiazole, cimetidine, itraconazole, fluconazole, miconazole, fluvoxamine, fluoxetine, nefazodone, sertraline, indinavir, nelfinavir, amprenavir, fosamprenavir, saquinavir, lopinavir, delavirdine, erythromycin, VX-944, and VX-497. Preferred CYP inhibitors include ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazole.

It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each formulation, containing within a package insert instructing the patient to the correct use of the invention is a desirable additional feature of this invention.

According to a further aspect of the invention is a pack comprising at least a compound of the invention and a CYP inhibitor of the invention and an information insert containing directions on the use of the combination of the invention. In an alternative embodiment of this invention, the pharmaceutical pack further comprises one or more of additional agent as described herein. The additional agent or agents may be provided in the same pack or in separate packs.

Another aspect of this invention is a packaged kit for a patient to use in the treatment of HCV infection or in the prevention of HCV infection, comprising: a single or a plurality of pharmaceutical formulation of each pharmaceutical component; a container housing the

pharmaceutical formulation (s) during storage and prior to administration; and instructions for carrying out drug administration in a manner effective to treat or prevent HCV infection.

Accordingly, this invention provides kits for the simultaneous or sequential administration of a NS3/4A protease inhibitor of the invention and a CYP inhibitor (and optionally an additional agent) or derivatives thereof are prepared in a conventional manner. Typically, such a kit will comprise, e. g. a composition of each inhibitor and optionally the additional agent (s) in a pharmaceutically acceptable carrier (and in one or in a plurality of pharmaceutical formulations) and written instructions for the simultaneous or sequential administration.

In another embodiment, a packaged kit is provided that contains one or more dosage forms for self administration; a container means, preferably sealed, for housing the dosage forms during storage and prior to use; and instructions for a patient to carry out drug administration. The instructions will typically be written instructions on a package insert, a label, and/or on other components of the kit, and the dosage form or forms are as described herein. Each dosage form may be individually housed, as in a sheet of a metal foil- plastic laminate with each dosage form isolated from the others in individual cells or bubbles, or the dosage forms may be housed in a single container, as in a plastic bottle. The present kits will also typically include means for packaging the individual kit components, i. e. , the dosage forms, the container means, and the written instructions for use. Such packaging means may take the form of a cardboard or paper box, a plastic or foil pouch, etc.

DEFINITIONS

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "viral infection" refers to the introduction of a virus into cells or tissues, e.g., hepatitis C virus (HCV). In general, the introduction of a virus is also associated with replication. Viral infection may be determined by measuring virus antibody titer in samples of a biological fluid, such as blood, using, e.g., enzyme immunoassay. Other suitable diagnostic methods include molecular based techniques, such as RT-PCR, direct hybrid capture assay, nucleic acid sequence based amplification, and the like. A virus may infect an

organ, e.g., liver, and cause disease, e.g., hepatitis, cirrhosis, chronic liver disease and hepatocellular carcinoma.

The term "anti-cancer agent" refers to a compound or drug capable of preventing or inhibiting the advancement of cancer. Examples of such agents include cis-platin,
5 actinomycin D, doxorubicin, vincristine, vinblastine, etoposide, amsacrine, mitoxantrone, tenipaside, taxol, colchicine, cyclosporin A, phenothiazines or thioxantheres.

The term "anti-fungal agent" shall used to describe a compound which may be used to treat a fungus infection other than 3-AP, 3-AMP or prodrugs of 3-AP and 3-AMP according to the present invention. Anti-fungal agents according to the present invention
10 include, for example, terbinafine, fluconazole, itraconazole, posaconazole, clotrimazole, griseofulvin, nystatin, tolnaftate, caspofungin, amphotericin B, liposomal amphotericin B, and amphotericin B lipid complex.

The term "antibacterial agent" refers to both naturally occurring antibiotics produced by microorganisms to suppress the growth of other microorganisms, and agents synthesized
15 or modified in the laboratory which have either bactericidal or bacteriostatic activity, e.g., β -lactam antibacterial agents, glycopeptides, macrolides, quinolones, tetracyclines, and aminoglycosides. In general, if an antibacterial agent is bacteriostatic, it means that the agent essentially stops bacterial cell growth (but does not kill the bacteria); if the agent is bacteriocidal, it means that the agent kills the bacterial cells (and may stop growth before
20 killing the bacteria).

The term "immune modulator" refers to any substance meant to alter the working of the humoral or cellular immune system of a subject. Such immune modulators include inhibitors of mast cell-mediated inflammation, interferons, interleukins, prostaglandins, steroids, cortico-steroids, colony-stimulating factors, chemotactic factors, etc.

25 The term "C₁-C₆ alkyl," or "C₁-C₈ alkyl," as used herein, refer to saturated, straight- or branched-chain hydrocarbon radicals containing between one and six, or one and eight carbon atoms, respectively. Examples of C₁-C₆ alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, *n*-hexyl radicals; and examples of C₁-C₈ alkyl radicals include, but are not limited to, methyl, ethyl, propyl,
30 isopropyl, *n*-butyl, *tert*-butyl, neopentyl, *n*-hexyl, heptyl, octyl radicals.

The term "C₂-C₆ alkenyl," or "C₂-C₈ alkenyl," as used herein, denote a group derived from a hydrocarbon moiety, wherein the hydrocarbon moiety has at least one carbon-carbon double bond and contains from two to six, or two to eight carbon atoms, respectively.

Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl and the like.

The term "C₂-C₆ alkynyl," or "C₂-C₈ alkynyl," as used herein, denote a group derived from a hydrocarbon moiety, wherein the hydrocarbon moiety has at least one carbon-carbon triple bond and contains from two to six, or two to eight carbon atoms, respectively.

Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butyne, heptynyl, octynyl and the like.

The term "C₃-C₈-cycloalkyl," or "C₃-C₁₂-cycloalkyl," as used herein, denotes a group derived from a monocyclic or polycyclic saturated carbocyclic ring, where the saturated carbocyclic ring compound has from 3 to 8, or from 3 to 12, ring atoms, respectively.

Examples of C₃-C₈-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; and examples of C₃-C₁₂-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl.

The term "C₃-C₈-cycloalkenyl," or "C₃-C₁₂-cycloalkenyl" as used herein, denote a group derived from a monocyclic or polycyclic carbocyclic ring compound having at least one carbon-carbon double, where the carbocyclic ring compound has from 3 to 8, or from 3 to 12, ring atoms, respectively. Examples of C₃-C₈-cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like; and examples of C₃-C₁₂-cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like.

The term "aryl," as used herein, refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like.

The term "arylalkyl," as used herein, refers to a C₁-C₃ alkyl or C₁-C₆ alkyl residue attached to an aryl ring. Examples include, but are not limited to, benzyl, phenethyl and the like.

The term "heteroaryl," as used herein, refers to a mono-, bi-, or tri-cyclic aromatic radical or ring having from five to ten ring atoms of which at least one ring atom is selected from S, O and N; wherein any N or S contained within the ring may be optionally oxidized.

Heteroaryl includes, but is not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl,

5 pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl, and the like.

The term "heteroarylalkyl," as used herein, refers to a C₁–C₃ alkyl or C₁–C₆ alkyl residue residue attached to a heteroaryl ring. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl and the like.

10 The term "substituted" as used herein, refers to independent replacement of one, two, or three or more of the hydrogen atoms thereon with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -CN, -NH₂, N₃, protected amino, alkoxy, thioalkoxy, oxo, -halo- C₁–C₁₂-alkyl, -halo- C₂–C₁₂-alkenyl, -halo- C₂–C₁₂-alkynyl, -halo-C₃–C₁₂-cycloalkyl, -NH -C₁–C₁₂-alkyl, -NH -C₂–C₁₂-alkenyl, -NH -C₂–C₁₂-alkynyl, -NH -C₃–C₁₂-cycloalkyl, -NH -aryl, -NH -heteroaryl, -NH -heterocycloalkyl, -dialkylamino, -diaryl amino, -diheteroaryl amino, -O-C₁–C₁₂-alkyl, -O-C₂–C₁₂-alkenyl, -O-C₂–C₁₂-alkynyl, -O-C₃–C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)- C₁–C₁₂-alkyl, -C(O)- C₂–C₁₂-alkenyl, -C(O)- C₂–C₁₂-alkynyl, -C(O)-C₃–C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH- C₁–C₁₂-alkyl, -CONH- C₂–C₁₂-alkenyl, -CONH- C₂–C₁₂-alkynyl, -CONH-C₃–C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂- C₁–C₁₂-alkyl, -OCO₂- C₂–C₁₂-alkenyl, -OCO₂- C₂–C₁₂-alkynyl, -OCO₂-C₃–C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH- C₁–C₁₂-alkyl, -OCONH- C₂–C₁₂-alkenyl, -OCONH- C₂–C₁₂-alkynyl, -OCONH- C₃–C₁₂-cycloalkyl, -OCONH- aryl, -OCONH- heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)- C₁–C₁₂-alkyl, -NHC(O)-C₂–C₁₂-alkenyl, -NHC(O)-C₂–C₁₂-alkynyl, -NHC(O)-C₃–C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂- C₁–C₁₂-alkyl, -NHCO₂- C₂–C₁₂-alkenyl, -NHCO₂- C₂–C₁₂-alkynyl, -NHCO₂- C₃–C₁₂-cycloalkyl, -NHCO₂- aryl, -NHCO₂- heteroaryl, -NHCO₂-heterocycloalkyl, -NHC(O)NH₂, -NHC(O)NH- C₁–C₁₂-alkyl, -NHC(O)NH-C₂–C₁₂-alkenyl, -NHC(O)NH-C₂–C₁₂-alkynyl, -NHC(O)NH-C₃–C₁₂-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, NHC(S)NH₂, -NHC(S)NH- C₁–C₁₂-

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alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-alkynyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, -NHC(NH)NH-C₁-C₁₂-alkyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkynyl, -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₂-C₁₂-alkynyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₂-C₁₂-alkynyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₁₂-alkenyl, -S(O)-C₂-C₁₂-alkynyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl -SO₂NH₂, -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₂-C₁₂-alkynyl, -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkynyl, -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-alkenyl, -S-C₂-C₁₂-alkynyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, methylthiomethyl, or -L'-R', wherein L' is C₁-C₆alkylene, C₂-C₆alkenylene or C₂-C₆alkynylene, and R' is aryl, heteroaryl, heterocyclic, C₃-C₁₂cycloalkyl or C₃-C₁₂cycloalkenyl. It is understood that the aryls, heteroaryls, alkyls, and the like can be further substituted. In some cases, each substituent in a substituted moiety is additionally optionally substituted with one or more groups, each group being independently selected from -F, -Cl, -Br, -I, -OH, -NO₂, -CN, or -NH₂. When there is at least two replacements of the hydrogen atoms with substituents, the two substituents can be taken together to form a cycloalkyl, cycloalkenyl or heterocyclic ring.

In accordance with the invention, any of the aryls, substituted aryls, heteroaryls and substituted heteroaryls described herein, can be any aromatic group. Aromatic groups can be substituted or unsubstituted.

It is understood that any alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl moiety described herein can also be an aliphatic group, an alicyclic group or a heterocyclic group.

An "aliphatic group" is non-aromatic moiety that may contain any combination of carbon atoms, hydrogen atoms, halogen atoms, oxygen, nitrogen or other atoms, and optionally contain one or more units of unsaturation, e.g., double and/or triple bonds. An aliphatic group may be straight chained, branched or cyclic and preferably contains between about 1 and about 24 carbon atoms, more typically between about 1 and about 12 carbon atoms. In addition to aliphatic hydrocarbon groups, aliphatic groups include, for example, polyalkoxyalkyls, such as polyalkylene glycols, polyamines, and polyimines, for example. Such aliphatic groups may be further substituted. It is understood that aliphatic groups may be used in place of the alkyl, alkenyl, alkynyl, alkylene, alkenylene, and alkynylene groups described herein.

The term "alicyclic," as used herein, denotes a group derived from a monocyclic or polycyclic saturated carbocyclic ring compound. Examples include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl. Such alicyclic groups may be further substituted.

The term "heterocycloalkyl" and "heterocyclic" can be used interchangeably and refer to a non-aromatic 3-, 4-, 5-, 6- or 7-membered ring or a bi- or tri-cyclic group fused system, where (i) each ring contains between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, (ii) each 5-membered ring has 0 to 1 double bonds and each 6-membered ring has 0 to 2 double bonds, (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iv) the nitrogen heteroatom may optionally be quaternized, (v) any of the above rings may be fused to a benzene ring, and (vi) the remaining ring atoms are carbon atoms which may be optionally oxo-substituted. Representative heterocycloalkyl groups include, but are not limited to, [1,3]dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, and tetrahydrofuryl. Such heterocyclic groups may be further substituted to give substituted heterocyclic.

It will be apparent that in various embodiments of the invention, the substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, arylalkyl, heteroarylalkyl, and heterocycloalkyl are intended to be monovalent or divalent. Thus, alkylene, alkenylene, and alkynylene, cycloalkylene, cycloalkenylene, cycloalkynylene,

arylalkylene, hetroerarylalkylene and heterocycloalkylene groups are to be included in the above definitions, and are applicable to provide the formulas herein with proper valency.

The term "hydroxy activating group", as used herein, refers to a labile chemical moiety which is known in the art to activate a hydroxy group so that it will depart during synthetic procedures such as in a substitution or elimination reactions. Examples of hydroxy activating group include, but not limited to, mesylate, tosylate, triflate, *p*-nitrobenzoate, phosphonate and the like.

The term "activated hydroxy", as used herein, refers to a hydroxy group activated with a hydroxy activating group, as defined above, including mesylate, tosylate, triflate, *p*-nitrobenzoate, phosphonate groups, for example.

The term "protected hydroxy," as used herein, refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups.

The terms "halo" and "halogen," as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques, which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, et al., Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text

so states; thus a carbon-carbon double bond depicted arbitrarily herein as *trans* may be *cis*, *trans*, or a mixture of the two in any proportion.

The term "subject" as used herein refers to a mammal. A subject therefore refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, and the like. Preferably the subject is a human. When the subject is a human, the subject may be referred to herein as a patient.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art.

The term "hydroxy protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect a hydroxy group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the hydroxy protecting group as described herein may be selectively removed. Hydroxy protecting groups as known in the art are described generally in T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of hydroxy protecting groups include benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, methoxycarbonyl, tert-butoxycarbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-furfuryloxycarbonyl, allyloxycarbonyl, acetyl, formyl, chloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, methyl, t-butyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, benzyl, para-methoxybenzyl, diphenylmethyl, triphenylmethyl (trityl), tetrahydrofuryl, methoxymethyl, methylthiomethyl, benzyloxymethyl, 2,2,2-trichloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, and the like. Preferred hydroxy protecting groups for the present invention are acetyl (Ac or -C(O)CH₃), benzoyl (Bz or -C(O)C₆H₅), and trimethylsilyl (TMS or -Si(CH₃)₃). Berge, *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts can be prepared *in situ*

during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts e.g., salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

The term "amino protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect an amino group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the amino protecting group as described herein may be selectively removed. Amino protecting groups as known in the art are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of amino protecting groups include, but are not limited to, *t*-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, benzyloxycarbonyl, and the like.

As used herein, the term "pharmaceutically acceptable ester" refers to esters of the compounds formed by the process of the present invention which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a

salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates,

5 acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like,

10 commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present invention.

"Prodrug", as used herein means a compound, which is convertible in vivo by metabolic means (e.g. by hydrolysis) to afford any compound delineated by the formulae of the instant invention. Various forms of prodrugs are known in the art, for example, as discussed in

15 Bundgaard, (ed.), *Design of Prodrugs*, Elsevier (1985); Widder, et al. (ed.), *Methods in Enzymology*, vol. 4, Academic Press (1985); Krogsgaard-Larsen, et al., (ed.) "Design and Application of Prodrugs, *Textbook of Drug Design and Development*, Chapter 5, 113-191 (1991); Bundgaard, et al., *Journal of Drug Deliver Reviews*, 8:1-38(1992); Bundgaard, J. of *Pharmaceutical Sciences*, 77:285 et seq. (1988); Higuchi and Stella (eds.) *Prodrugs as Novel*
20 *Drug Delivery Systems*, American Chemical Society (1975); and Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry And Enzymology," John Wiley and Sons, Ltd. (2002).

The term "acyl" includes residues derived from acids, including but not limited to carboxylic acids, carbamic acids, carbonic acids, sulfonic acids, and phosphorous acids.

25 Examples include aliphatic carbonyls, aromatic carbonyls, aliphatic sulfonyls, aromatic sulfonyls, aliphatic sulfinyls, aromatic phosphates and aliphatic phosphates. Examples of aliphatic carbonyls include, but are not limited to, acetyl, propionyl, 2-fluoroacetyl, butyryl, 2-hydroxy acetyl, and the like.

The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to
30 proton activity, i.e., not acting as a proton-donor. Examples include, but are not limited to, hydrocarbons, such as hexane and toluene, for example, halogenated hydrocarbons, such as,

for example, methylene chloride, ethylene chloride, chloroform, and the like, heterocyclic compounds, such as, for example, tetrahydrofuran and N-methylpyrrolidinone, and ethers such as diethyl ether, bis-methoxymethyl ether. Such solvents are well known to those skilled in the art, and individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of aprotic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

The terms "protogenic organic solvent" or "protic solvent" as used herein, refer to a solvent that tends to provide protons, such as an alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like. Such solvents are well known to those skilled in the art, and individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of protogenic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. In addition, the solvents, temperatures, reaction durations, etc. delineated herein are for purposes of illustration only and variation of the reaction conditions can produce the desired bridged macrocyclic

products of the present invention. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein include, for example, those described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995).

The compounds of this invention may be modified by appending various functionalities via synthetic means delineated herein to enhance selective biological properties. Such modifications include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

PHARMACEUTICAL COMPOSITIONS

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. The pharmaceutical compositions

of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

5 The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to
10 enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

Liquid dosage forms for oral administration include pharmaceutically acceptable
15 emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular,
20 cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

25 Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable
30 vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a

solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

5 The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

10 In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

15 20 Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

25 Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain

30

silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes,

paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Antiviral Activity

An inhibitory amount or dose of the compounds of the present invention may range from about 0.01 mg/Kg to about 500 mg/Kg, alternatively from about 1 to about 50 mg/Kg. Inhibitory amounts or doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

According to the methods of treatment of the present invention, viral infections are treated or prevented in a subject such as a human or lower mammal by administering to the subject an anti-hepatitis C virally effective amount or an inhibitory amount of a compound of the present invention, in such amounts and for such time as is necessary to achieve the desired result. An additional method of the present invention is the treatment of biological samples with an inhibitory amount of a compound of composition of the present invention in such amounts and for such time as is necessary to achieve the desired result.

The term "anti-hepatitis C virally effective amount" of a compound of the invention, as used herein, mean a sufficient amount of the compound so as to decrease the viral load in a biological sample or in a subject (e.g., resulting in at least 10%, preferably at least 50%, more preferably at least 80%, and most preferably at least 90% or 95%, reduction in viral load). As well understood in the medical arts, an anti-hepatitis C virally effective amount of a compound of this invention will be at a reasonable benefit/risk ratio applicable to any medical treatment.

The term “inhibitory amount” of a compound of the present invention means a sufficient amount to decrease the hepatitis C viral load in a biological sample or a subject (e.g., resulting in at least 10%, preferably at least 50%, more preferably at least 80%, and most preferably at least 90% or 95%, reduction in viral load). It is understood that when said
5 inhibitory amount of a compound of the present invention is administered to a subject it will be at a reasonable benefit/risk ratio applicable to any medical treatment as determined by a physician. The term “biological sample(s),” as used herein, means a substance of biological origin intended for administration to a subject. Examples of biological samples include, but are not limited to, blood and components thereof such as plasma, platelets, subpopulations of
10 blood cells and the like; organs such as kidney, liver, heart, lung, and the like; sperm and ova; bone marrow and components thereof; or stem cells. Thus, another embodiment of the present invention is a method of treating a biological sample by contacting said biological sample with an inhibitory amount of a compound or pharmaceutical composition of the present invention.

15 Upon improvement of a subject’s condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. The subject
20 may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific inhibitory dose for any particular patient will
25 depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the
30 specific compound employed; and like factors well known in the medical arts.

The total daily inhibitory dose of the compounds of this invention administered to a subject in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in single or multiple doses.

Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art. All publications, patents, published patent applications, and other references mentioned herein are hereby incorporated by reference in their entirety.

Abbreviations

Abbreviations which have been used in the descriptions of the schemes and the examples that follow are:

ACN for acetonitrile;

BME for 2-mercaptoethanol;

BOP for benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate;

COD for cyclooctadiene;

DAST for diethylaminosulfur trifluoride;

DABCYL for 6-(N-4'-carboxy-4-(dimethylamino)azobenzene)- aminoethyl-1-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite;

DCM for dichloromethane;

DIAD for diisopropyl azodicarboxylate;

DIBAL-H for diisobutylaluminum hydride;

DIEA for diisopropyl ethylamine;

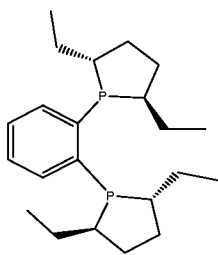
DMAP for N,N-dimethylaminopyridine;

DME for ethylene glycol dimethyl ether;

DMEM for Dulbecco's Modified Eagles Media;

DMF for N,N-dimethyl formamide;

DMSO for dimethylsulfoxide;



DUPHOS for ;

EDANS for 5-(2-Amino-ethylamino)-naphthalene-1-sulfonic acid;

EDCI or EDC for 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride;

5 EtOAc for ethyl acetate;

HATU for O (7-Azabenzotriazole-1-yl)-N,N,N',N' – tetramethyluronium
hexafluorophosphate;

Hoveyda's Cat. for Dichloro(*o*-isopropoxyphenylmethylene)
(tricyclohexylphosphine)ruthenium(II);

10 KHMDS is potassium bis(trimethylsilyl) amide;

Ms for mesyl;

NMM for N-4-methylmorpholine;

PyBrOP for Bromo-tri-pyrolidino-phosphonium hexafluorophosphate;

Ph for phenyl;

15 RCM for ring-closing metathesis;

RT for reverse transcription;

RT-PCR for reverse transcription-polymerase chain reaction;

TEA for triethyl amine;

TFA for trifluoroacetic acid;

20 THF for tetrahydrofuran;

TLC for thin layer chromatography;

TPP or PPh₃ for triphenylphosphine;

tBOC or Boc for tert-butyloxy carbonyl; and

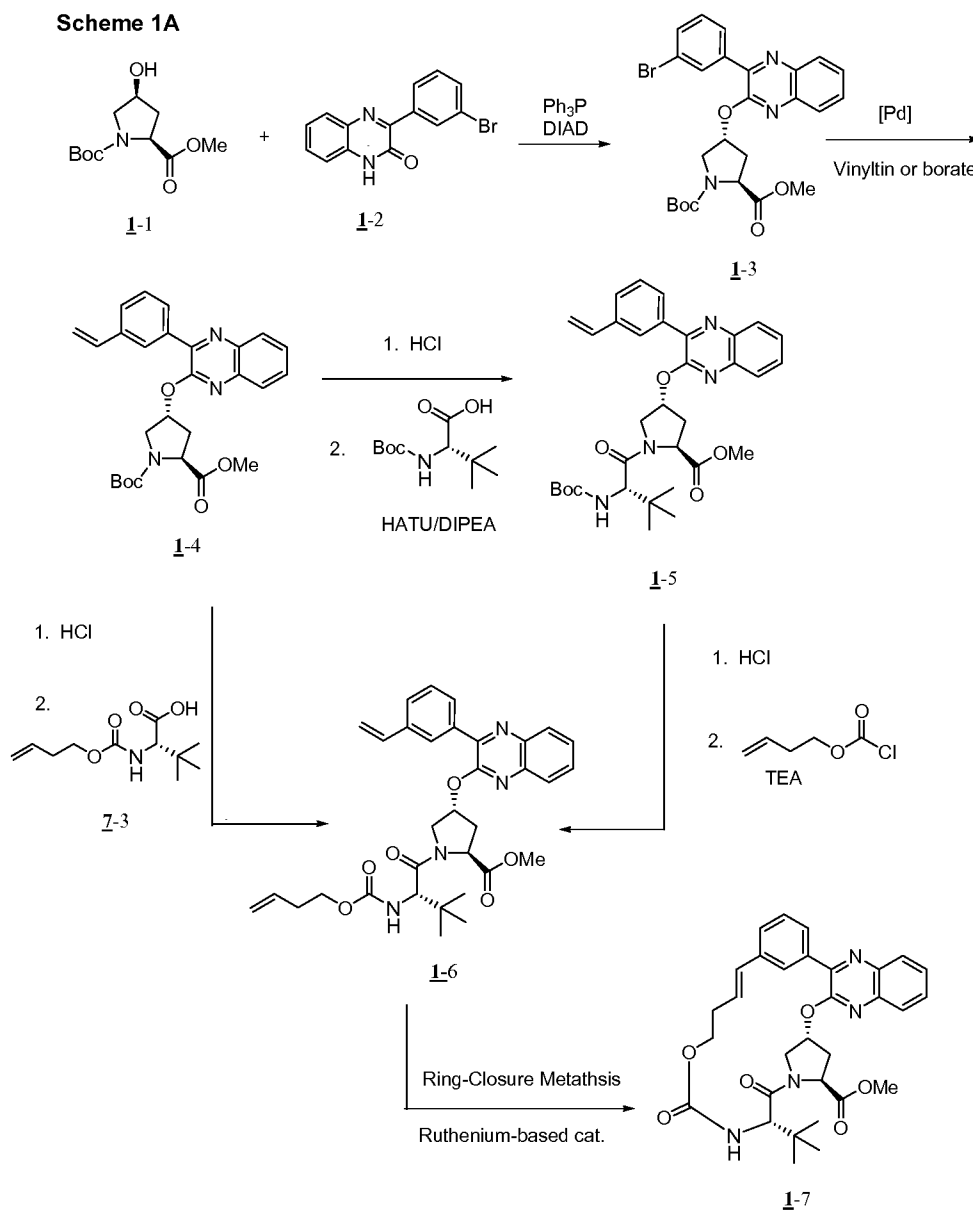
Xantphos for 4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene.

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Synthetic Methods

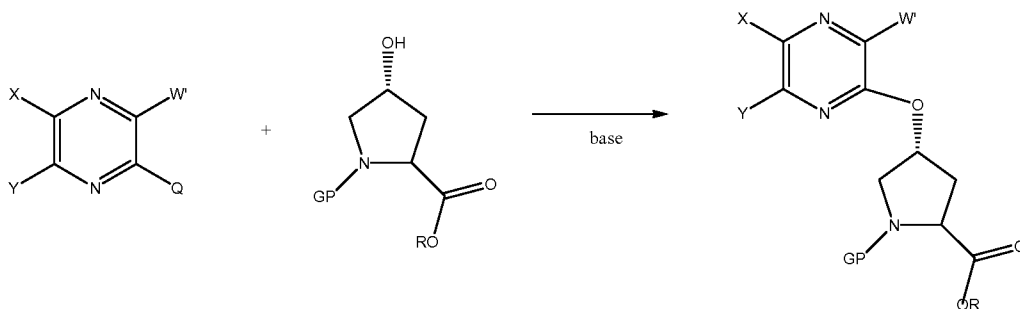
The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes that illustrate the methods by which the compounds of the invention may be prepared, which are intended as an illustration only and not to limit the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

Scheme 1A



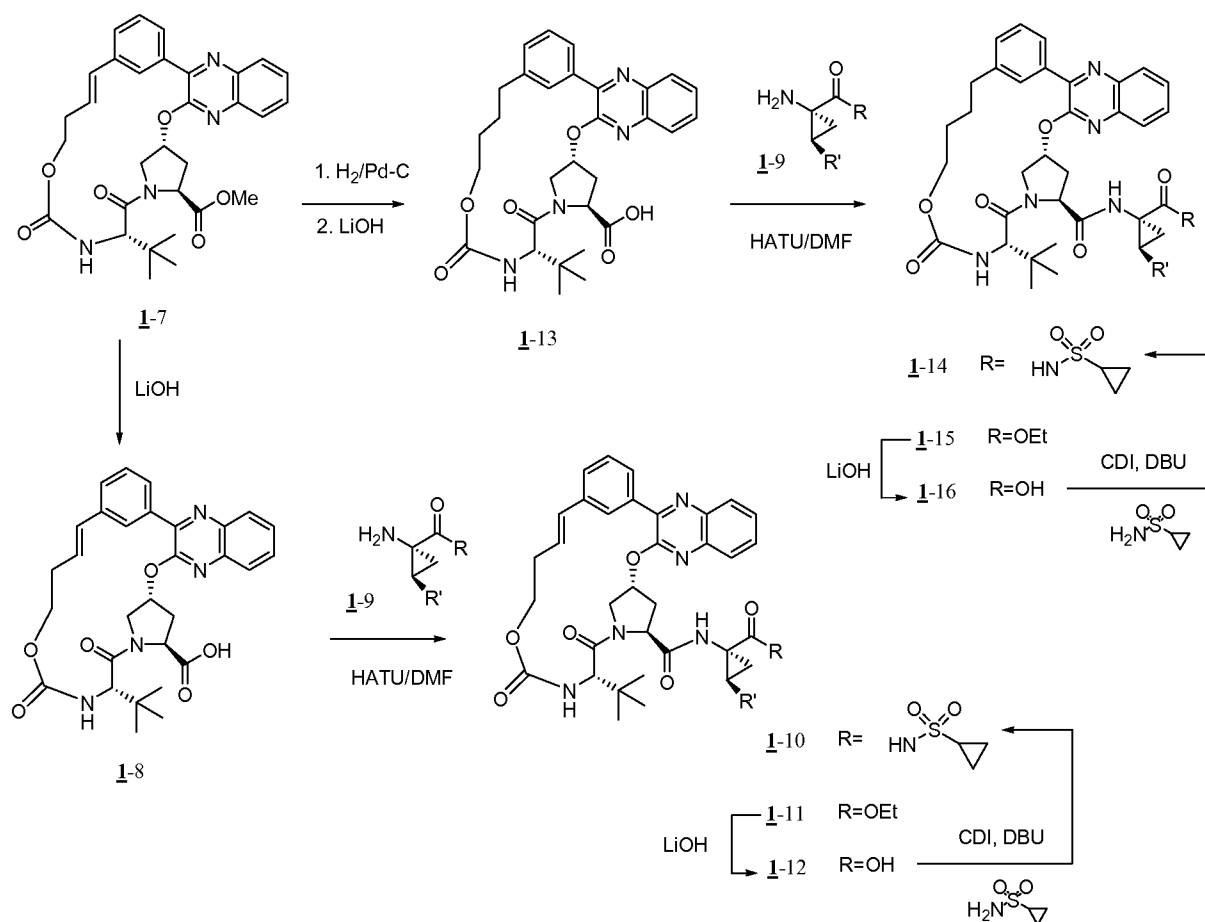
The preparation of quinoxaliny macrocyclic core compounds is exemplified in Scheme 1A. Commercially available Boc-hydroxyproline **1-1** was coupled with quinoxaline derivative **1-2** (for the preparation of quinoxaline analogs, see Schemes 3-6) under Mitsunobu conditions giving compound **1-3**. Attachment at the carbonyl oxygen was observed to form the desired compound. A detailed discussion of the identification and characterization of the unexpected oxo Mitsunobu addition product appears in the examples herein. For further details on the Mitsunobu reaction, see O. Mitsunobu, *Synthesis* **1981**, 1-28; D. L. Hughes, *Org. React.* **29**, 1-162 (1983); D. L. Hughes, *Organic Preparations and Procedures Int.* **28**, 127-164 (1996); and J. A. Dodge, S. A. Jones, *Recent Res. Dev. Org. Chem.* **1**, 273-283 (1997). Introduction of vinyl group was accomplished via Suzuki (vinylborate/palladium) or Still (vinyltin/Palladium) reaction to afford compound **1-4**. Deprotection of **1-4** with HCl followed by coupling reaction (HATU/DMF) with Boc-L-tert.-leucine gave compound **1-5**. Deprotection of **1-5** with HCl followed by reacting with 3-butenyl chloroformate resulted in the macrocyclic compound precursor **1-6**. Alternatively, compound **1-6** can be prepared from the direct coupling of intermediate **1-4** (after deprotection of Boc group) with the corresponding carbamate aminoacid **7-3** (for the preparation of the carbamate aminoacid derivatives see Scheme 7). Ring-closing metathesis of compound **1-6** with a ruthenium-based catalyst gives the desired macrocyclic intermediate **1-7** (for further details on ring closing metathesis see recent reviews: Grubbs et al., *Acc. Chem. Res.*, **1995**, 28, 446; Shrock et al., *Tetrahedron* **1999**, 55, 8141; Furstner, A. *Angew. Chem. Int. Ed.* **2000**, 39, 3012; Trnka et al., *Acc. Chem. Res.* **2001**, 34, 18, and Hoveyda et al., *Chem. Eur. J.* **2001**, 7, 945).

Scheme 1B



An alternate route to quinoxaline core structures is set forth in Scheme 1B, which illustrates the displacement reaction of a substituted quinoxaline halide with amino-protected hydroxyproline in the presence of base, such as NaH or NaO^tBu. In this scheme, PG is an amino protecting group, Q is a halogen, preferably bromine, chlorine or iodine, X and Y have the meanings given for these variables in Formula I, W' has the meanings given for L₁₀₁-W₁₀₁- in Formula I and Z-W- in Formula II and R is hydrogen or alkyl.

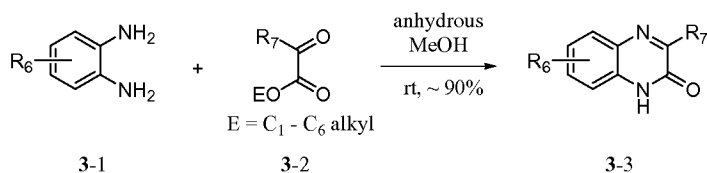
Scheme 2



The syntheses of quinoxalinyll macrocyclic compounds as HCV protease inhibitors are exemplified in Scheme 2. Hydrolysis of compound **1-7** gives the corresponding carboxylic acid **1-8**, which is coupled with amino sulfonimide or amino acid ester **1-9** (for the preparation, see Schemes 8 and 9) to afford compound **1-10** or ester **1-11**. Hydrolysis of **1-**

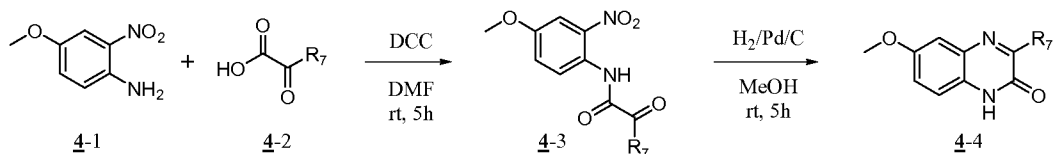
11 gives **1**-12. Compound **1**-10 can also be prepared from the acid **1**-12 as shown in scheme 2. Hydrogenation of **1**-7 gives compound **1**-13, which is transformed into compounds **1**-14 and **1**-16 using the same chemistry as in the preparation of compounds **1**-10 and **1**-12.

Scheme 3



Various quinoxaline derivatives of compound **1**-2 (i.e. formula **3**-3) can be made via the condensation of phenyl diamines of formula **3**-1, wherein R_6 is previously defined, with keto acids or esters of formula **3**-2, wherein R_7 is W-Z as previously defined, in anhydrous methanol at room temperature (see Bekerman et al., *J. Heterocycl. Chem.* **1992**, 29, 129-133 for further details of this reaction). Examples of phenyl diamines suitable for creating quinoxaline derivatives of formula **3**-3 include, but are not limited to, 1,2-diamino-4-nitrobenzene, o-phenylenediamine, 3,4-diaminotoluene, 4-chloro-1,2-phenylenediamine, methyl-3,4-diaminobenzoate, benzo[1,3]dioxole-5,6-diamine, 1,2-diamino-4,5-methylene dioxybenzene, 4-chloro-5-(trifluoromethyl)-1,2-benzenediamine, and the like. Examples of keto acids suitable for the reaction described in Scheme 3 include, but are not limited to, benzoylformic acid, phenylpyruvic acid, indole-3-glyoxylic acid, indole-3-pyruvic acid, nitrophenylpyruvic acid, (2-furyl)glyoxylic acid, and the like. Examples of keto esters suitable for the reaction described in Scheme 3 include, but are not limited to ethyl thiophene-2-glyoxylate, ethyl 2-oxo-4-phenylbutyrate, ethyl 2-(formylamino)-4-thiazolyl glyoxylate, ethyl-2-amino-4-thiazolyl glyoxylate, ethyl-2-oxo-4-phenylbutyrate, ethyl-(5-bromothien-2-yl)glyoxylate, ethyl-3-indolylglyoxylate, ethyl-2-methylbenzoyl formate, ethyl-3-ethylbenzoyl formate, ethyl-3-ethylbenzoyl formate, ethyl-4-cyano-2-oxobutyrate, methyl(1-methylindolyl)-3-glyoxylate, and the like.

Scheme 4



3,6-substituted quinoxalin-2-ones of formula **4-4**, wherein R₇ is W-Z as previously defined, can be made in a regioselective manner to favor the 6-position substitution

beginning with the amide coupling of 4-methoxy-2-nitro aniline **4-1** and substituted glyoxylic acid **4-2** to yield compound **4-3**. The 3,6-substituted quinoxalin-2-one **4-4** was created via catalytic reduction of the nitro of compound **4-3** followed by condensation.

Other substituents may be introduced into **4-4** through the use of other 2-nitroanilines.

Examples of keto acids suitable for the reaction described in Scheme 4 include, but are not

limited to, benzoylformic acid, phenylpyruvic acid, indole-3-glyoxylic acid, indole-3-pyruvic acid, nitrophenylpyruvic acid, (2-furyl)glyoxylic acid, and the like. Examples of 2-nitro

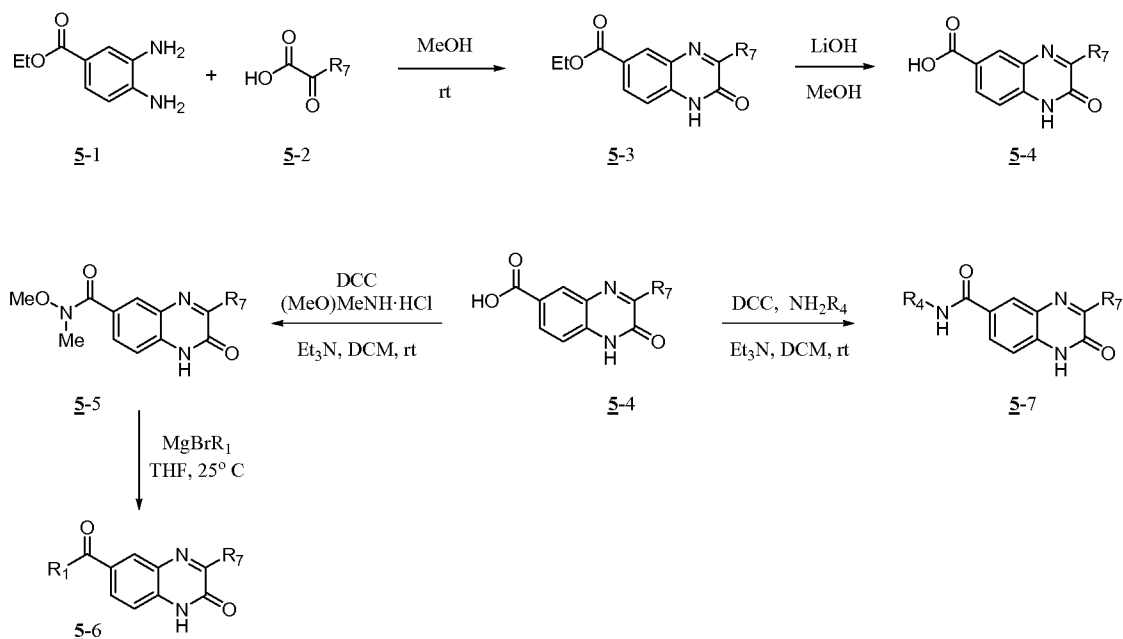
anilines suitable for the reaction described in Scheme 4 include, but are not limited to, 4-

ethoxy-2-nitroaniline, 4-amino-3-nitrobenzotrifluoride, 4,5-dimethyl-2-nitroaniline, 4-fluoro-2-nitroaniline, 4-chloro-2-nitroaniline, 4-amino-3-nitromethylbenzoate, 4-benzoyl-2-

nitroaniline, 3-bromo-4-methoxy-2-nitroaniline, 3'-amino-4'-methyl-2-nitroacetophenone, 5-ethoxy-4-fluoro-2-nitroaniline, 4-bromo-2-nitroaniline, 4-(trifluoromethoxy)- 2-nitroaniline,

ethyl-4-amino-3-nitrobenzoate, 4-bromo-2-methyl-6-nitroaniline, 4-propoxy-2-nitroaniline, 5-(propylthio)- 2-nitroaniline, and the like.

Scheme 5

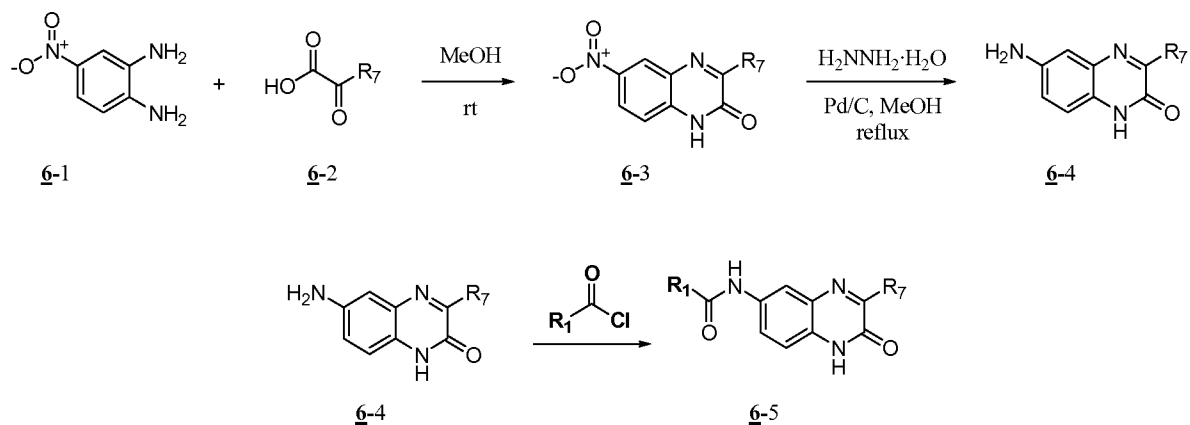
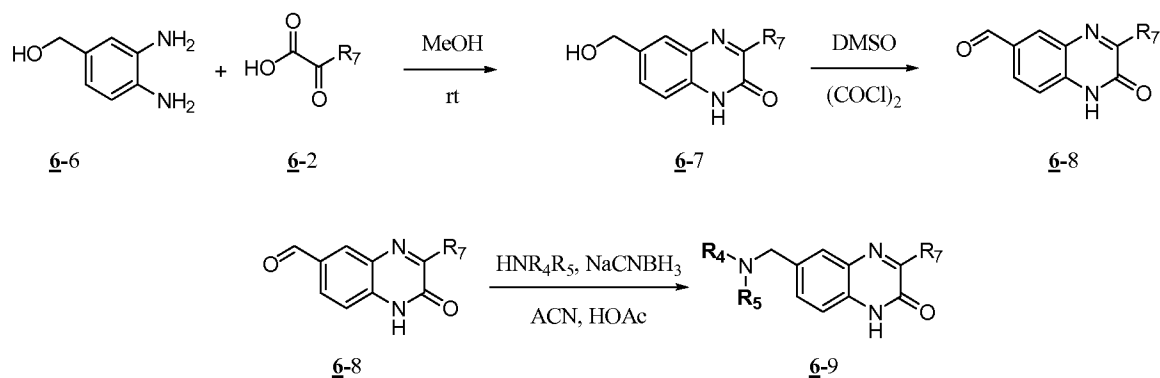


The 3-substituted 2-oxo-1,2-dihydro-quinoxaline-6-carboxylic acid intermediate **5-4** can be formed via condensation of ethyl 3,4-diaminobenzoate (**5-1**) with oxo acetic acid of formula **5-2**, wherein R₇ = W-Z as previously defined, using the method described previously in Scheme 3 (see Bekerman et al., *J. Heterocycl. Chem.* **1992**, 29, 129-133 for further details). The resulting ethyl ester **5-3** was then hydrolyzed with LiOH in MeOH at room temperature to yield carboxylic acid intermediate **5-4**.

Carboxylic acid **5-4** then may be converted to substituted ketone **5-6** (wherein R₁ is as previously defined) via Weinreb's amide **5-5** and subsequent treatment with various Grignard Reagents (see Weinreb et al. *Tetrahedron Lett.* **1977**, 33, 4171; Weinreb et al, *Synth. Commun.* **1982**, 12, 989 for details of the formation and use of Weinreb's amide; and see B.S. Furniss, A.J. Hannaford, P.W.G. Smith, A.R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, 1989). The addition was performed in an inert solvent, generally at low temperatures. Suitable solvents include, but are not limited to, tetrahydrofuran, diethylether, 1,4-dioxane, 1,2-dimethoxyethane, and hexanes. Preferably the solvent was tetrahydrofuran or diethylether. Preferably the reaction was carried out at -78°C to 0°C.

Alternatively, carboxylic acid **5-4** may be used to form various amides of formula **5-7**, wherein R_4 is as previously defined, in a manner generally described in Scheme 5. All of the various quinoxalin-2-one compounds described in Scheme 5 are further coupled to the macrocyclic precursor via the Mitsunobu conditions described above.

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Scheme 6**A****B**

Further 6-substituted quinoxalin-2-one compounds can be made via the general procedures set forth in Scheme 6.

10

A. Reduction of 6-nitro and Amide Formation

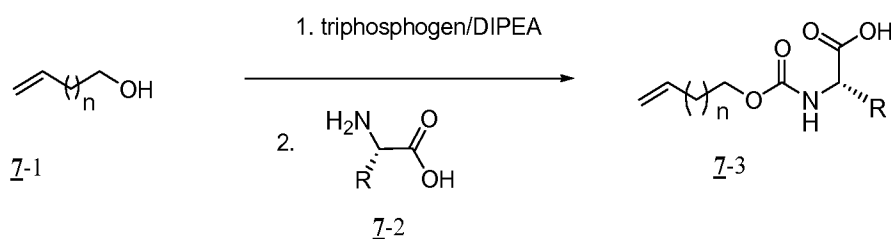
6-nitro-1H-quinoxalin-2-one (**6-3**) can be formed in the manner previously described from 3,4-diaminonitrobenzene and the oxo acetic acid of formula **6-2**, wherein $R_7 = W-Z$ as is previously described. Reduction of the nitro group at the 6-position can be achieved via

5 Pd/C with $H_2NNH_2 \cdot H_2O$ in refluxing MeOH. The 6-position of amine **6-4** then can be treated with a wide array of acid chlorides to give various amides of formula **6-5** where R_1 is as previously defined.

B. Oxidation of Benzyl alcohol and Reductive Amination

10 Quinoxalin-2-one of formula **6-7** can be formed via the condensation of 3,4-diaminobenzyl alcohol and various oxo acetic acids of formula **6-2**, wherein $R_7 = W-Z$ as is previously described. The resulting benzyl alcohol **6-7** may then be oxidized under Swern conditions, or any other oxidation conditions, to generate aldehyde of formula **6-8**. For further details concerning the Swern reaction see A. J. Mancuso, D. Swern, *Synthesis* **1981**,

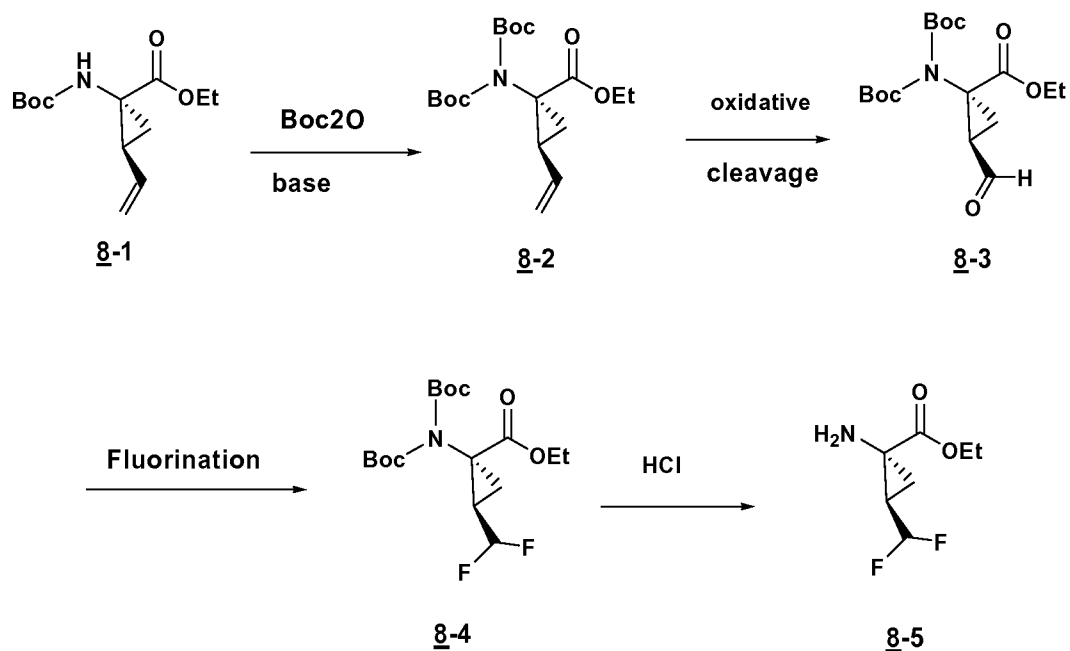
15 165-185 *passim*; T. T. Tidwell, *Org. React.* **1990**, 39, 297-572 *passim*. For other oxidation conditions see B.S. Furniss, A.J. Hannaford, P.W.G. Smith, A.R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, 1989. Subsequent reductive amination reactions with primary or secondary amines in the presence of $NaCNBH_3$ and acetic acid can yield compounds of formula **6-9** wherein R_4 and R_5 are as previously defined.

Scheme 7

The preparation of carbamate amino acids **7-3** is shown in Scheme 7; n is an integer from 0 to 5. The corresponding olefin alcohol reacts with triphosphogen in presence of

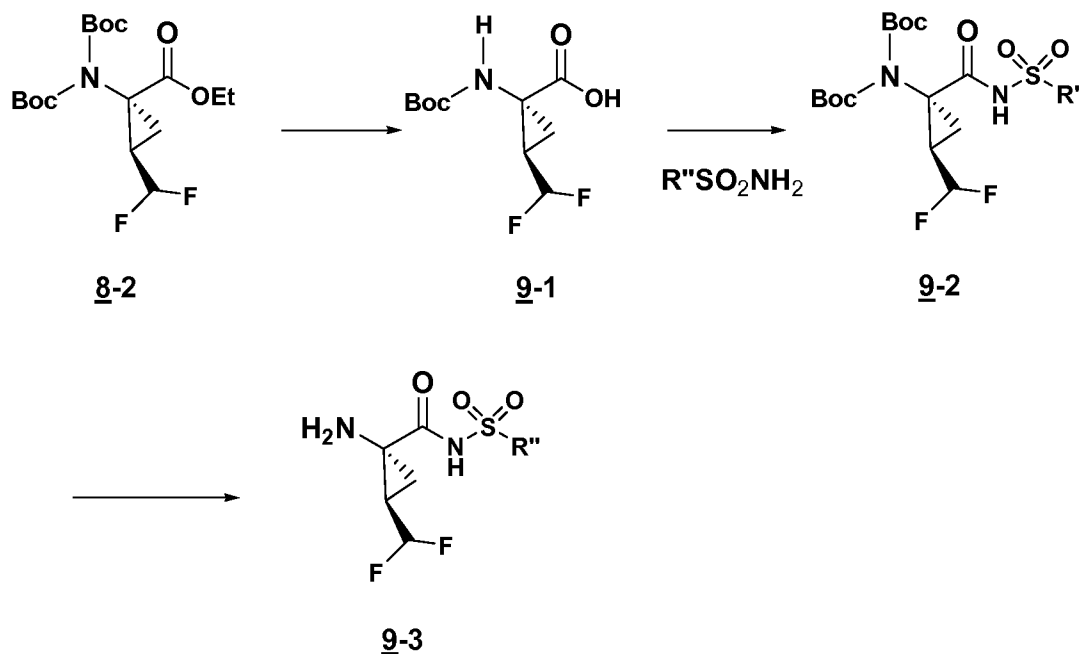
25 DIPEA, followed by adding the appropriate amino acids **7-2** to give the desired carbamate aminoacids **7-3**.

Scheme 8



5 The synthesis of difluoromethyl P1 amino acid derivatives **8-5** (i.e. **1-9** with R=OEt and R'=CF₂H) is outlined in Scheme 8. Mono-Boc amino acid ester was further protected as bis-Boc amino acid ester **8-2**. Oxidative cleavage of compound **8-2** resulted in the aldehyde **8-3**, which was then converted to difluoromethyl compound **8-4** using aminosulfur trifluoride derivatives such as diethylaminosulfur trifluoride (DAST). Deprotection of **8-4** using HCl afforded the desired difluoromethyl P1 compound **8-5**.

Scheme 9



Difluoromethyl P1 sulfonamide derivative **9-3** (i.e. **1-9** with $R=NHS(O)_2R''$ and $R'=CF_2H$) was prepared as shown in Scheme 9. The hydrolysis of compound **8-2** gave the acid **9-1**, which was converted to **9-2** using CDI/ $R''SO_2NH_2$ /DBU or EDC/DMAP/

5 $R''SO_2NH_2$. Deprotection of **9-2** afforded the desired intermediate **9-3**.

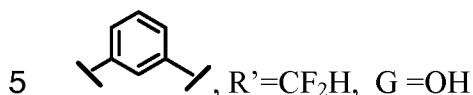
All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, internet web sites, databases, patents, and patent publications.

Examples

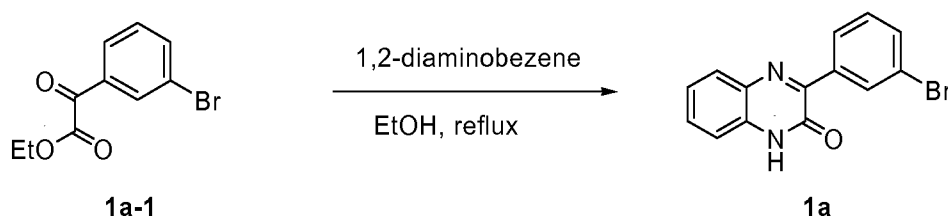
The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not to limit the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents,

derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

Example 1. Compound of Formula XV, wherein $R = \text{---}\text{C}(\text{CH}_3)_2\text{---}$, $M-L = \text{---}\text{OCH}_2\text{CH}_2\text{CH}_2\text{---}$, $\text{Ar} =$

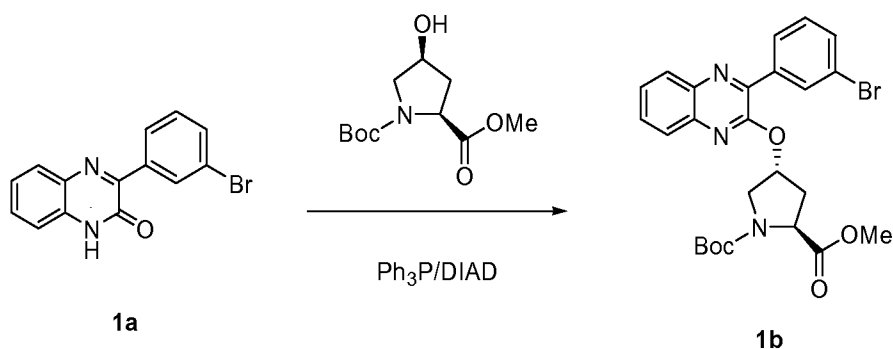


Step 1A



10 A mixture of compound **1a-1** (0.84g, 7.77mmol), 1,2-diaminobenzene (2g, 7.77mmol) and ethanol (10m) was heated under reflux for 2h, cooled to room temperature, filtered, washed with cold ethanol and dried under reduced pressure to afford compound **1a** (2.12g) directly used in next step.

Step 1B

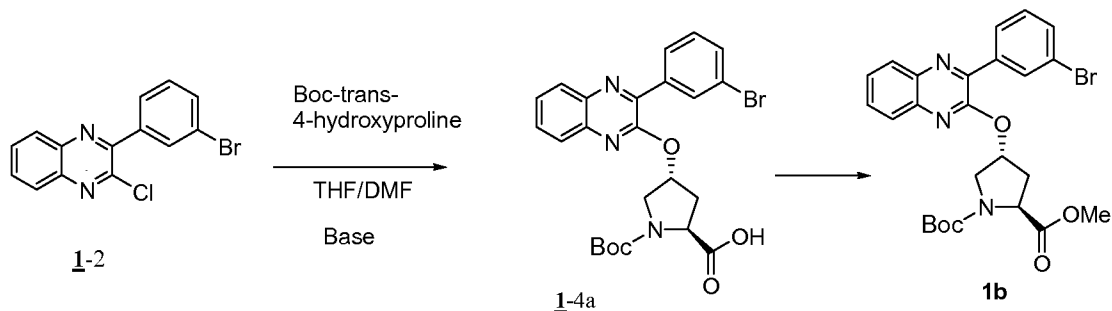


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To a mixture of the above **1a** (1.02g, 3.39mmol), Boc-L-cis-hydroxyproline methyl ester (0.831g, 3.38mmol) and triphenylphosphine (1.8g, 6.86mmol) in THF at 0°C was added dropwise DIAD (1.33ml, 6.76mmol). The resulting mixture was held at 0°C for 15 min. before being warmed to room temperature. After 18 hours, the mixture was

concentrated under vacuum and the residue was purified by chromatography (Hexane/EtOAc = 1:0 to 4:1) to give **1b** (1.74g). MS(ESI): m/e 528.02 (M+H).

Alternatively, intermediate **1b** was prepared from **1-2** as shown below:

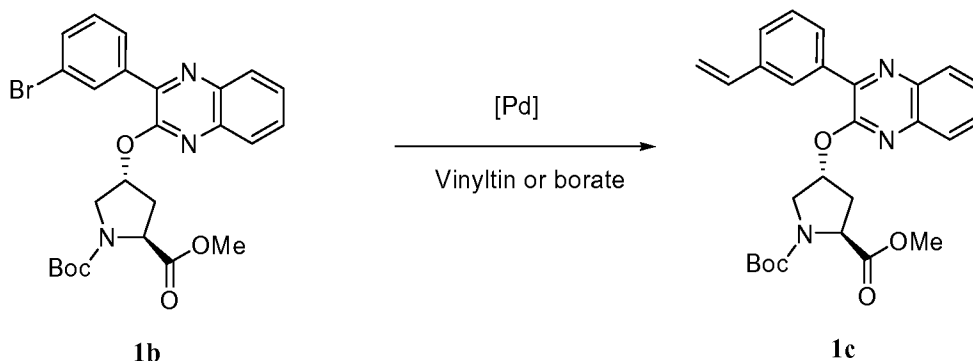


5

A 12L round bottom flask was charged with Boc-trans-4-hydroxyproline (141g, 0.61 mol), THF (3.3L). The mixture was cooled to 0°C, a solution of NaOtBu (175.9g, 1.83 mol) in DMF (0.8L) was added slowly via addition funnel while the internal temperature did not exceed 10°C. The ice bath was removed and the mixture was stirred at room temperature for 1.5h. The reaction flask was placed again at 0°C, and compound **1-2** (195g, 0.61 mol) was added portion wise. Thin layer chromatography showed no starting material left after 2h. The reaction mixture was quenched with water (2L) and concentrated to remove most of the THF. Another 2L of water was added, and the mixture was extracted with t-butylmethyl ether twice (4L+3L). 4L of EtOAc was added to the aqueous layer, 10% citric acid was added slowly to adjust the pH to 4-5. Two phases were separated, the aqueous layer was extracted with EtOAc (2X 3L). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated to afford a brown oil (356g). This crude material was dissolved in MeOH/CH₂Cl₂ (1.5L/1.6L), cooled to 0°C, and Me₃SiCH₂N₂ (2M in hexane, 640mL, 1.28 mol) was added dropwise. After 3.5h the addition was completed and thin layer chromatography showed starting material left. The reaction mixture was concentrated and the residue was crystallized from MeOH (~500mL) to yield 275g of compound **1b**. The mother liquor was purified with silica gel column to afford 22g more of the product. (combined yield: 88% from **1-2**).

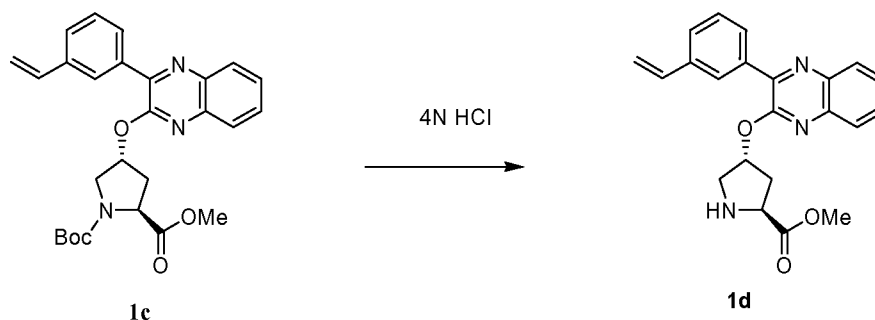
25

Step 1C



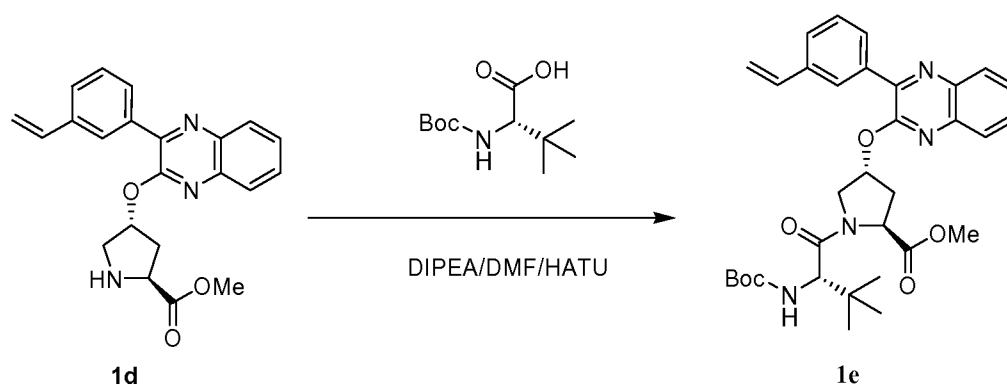
To a mixture of compound **1b** (0.6g, 1mmol), potassium vinyltrifluoroborate (0.52g, 2mmol), triethylamine (0.55ml) and ethanol (20ml) was added 1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride complex with CH₂Cl₂ (40mg, 0.048mmol). The resulting mixture was stirred at 75°C for 15h, cooled to room temperature, quenched with 10% KHSO₄ aq. solution, extracted with ethyl acetate (3x). The combined organic layers were dried (MgSO₄), concentrated under vacuum, and the residue was purified by chromatography (Hexane/EtOAc = 1:0 to 4:1) to give **1c** (0.49g). MS(ESI): m/z 476.21(M+H).

Step 1D



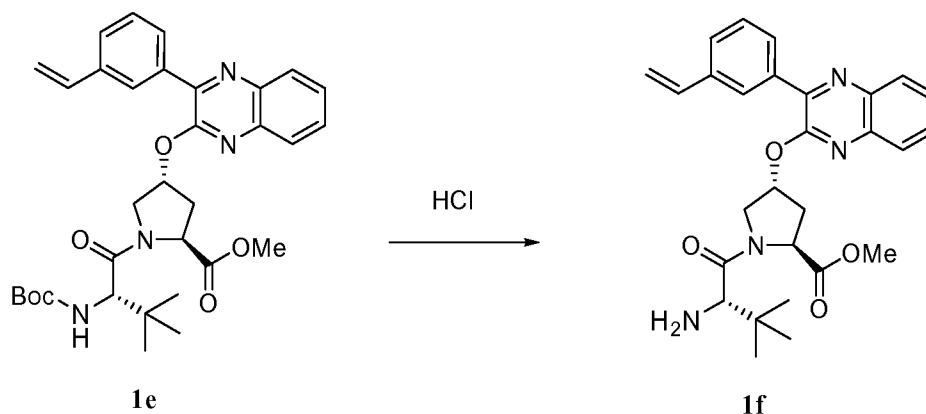
A solution of compound **1c** (1mmol) in dichloromethane (2ml) was treated with 4M HCl/dioxane (4ml, 16mmol). The resulting mixture was stirred at room temperature for 1 hour, and concentrated in vacuo to dryness to afford HCl salt of compound **1d** (100%). MS (ESI): m/e 376.15 (M+H).

Step 1E



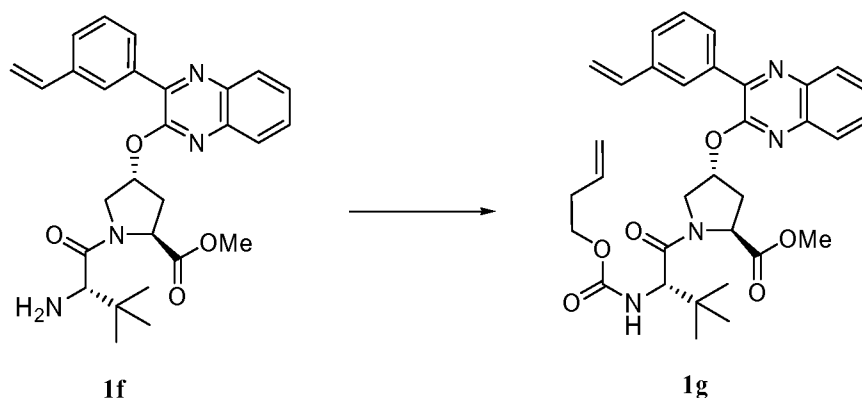
To a solution of compound **1d** (HCl salt, 100mg, 0.223mmol), Boc-L-t-leucine (67mg, 0.29mmol) and DIPEA (0.24ml, 1.37mmol) in DMF (3ml) at 0 °C was added HATU (110mg, 0.29mmol). The mixture was stirred at rt for 18h, diluted with EtOAc and washed with half-sat.-aq. NaCl four times. The organic phase was dried over anhydrous MgSO₄, filtered, and then concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 9 : 1 to 4 : 1) to afford compound **1e** (128mg). MS (ESI): m/e 589.44 (M+H), 489.36 (M-Boc).

Step 1F



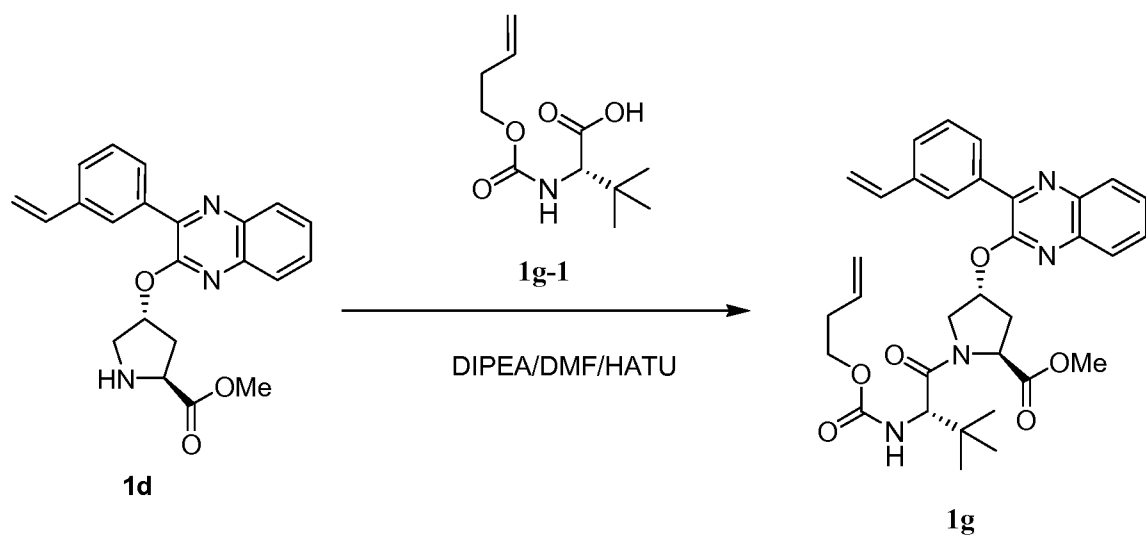
A solution of compound **1e** (117mg, 0.2mmol) in dichloromethane (1ml) was treated with 4M HCl/dioxane (3ml, 12mmol). The resulting mixture was stirred at room temperature for 1 hour, and concentrated in vacuo to dryness to afford HCl salt of compound **1f** (100%). MS (ESI): m/z 489.45(M+H).

Step1G



Compound **1f** (0.198mmol) was dissolved in dichloromethane (3m), cooled to 0°C, treated with triethylamine (120ul, 4eq.) followed by 3-butenyl chloroformate (0.041ml, 0.33mmol). The mixture was stirred at room temperature for 0.5 to 1 hour, diluted with ethyl acetate, washed with half-sat.-aq. NaCl twice, dried (MgSO₄) and concentrated in vacuo. The residue was purified by silica gel chromatography (Hexanes/ EtOAc = 6 : 1 to 4: 1) to give compound **1g** (95mg). MS(ESI): m/z 587.47 (M+H).

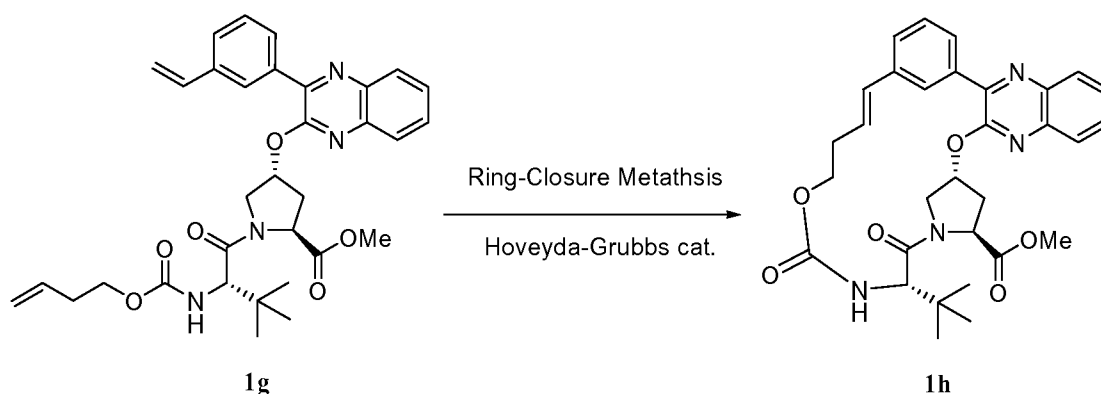
Alternatively, compound **1g** was prepared from the coupling of compound **1d** and **1g-1** as shown below:



a solution of compound **1d** (HCl salt, 10.78mmol), **1g-1** (2.97g, 13.12mmol) and DIPEA

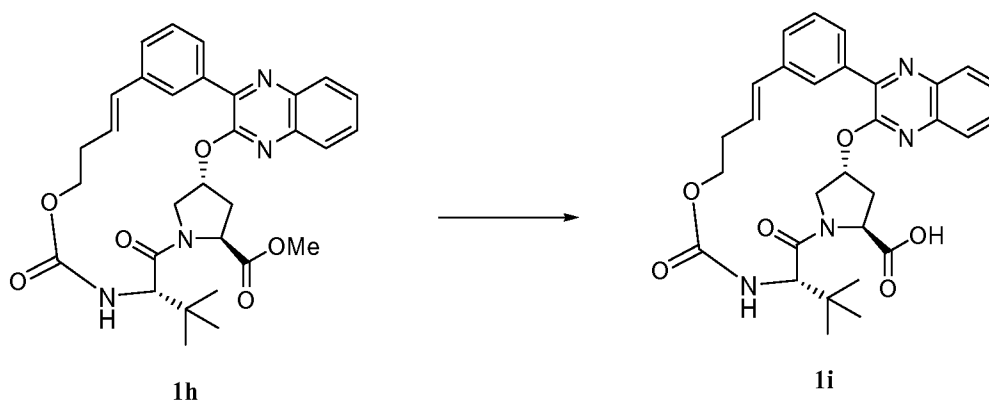
(5.6ml, 32.3mmol) in DMF (30ml) at 0 °C was added in portions HATU (5.12g, 13.5mmol). The mixture was stirred at rt for 18h, diluted with EtOAc and washed with half-sat.-aq. NaCl four times. The organic phase was dried over anhydrous MgSO₄, filtered, and then concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 9 : 1 to 4 : 1) to afford compound **1g** (6.1g).

Step 1H



To a solution of compound **1g** (95mg, 0.16mmol) in dichloromethane (20ml) was added Hoveyda-Grubbs' 1st generation catalyst or a similar catalyst (5 mol% eq.). The reaction mixture was stirred at 40°C for 20h. The solvent was then evaporated and the residue was purified by silica gel flash chromatography using gradient elution (Hexane/EtOAc = 9 : 1 to 7 : 3) to yield the macrocyclic compound **1h** (58mg). MS (ESI) *m/z* 559.30 (M+H).

Step 1I

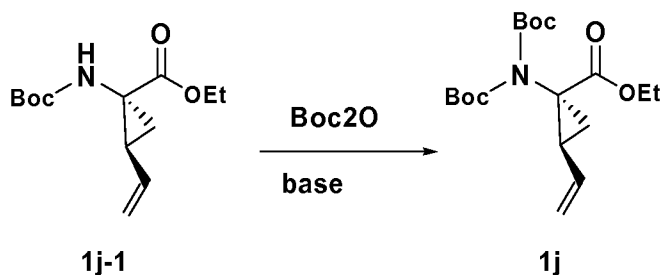


To a solution of compound **1h** (58mg, 0.103mmol) in THF/MeOH (3ml/1.5ml) was added 1N lithium hydroxide (1.5ml, 1.5mmol). The mixture was stirred at room temperature

for 20 hours. Most organic solvents were evaporated *in vacuo*, and the resulting residue was diluted with water and acidified to pH 5 to 6. The mixture was extracted with EtOAc three times. The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to afford **1i** (100%). MS(ESI): m/z 545.24 (M+H), 551.25 (M+Li).

5

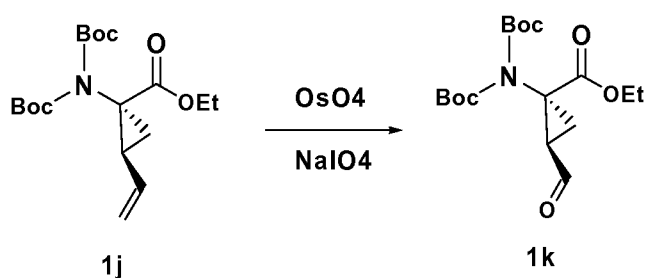
Step 1J



To a solution of compound **1j-1** (6.6g, 25.85mmol) in THF (115ml) at -78°C was added slowly NaHMDS (1.0M in THF, 28.5ml, 28.5mmol). After the mixture was stirred at -78°C for an hour, Boc₂O (6.8g, 1.2 eq.) in THF (15ml) was added. The resulting mixture was stirred, and the temperature allowed to rise gradually to rt overnight. The reaction mixture was diluted with EtOAc, washed with brine (2x), dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 1 : 0 to 85 : 15) to afford **1j** (8.05g).

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Step 1K

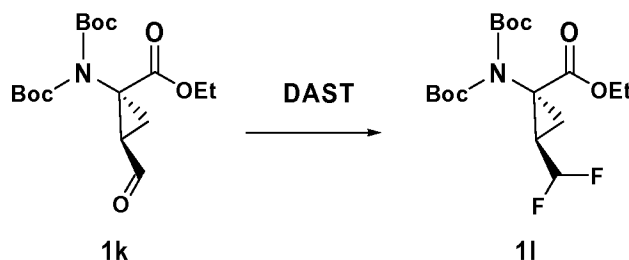


To a solution of compound **1j** (0.5g, 1.4mmol) in iso-propanol (5ml) was added NaIO₄ (0.9g, 4.2mmol), followed by water (5ml). To this vigorously stirred mixture was added OsO₄ (0.4% aq. solution, 0.22m, 2.5% eq.). The resulting mixture was stirred at rt for 4h, diluted with EtOAc, washed with aq. NaHCO₃, aq. Na₂S₂O₃, brine, dried (MgSO₄) and

20

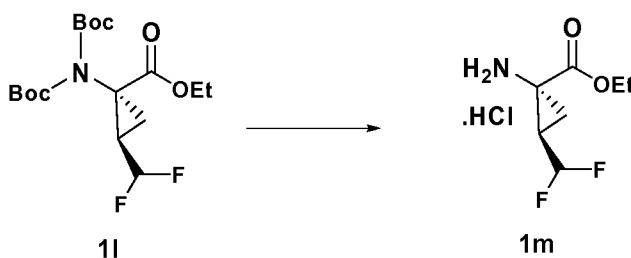
concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 1:0 to 85:15) to afford **1k** (0.37g).

Step 1L



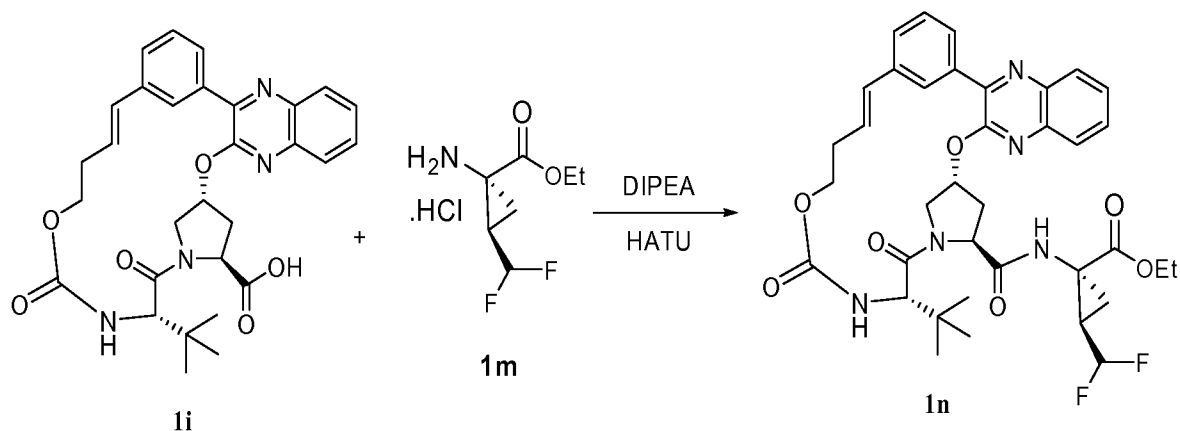
To a solution of compound **1k** (2.9g, 8.1mmol) in dichloromethane (25ml) at -78°C was added diethylaminosulfur trifluoride (DAST) (2.7ml, 20.25mmol). The resulting mixture was stirred at -78°C for an hour, then the temperature allowed to rise gradually to rt over 6h, diluted with EtOAc, washed with aq. NaHCO₃ (2x), brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 1 : 0 to 85 : 15) to afford **1l** (1.49g). Recovered starting material **1k** (1.2g).

Step 1M



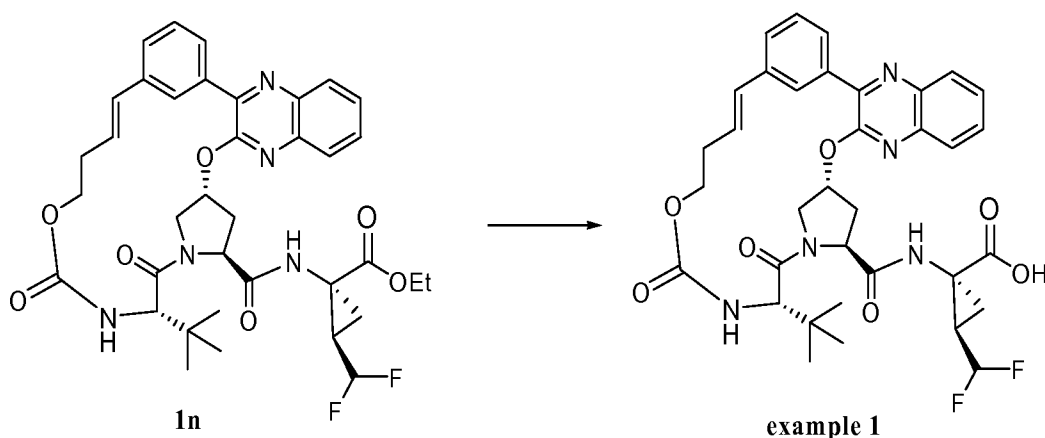
A solution of compound **1l** (491mg, 1.29mmol) in dichloromethane (1ml) was treated with 4N HCl in 1, 4-dioxane (6ml, 24mmol). The mixture was stirred at room temperature for an hour, concentrated to dryness to afford **1m** (~100%).

Step 1N



To a solution of **1i** (5.28mmol), compound **1m** (5.808mmol) and DIPEA (3.6ml, 3.9eq.) in DMF (22ml) at 0 °C was added HATU (2.31g, 6.07mmol). The mixture was stirred at room temperature for 4h, diluted with EtOAc and washed with half-sat.-aq. NaCl four times. The organic phase was dried over anhydrous MgSO₄, filtered, and then concentrated *in vacuo*. The residue was purified by silica gel column (Hexane/EtOAc = 9 : 1 to 6 : 4) to afford compound **1n** (2.85g). MS (ESI): *m/z* 706.53 (M+H).

Step 1O



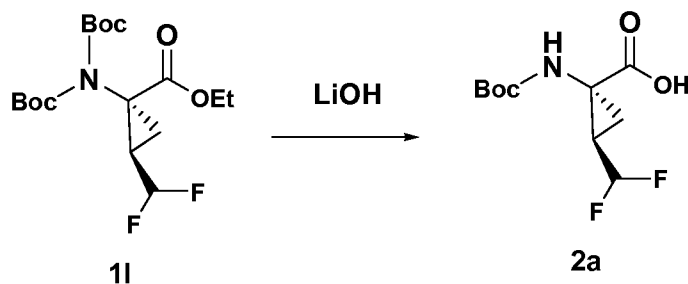
To a solution of compound **1n** (2.85g, 4.04mmol) in THF/MeOH (28ml-12ml) at 0°C was added lithium hydroxide monohydrate (1.02g, 24.2mmol) followed by water (12ml). The mixture was stirred at room temperature for 2 hours, cooled to 0°C, acidified with 1N HCl to pH 5 to 6. Some organic solvents were removed *in vacuo*, and the resulting mixture

was extracted with EtOAc three times (3x 150ml). The combined organic extracts were washed with brine (30ml), dried (MgSO₄), filtered and concentrated *in vacuo* to afford the title compound (~100%). MS(ESI): m/z 678.41 (M+H).

- 5 Example 2. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{CH}_2 \text{---} \text{CH}_2 \text{---} \text{CH}=\text{CH}_2$, $\text{Ar} = \text{---} \text{C}_6\text{H}_4 \text{---}$, $R' = \text{CF}_2\text{H}$, $G = \text{---} \text{NH} \text{---} \text{SO}_2 \text{---} \text{Cyclopropyl}$

Method I

Step 2A

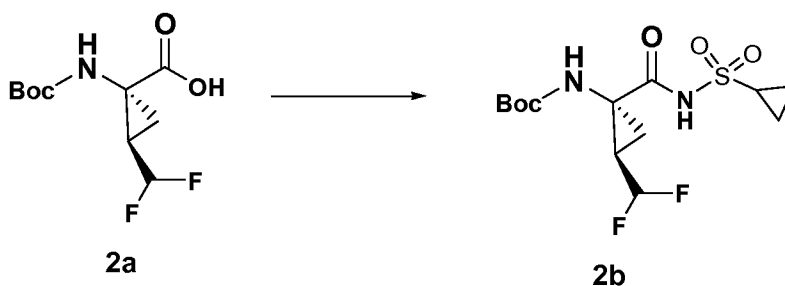


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Ethyl ester **11** (50 g, 132 mmol) was dissolved in THF (400 mL), then further diluted with MeOH (160 mL) and water (160 mL). LiOH·H₂O (27.6 g, 660 mmol) was added and the reaction mixture was stirred at rt overnight. The solution was acidified to pH ~ 2 using 1 M HCl, then extracted with DCM (3 x 500 mL). The combined organic portions were dried (Na₂SO₄), filtered, and concentrated. The crude carboxylic acid **2a** was carried directly on without any further purification.

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Step 2B

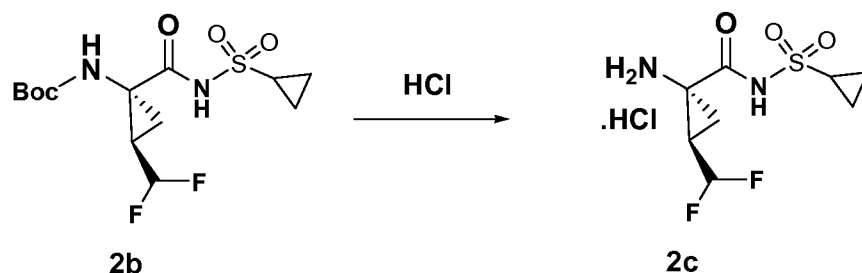


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Carboxylic acid **2a** (~ 132 mmol) was dissolved in DCM (400 mL) then cooled to 0 °C. DMAP (40.3 g, 330 mmol), sulfonamide (16.0 g, 132 mmol), and EDC (63.3 g, 330 mmol) were added and reaction was stirred at 0 °C for 1 h, warmed to rt, then stirred an additional
5 48 h. Reaction was diluted with EtOAc (1.5 L) and extracted with 1N HCl (2 x 750 mL). Combined aqueous layers were back-extracted with EtOAc, and the combined EtOAc layers were washed with brine (1 L). Organic portions were dried (Na₂SO₄), filtered, and concentrated. Crude oil was purified via SiO₂ chromatography using a 60% EtOAc/hexanes to yield the desired sulfonimide **2b** (40 g, 85%, two steps).

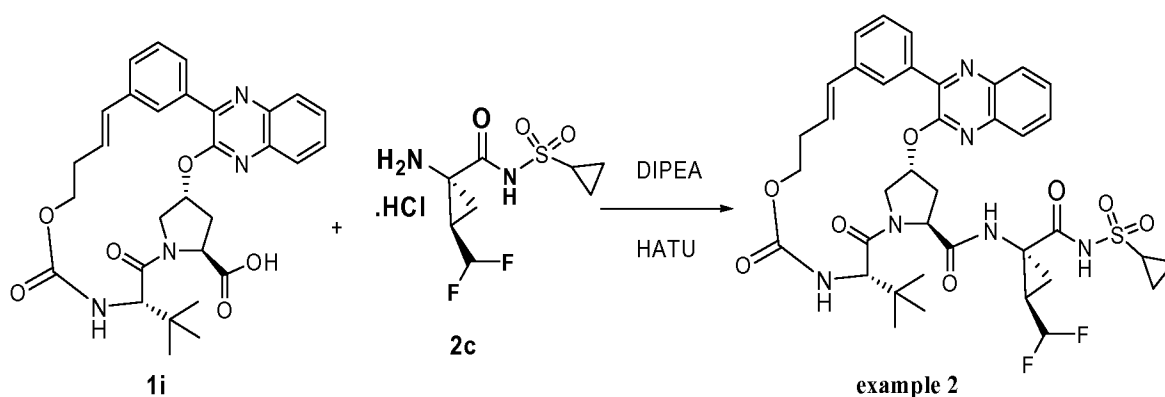
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Step 2C



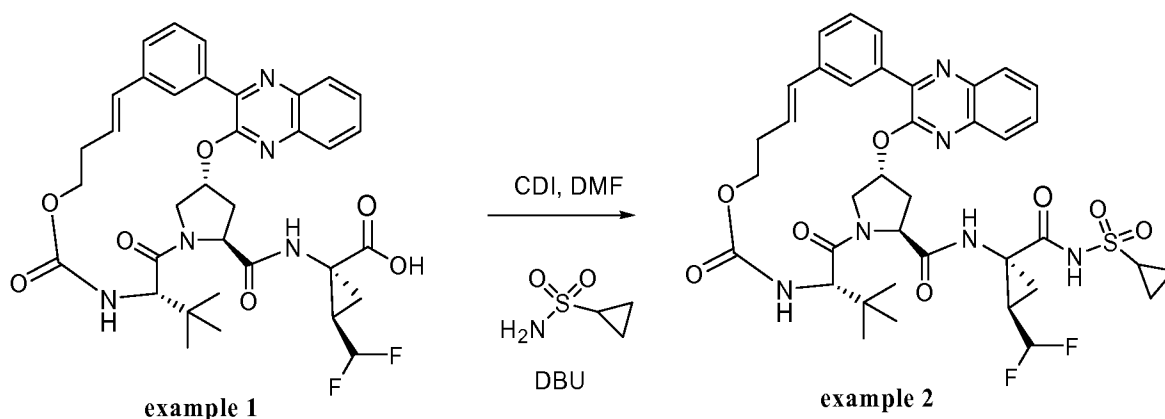
- 15 Sulfonimide **2b** (40 g, 112 mmol) was directly charged with a 4M HCl solution in dioxane (282 mL, 1.13 mol), and the resulting solution was stirred at rt for 1.5 h. The reaction mixture was concentrated *in vacuo*, and the crude oil dissolved in a minimum amount of DCM, and triturated with hexane (hexane/DCM = 3.5/1.5). The solid was then filtered and dried to give 32.4 g of the targeted compound **2c**.

Step2D



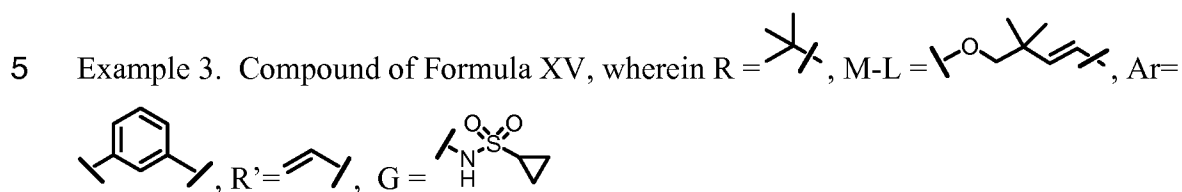
To a solution of compound **1i** (11mg, 0.02mmol), **2c** (1 eq.) and DIPEA (0.05ml, 0.287mmol) in DMF (1ml) at 0 °C was added HATU (24mg, 0.063mmol). The mixture was stirred at room temperature for 18h, diluted with EtOAc and washed with half-sat.-aq. NaCl four times. The organic phase was dried over anhydrous MgSO₄, filtered, and then concentrated *in vacuo*. The residue was purified by preparative HPLC to afford the title compound (6mg). MS(ESI); m/z 781.20 (M+H).

Method II

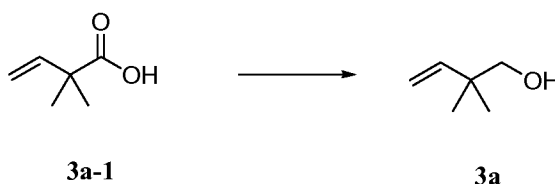


Compound of example 1 (2.78g, 4.04 mmol) and carbonyldiimidazole (1.11g, 6.85mmol) were dissolved in 22 ml of anhydrous DMF and the resulting solution was stirred at 40°C for 1 hour. Cyclopropylsulfonamide (1.22g, 10.06mmol) was added to the reaction followed by DBU (0.96ml, 6.4mmol). The reaction mixture was stirred at 40°C for 5 hours. The reaction mixture was diluted with ethyl acetate (400ml), washed with water (2x50ml), 0.5M KH₂PO₄

(2x50ml), saturated-aqueous NaCl solution (50ml), dried over anhydrous (MgSO₄) and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexans/EtOAc = 1 : 1 to 0 : 1) to give the title compound (2.4g). MS(ESI); m/z 781.20 (M+H).



Step3A

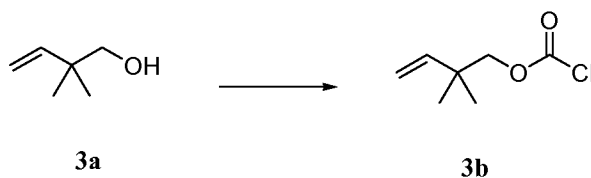


10

To a solution of compound **3a-1** (21.7g, 0.19mole) in diethyl ether (100ml) at 5-10°C was added dropwise LAH (1M in ether, 200ml, 0.2mole). The mixture was then stirred at rt for 1h, cooled to 0-5°C. EtOAc (5ml) was added slowly, followed by careful addition of 6N HCl (200ml), water (50ml) and ether (50ml). The separated aq. phase was further extracted with

15 ether (2x250ml). the combined organic layers were washed with brine (75ml), dried (sodium sulfate) and concentrated at 0°C to remove ether. Distillation under reduced pressure afforded compound **3a** (10.5g).

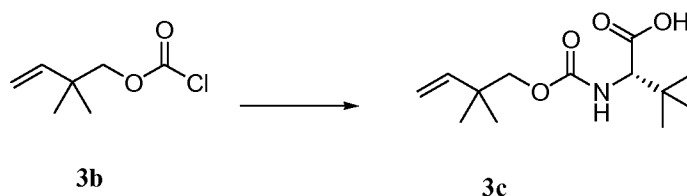
Step3B



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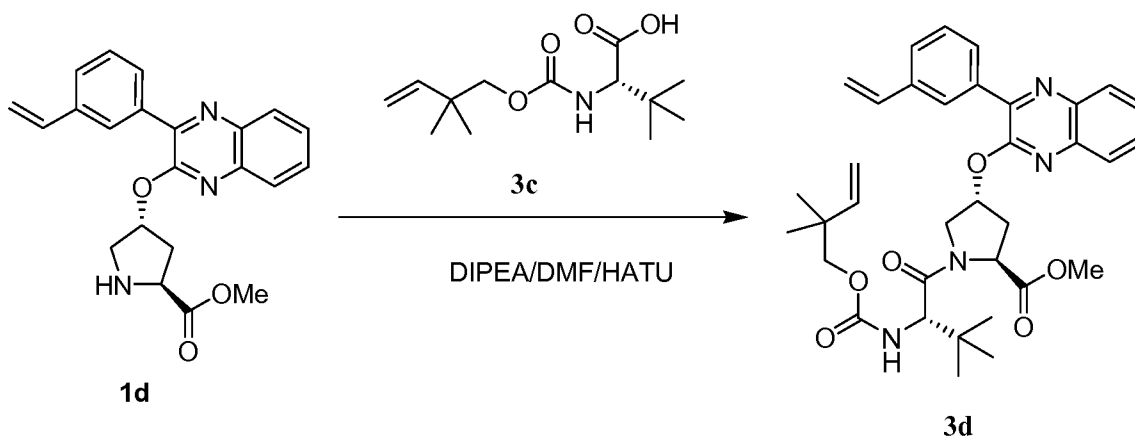
To a solution of phosgene solution in toluene (20% wt. 100ml, 188mmol) at 10°C was added dropwise compound **3a** over 20min. The mixture was stirred at rt for 3h, co-evaporated with methylene chloride (5x40ml) to afford compound **3b** (15.6g, 77% purity).

Step3C



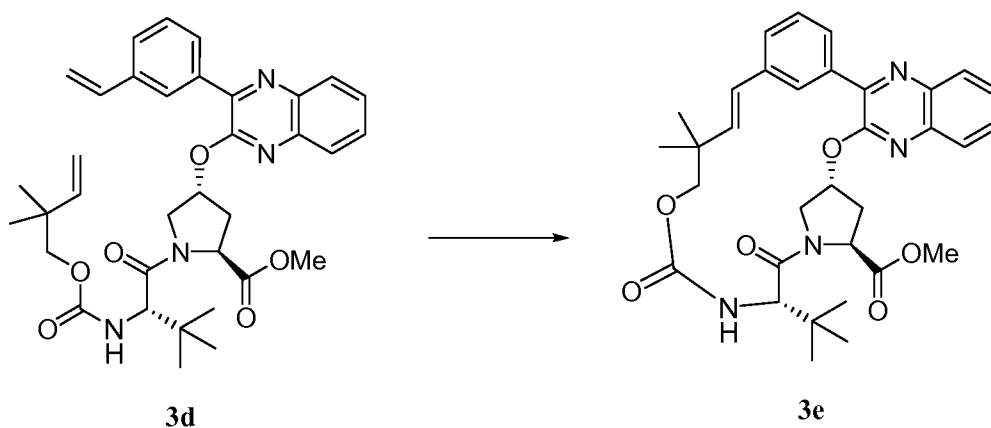
- 5 To a mixture of L-tert-leucine (5.36g, 40.8mmol) and 1,4-dioxane (22m) was added slowly 2N NaOH while the internal temperature did not exceed 30°C. The mix. was cooled to 10-15°C, compound **3b** (10.6g, 77%, 49mmol) was added slowly. The mixture was stirred at rt for 15h, then at 60°C for 3h, cooled to rt, washed with methylene chloride (3x35ml), The aqueous phase was adjusted to pH 2 to 3 with 6N HCl, extracted with EtOAc (3x70ml). The
- 10 combined EtOAc layers were washed with brine (20ml), dried (sodium sulfate) and concentrated to dryness to afford compound **3c** (8.3g).

Step3D



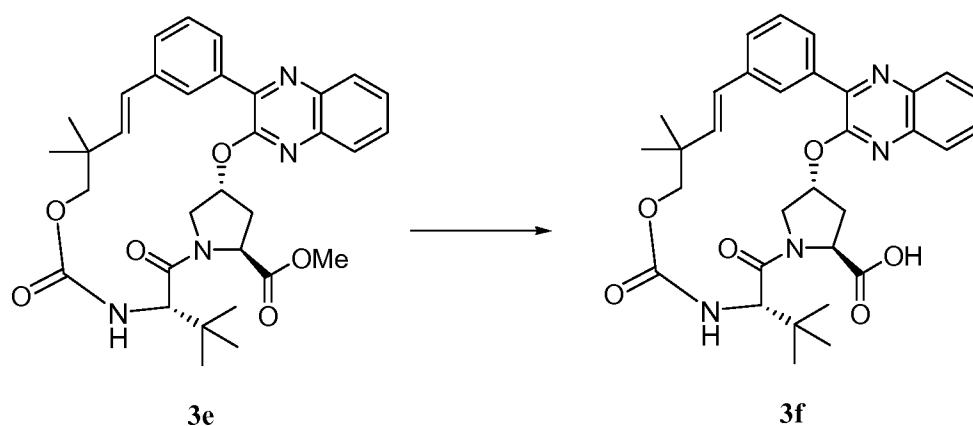
- 15 To a solution of compound **1d** (HCl salt, 13.57mmol), **3c** (3.84g, 14.9mmol) and DIPEA (7.1ml, 40.7mmol) in DMF (45ml) at 0 °C was added in portions HATU (5.95g, 15.6mmol). The mixture was stirred at rt for 18h, diluted with EtOAc (400m) and washed with water, half-sat.-aq. NaCl four times. The organic phase was dried over anhydrous Na₂SO₄, filtered,
- 20 and then concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 9 : 1 to 4 : 1) to afford compound **3d** (8.6g).

Step 3E



A solution of compound **3d** (4.04g, 6.75mmol) in toluene (1200ml) was purged with nitrogen for 0.5h and ruthenium-based catalyst Zhan 1B (0.5g 0.675mmol) was added. The mixture was stirred at 110°C for 8h, cooled to rt, 2-mercaptonicotinic acid (1.014g, 6.7mmol) and DIPEA (1.2ml, 6.75mmol) were added. The mixture was stirred at rt for 16h, filtered and concentrated. The residue was dissolved in EtOAc, washed with aq. NaHCO₃, brine, dried (sodium sulfate). The solvent was then evaporated and the residue was purified by silica gel flash chromatography using gradient elution (EtOAc/Hexane 0% to 25%) to yield compound **3e** (2.6g). MS (ESI) *m/z* 587.30 (M+H).

Step 3F



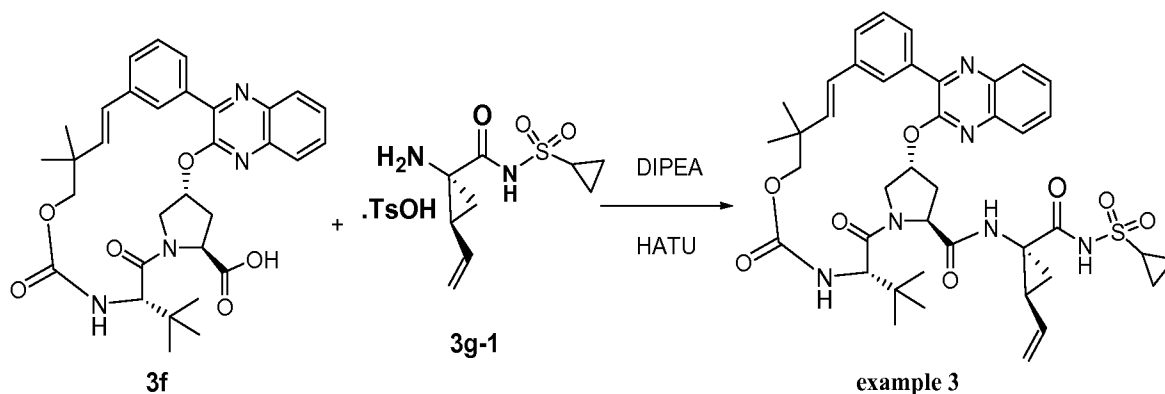
15

To a solution of compound **3e** (3.1g, 5.28mmol) in THF/MeOH (32ml/14ml) at 0°C was added lithium hydroxide hydrate (1.11g, 26.45mmol), followed by water (14ml). The

mixture was stirred at room temperature for an hour, placed at 0°C, 1N HCl (~29ml) was added dropwise until the mixture's pH = ~5. The mixture was extracted with EtOAc (3x80ml). the combined organic layers were washed with brine (30ml), dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford **3f** (~100%). MS(ESI): m/z 573.39 (M+H).

5

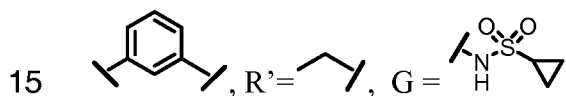
Step3G

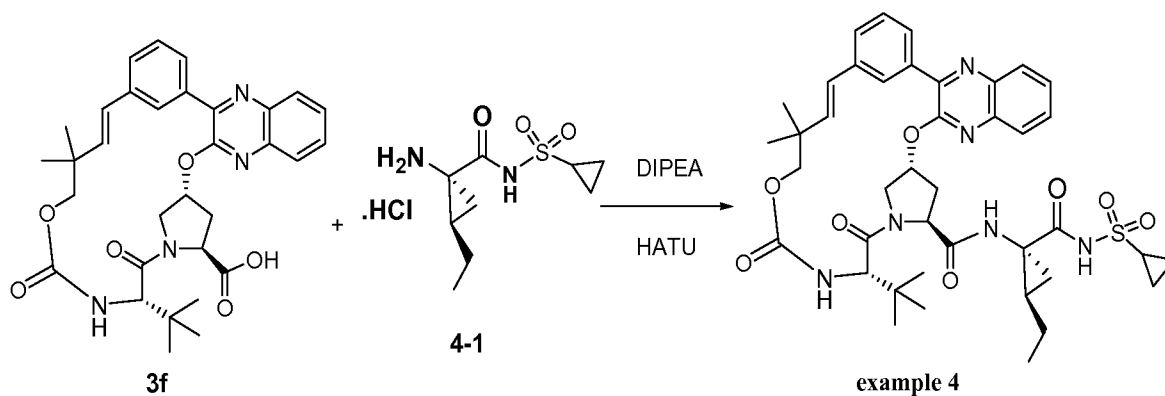


To a solution of compound **3f** (16mg, 0.028mmol), **3g-1** (14mg, 0.034.) and DIPEA (0.025ml, 0.14mmol) in DMF (1.8ml) at 0 °C was added HATU (15mg, 0.039mmol). The mixture was stirred at room temperature for 2h, and purified by preparative HPLC to afford the title compound (16mg). MS(ESI): m/z 785.26 (M+H).

10

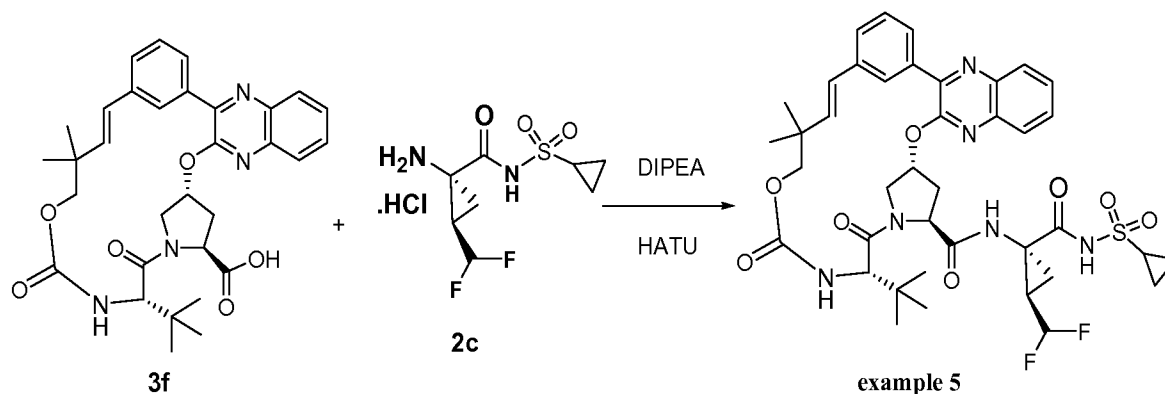
Example 4. Compound of Formula XV, wherein R = , M-L = , Ar =





To a solution of compound **3f** (15mg, 0.026mmol), **4-1** (8.4mg, 0.031.) and DIPEA (0.025ml, 0.14mmol) in DMF (1.8ml) at 0 °C was added HATU (15mg, 0.039mmol). The mixture was stirred at room temperature for 2h, and purified by preparative HPLC to afford the title compound (15mg). MS(ESI): m/z 787.39 (M+H).

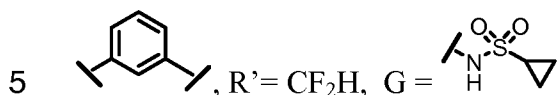
Example 5. Compound of Formula XV, wherein R = , M-L = , Ar = , R' = CF₂H, G =



To a solution of compound **3f** (1.284g, 2.07mmol), **2c** (0.681g, 2.34mmol) and DIPEA (1.1ml, 3eq.) in DMF (16ml) at 0 °C was added in portions HATU (0.914g, 2.4mmol). The mixture was stirred at room temperature for 1h, diluted with EtOAc (180ml), and washed with water (20ml), half-sat.-aq. NaCl (20ml), aq. 0.5M KH₂PO₄ (2x20ml), brine (20ml). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated *in*

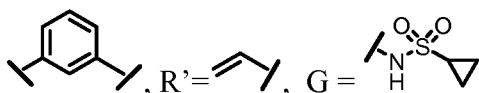
vacuo. The residue was purified by silica gel chromatography (EtOAc/Hexane 25% to 50%) to afford the title compound (1.3g). MS(ESI); m/z 809.55 (M+H).

Example 6. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{CH}_2 \text{---} \text{CH}=\text{CH}_2$, $\text{Ar} =$



This compound was prepared by the same procedures as described in Example 2 or Example 5. MS (ESI); m/e 767.35 (M+H).

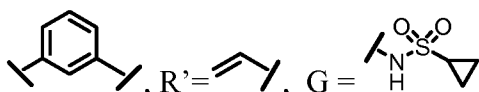
10 Example 7. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{CH}_2 \text{---} \text{CH}_2 \text{---} \text{CH}=\text{CH}_2$, $\text{Ar} =$



This compound was prepared by the same procedures as described in Example 3. MS (ESI); m/e 757.51 (M+H).

15

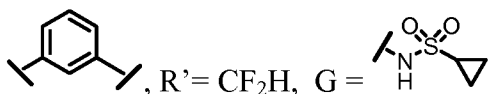
Example 8. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{CH}_2 \text{---} \text{CH}_2 \text{---} \text{CH}_2 \text{---} \text{CH}=\text{CH}_2$, $\text{Ar} =$



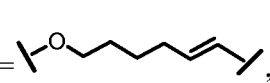
This compound was prepared by the same procedures as described in Example 3. MS (ESI); m/z 771.23 (M+H).

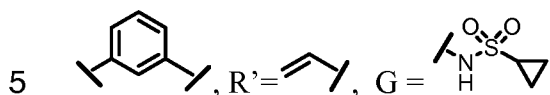
20

Example 9. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{CH}_2 \text{---} \text{CH}_2 \text{---} \text{CH}_2 \text{---} \text{CH}=\text{CH}_2$, $\text{Ar} =$

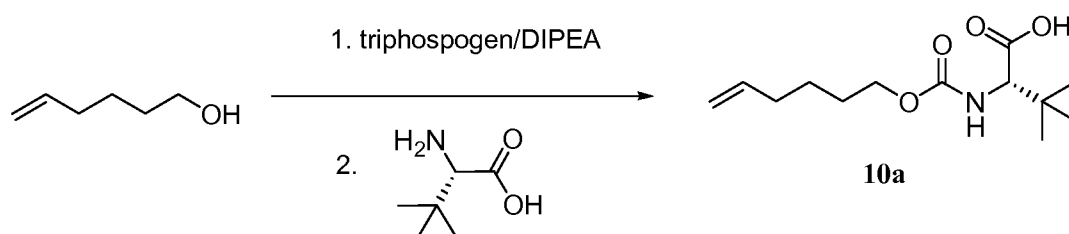


This compound was prepared by the same procedures as described in Example 2 or Example 5. MS (ESI): m/z 795.34 (M+H).

Example 10. Compound of Formula XV, wherein R = , M-L = , Ar =

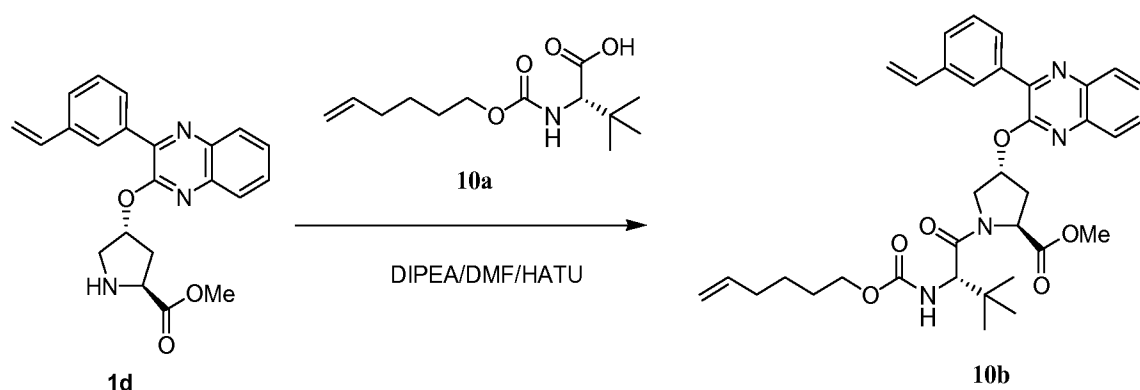


Step 10A



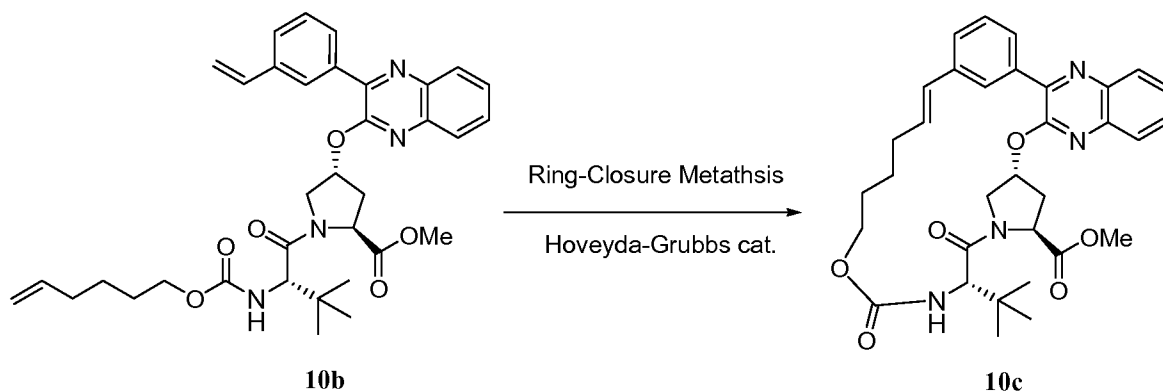
- 10 To a solution of hex-5-en-1-ol (1.3ml, 10.9mmol), triphosphogen (1.46g, 4.92mmol) in 1,4-dioxane (21ml) at 0°C was added dropwise DIPEA (1.7ml, 9.72mmol). The mixture was stirred at room temperature for an hour, cooled to 0°C. To this was added slowly L-t-leucine (1.28g, 9.72mmol) dissolved in 1N NaOH (9.8ml). The resulting mixture was stirred at room temperature overnight, concentrated to remove half volume of dioxane, treated with 1N
- 15 NaOH (25ml), washed with ether (3x30ml). The aqueous phase was acidified to pH 2~3 with 6N HCl, then extracted with dichloromethane (3x30ml). The combined organic layers were dried (MgSO₄), concentrated to dryness to give compound **10a** (2.5g) directly used in next step.

Step10B



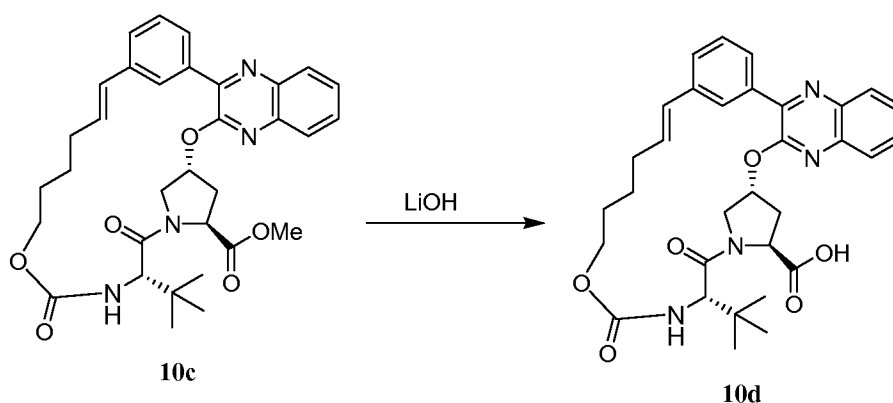
To a solution of compound **1d** (HCl salt, 98mg, 0.218mmol), compound **10a** (90mg, 0.35mmol) and DIPEA (0.24ml, 1.37mmol) in DMF (3ml) at 0 °C was added HATU (133mg, 0.35mmol). The mixture was stirred at rt for 18h, diluted with EtOAc and washed with half-sat.-aq. NaCl four times. The organic phase was dried over anhydrous MgSO₄, filtered, and then concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 6 : 1 to 4 : 1) to afford compound **10b** (119mg). MS (ESI): m/e 615.45 (M+H).

Step10C



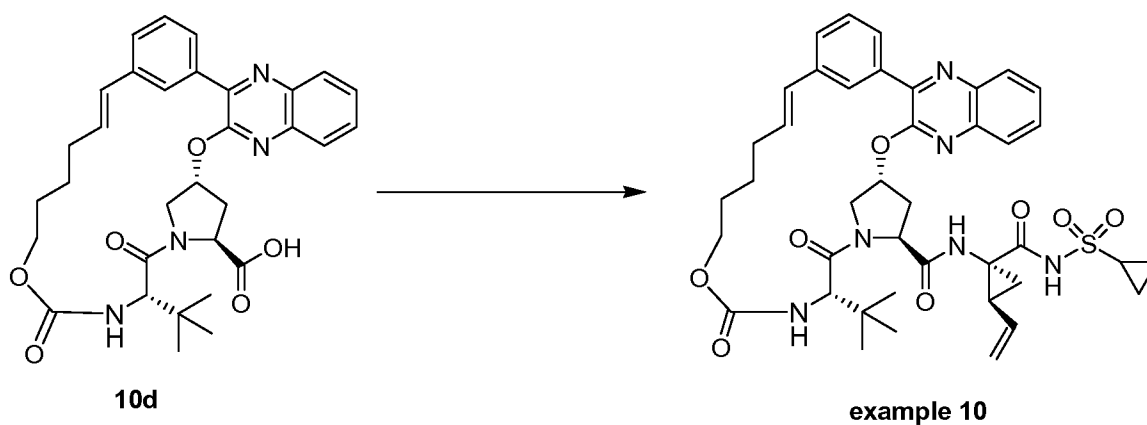
To a solution of compound **10b** (119mg, 0.19mmol) in dichloromethane (20ml) was added Hoveyda-Grubbs' 1st generation catalyst (5 mol% eq.). The reaction mixture was stirred at 40°C for 20h. The solvent was then evaporated and the residue was purified by silica gel flash chromatography using gradient elution (Hexane/EtOAc = 9 : 1 to 7 : 3) to yield the macrocyclic compound **10c** (58mg). MS (ESI) m/z 587.44 (M+H).

Step 10D



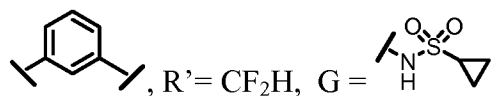
To a solution of compound **10c** (58mg, 0.099mmol) in THF/MeOH (3ml/1.5ml) was added 1N lithium hydroxide (1.5ml, 1.5mmol). The mixture was stirred at room temperature for 20 hours. Most organic solvents were evaporated *in vacuo*, and the resulting residue was diluted with water and acidified to pH 5 to 6. The mixture was extracted with EtOAc three times. The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to afford **10d** (100%). MS(ESI): m/z 573.31 (M+H), 579.32 (M+Li).

10 Step10E



This compound was prepared from **10d** by the same procedure as described in Example 3.
MS (ESI): m/z 785.31 (M+H).

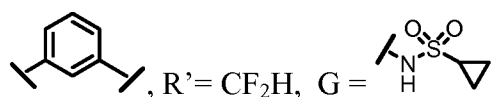
Example 11. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{CH}_2 \text{---} \text{CH}(\text{CH}_3) \text{---} \text{CH}=\text{CH}_2$, $\text{Ar} =$



This compound was prepared by the same procedures as described in Example 2 or Example 5. MS (ESI): m/z 795.53 (M+H).

5

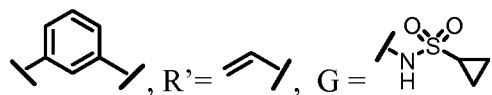
Example 12. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{CH}_2 \text{---} \text{CH}(\text{CH}_3) \text{---} \text{CH}=\text{CH}_2$, $\text{Ar} =$



This compound was prepared by the same procedures as described in Example 2 or Example 10. MS (ESI): m/z 795.58 (M+H).

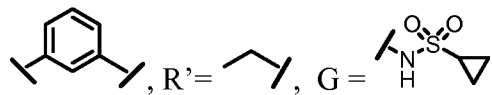
10

Example 13. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{C}(\text{CH}_3)_2 \text{---} \text{CH}=\text{CH}_2$, $\text{Ar} =$



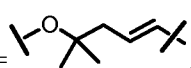
15 This compound was prepared by the same procedures as described in Example 3. MS (ESI): m/z 785.29 (M+H).

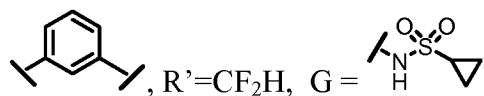
Example 14. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{C}(\text{CH}_3)_2 \text{---} \text{CH}=\text{CH}_2$, $\text{Ar} =$



20

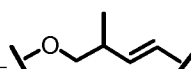
This compound was prepared by the same procedures as described in Example 4. MS (ESI): m/z 787.39 (M+H).

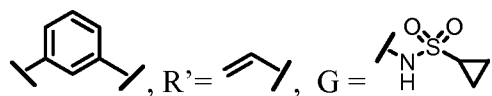
Example 15. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$



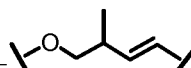
This compound was prepared by the same procedures as described in Example 2 or Example

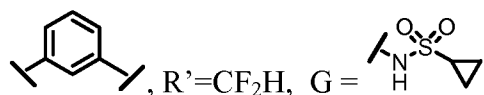
5. MS (ESI): m/e 809.28 (M+H).

Example 16. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$



10 This compound was prepared by the same procedures as described in Example 3. MS (ESI): m/e 771.11 (M+H).

Example 17. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$

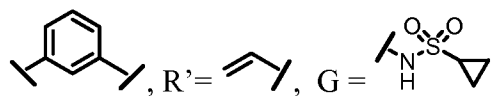


15

This compound was prepared by the same procedure as described in Example 2 or Example

5. MS (ESI): m/z 795.21 (M+H).

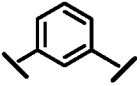
Example 18. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$



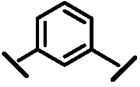
20

This compound was prepared by the same procedures as described in Example 3. MS (ESI):

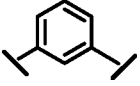
m/z 799.25 (M+H).

Example 19. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{C}(\text{CH}_3)_2 \text{CH}_2 \text{CH}=\text{CH}_2$, $\text{Ar} =$
, $R' = \text{---} \text{CH}_2 \text{CH}_2 \text{---}$, $G = \text{---} \text{N}(\text{H}) \text{---} \text{S}(=\text{O})_2 \text{---} \text{Cyclopropyl}$

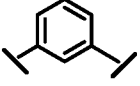
This compound was prepared by the same procedures as described in Example 4. MS (ESI):
 5 m/z 801.22 (M+H).

Example 20. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{C}(\text{CH}_3)_2 \text{CH}_2 \text{CH}=\text{CH}_2$, $\text{Ar} =$
, $R' = \text{---} \text{CF}_2 \text{H}$, $G = \text{---} \text{N}(\text{H}) \text{---} \text{S}(=\text{O})_2 \text{---} \text{Cyclopropyl}$

10 This compound was prepared by the same procedures as described in Example 2 or Example
 5. MS (ESI): m/z 823.21 (M+H).

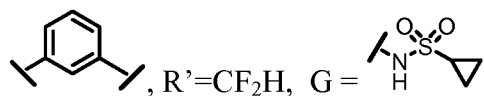
Example 21. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{C}(\text{CH}_3)_2 \text{CH}_2 \text{CH}=\text{CH}_2$, $\text{Ar} =$
, $R' = \text{---} \text{CH}=\text{CH}_2$, $G = \text{---} \text{N}(\text{H}) \text{---} \text{S}(=\text{O})_2 \text{---} \text{Cyclopropyl}$

15 This compound was prepared by the same procedures as described in Example 3. MS (ESI):
 m/z 813.42 (M+H).

Example 22. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{C}(\text{CH}_3)_2 \text{CH}_2 \text{CH}=\text{CH}_2$, $\text{Ar} =$
, $R' = \text{---} \text{CH}_2 \text{CH}_2 \text{---}$, $G = \text{---} \text{N}(\text{H}) \text{---} \text{S}(=\text{O})_2 \text{---} \text{Cyclopropyl}$

20 This compound was prepared by the same procedures as described in Example 4. MS (ESI):
 m/z 815.43 (M+H).

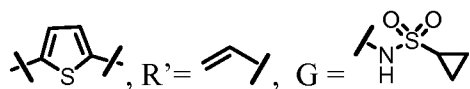
Example 23. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{C}(\text{CH}_3)_2 \text{CH}_2 \text{CH}=\text{CH}_2$, $\text{Ar} =$



This compound was prepared by the same procedures as described in Example 2 or Example

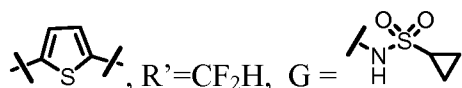
5. MS (ESI): m/z 837.41 (M+H).

Example 24. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{CH}_2 \text{CH}_2 \text{CH}=\text{CH}_2$, $\text{Ar} =$



10 This compound was prepared by the same procedures as described in Example 3. MS (ESI): m/z 763.25 (M+H).

Example 25. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{CH}_2 \text{CH}_2 \text{CH}=\text{CH}_2$, $\text{Ar} =$

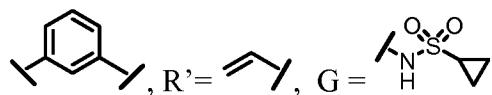


15

This compound was prepared by the same procedures as described in Example 2 or Example

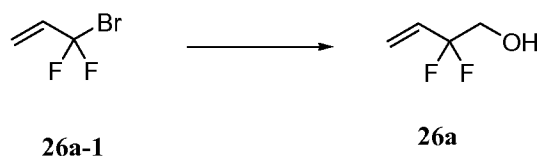
5. MS (ESI): m/z 787.22 (M+H).

Example 26. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{C}(\text{F})_2 \text{CH}_2 \text{CH}=\text{CH}_2$, $\text{Ar} =$



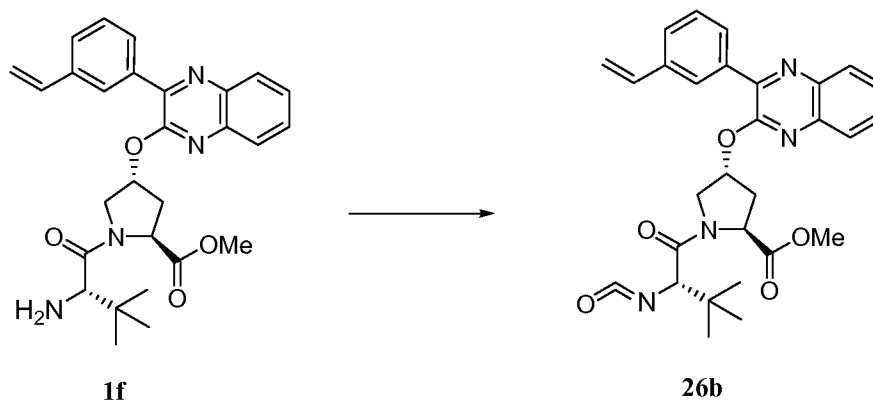
20

Step 26A



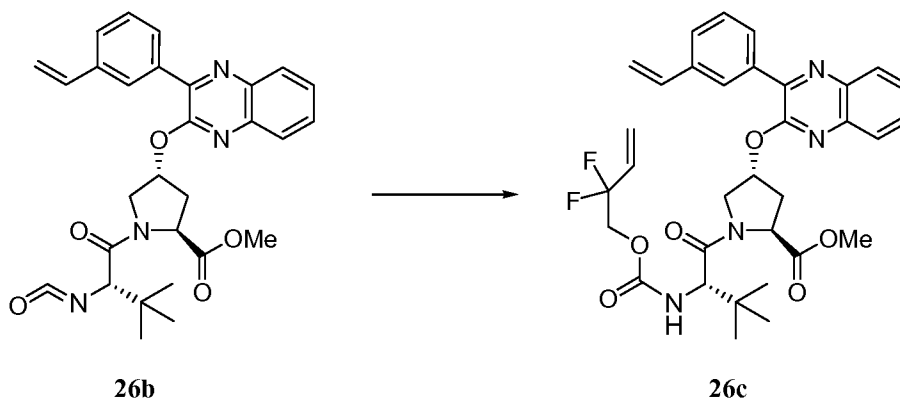
To a solution of **26a-1** (3.4g, 21.6mmol), HCOOEt (3.5ml, 43.2mmol) in THF (100ml)-
 5 ether (30ml)-pentane (30ml) at -95°C (liquid N₂ and toluene bath) was added dropwise n-BuLi (2.5 M in hexane, 10ml, 25mmol). The mix. was stirred at that temperature for 1.5h and the bath temperature was allowed to rise gradually to 0°C over 2-3h, quenched with aq. solution of NH₄Cl (1.4g in 20ml of water). The mix. was stirred for 15min. To the separated organic layer was added MeOH (50ml), followed by adding NaBH₄ (1g) in portions at 0°C.
 10 The mixture was stirred at rt for 0.5h, cooled to 0°C, quenched carefully with 1N HCl, to pH ~3, extracted with ether (3x). The combined organic layers were washed with aq. NaHCO₃, brine, dried (Na₂SO₄) and concentrated at 0°C. The residue was purified by distillation to yield **26a** (1.3g).

15 Step 26B



To a solution of compound **1f** (6.23g, 11.10mmol) in methylene chloride (100ml) at 0°C was added pyridine (5.4ml, 67mmol), followed by dropwise addition of phosgene solution (20% wt. in toluene, 17mmol) over a period of 0.5h. the mixture was stirred at rt for 0.5h, diluted
 20 with EtOAc (500ml), washed with water (70ml), brine (2x70ml), dried (sodium sulfate), filtered and concentrated to dryness to afford compound **26b** (5.3g). MS(ESI): m/z 515.28 (M+H)

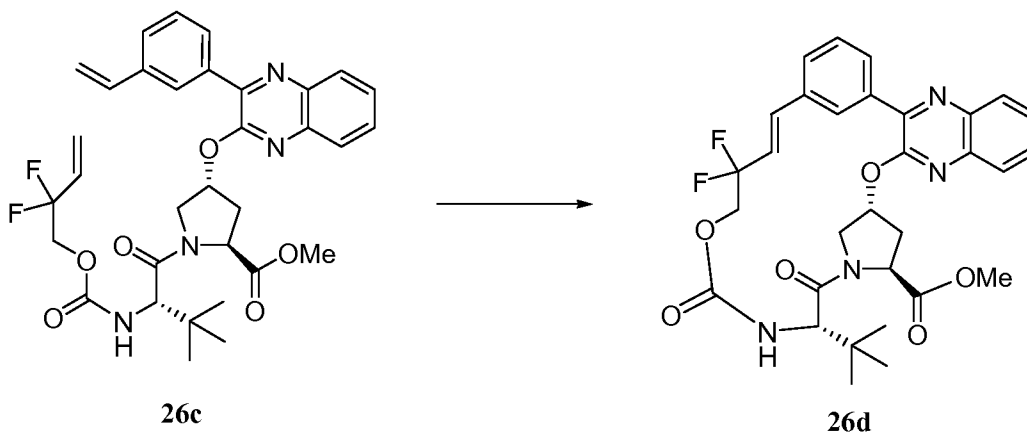
Step 26C



To a solution of compound **26b** (4.89g, 9.5mmol) and **26a** (~1.4eq.) in methylene chloride
 5 (65ml) was added molecular sieve (4A, 5g). After the mixture was stirred at rt for 0.5h, DBU
 (2.1ml, 16=4mmol) was added. The resulting mixture was stirred at rt for 2h and
 concentrated. The residue was purified by silica gel flash chromatography using gradient
 elution (EtOAc/Hexane 0% to 25%) to yield compound **26c** (6.1g). MS (ESI) m/z 623.34
 (M+H).

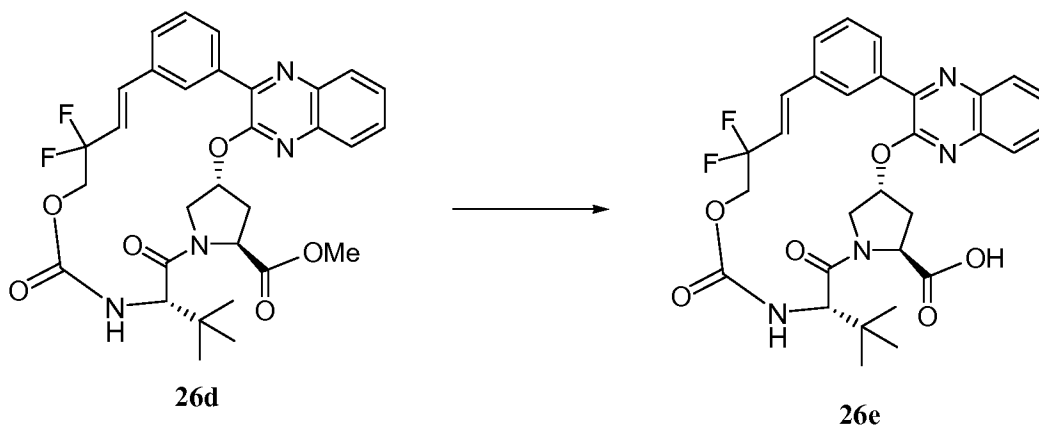
10

Step 26D



Compound **26d** was prepared from compound **26c** by the same procedure as described in
 15 Step3E of example 3. MS (ESI) m/z 595.01 (M+H).

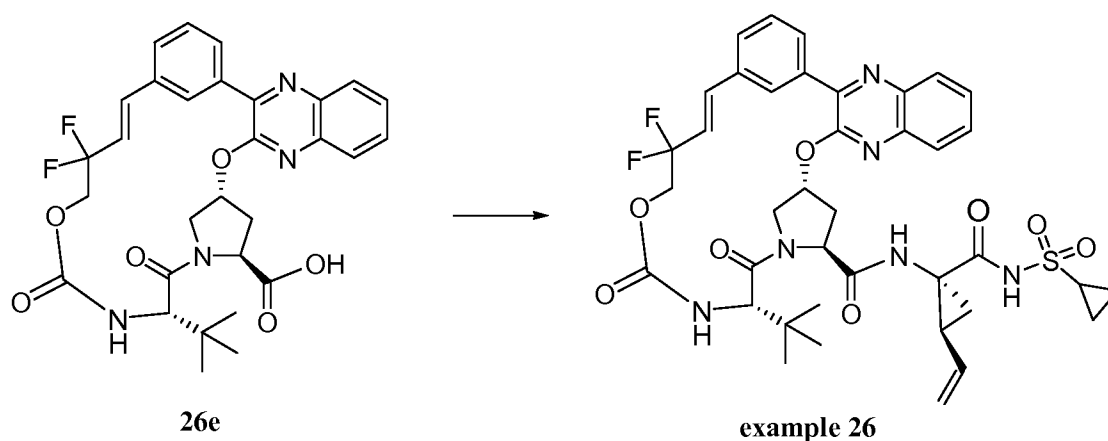
Step 26E



Compound **26e** was prepared from compound **26d** by the same procedure as described in Step3F of example 3. MS (ESI) m/z 581.15 (M+H).

5

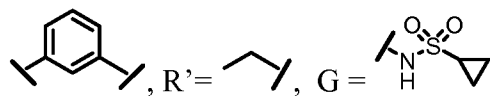
Step 26F



Compound example 26 was prepared from **26e** by the same procedures as described in Example 3. MS (ESI): m/z 793.20 (M+H).

10

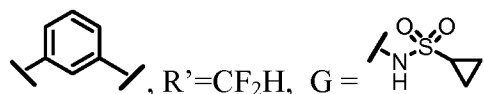
Example 27. Compound of Formula XV, wherein $R =$, $M-L =$, $Ar =$



This compound was prepared from compound **26e** by the same procedures as described in Example 4. MS (ESI): m/z 795.43 (M+H).

15

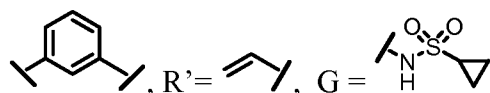
Example 28. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{C}(\text{F})(\text{F}) \text{---} \text{CH}=\text{CH} \text{---}$, $\text{Ar} =$



This compound was prepared from compound **26e** by the same procedures as described in

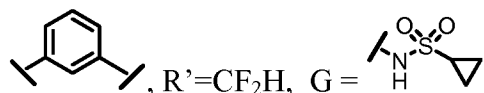
5 Example 5. MS (ESI): m/z 817.27 (M+H).

Example 29. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{N}(\text{H}) \text{---} \text{CH}_2 \text{CH}_2 \text{CH}=\text{CH} \text{---}$, $\text{Ar} =$



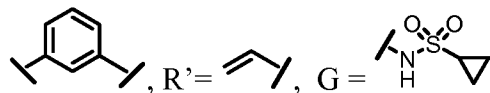
10 This compound was prepared by the same procedures as described in Example 3. MS (ESI): m/z 756.23 (M+H).

Example 30. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{N}(\text{H}) \text{---} \text{CH}_2 \text{CH}_2 \text{CH}=\text{CH} \text{---}$, $\text{Ar} =$



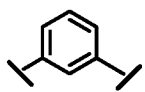
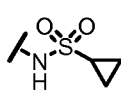
15 This compound was prepared by the same procedures as described in Example 2 or Example 5. MS (ESI): m/z 780.19 (M+H).

Example 31. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}=\text{CH} \text{---}$, $\text{Ar} =$



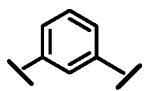
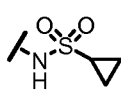
20

This compound was prepared by the same procedures as described in Example 3. MS (ESI): m/z 755.13 (M+H).

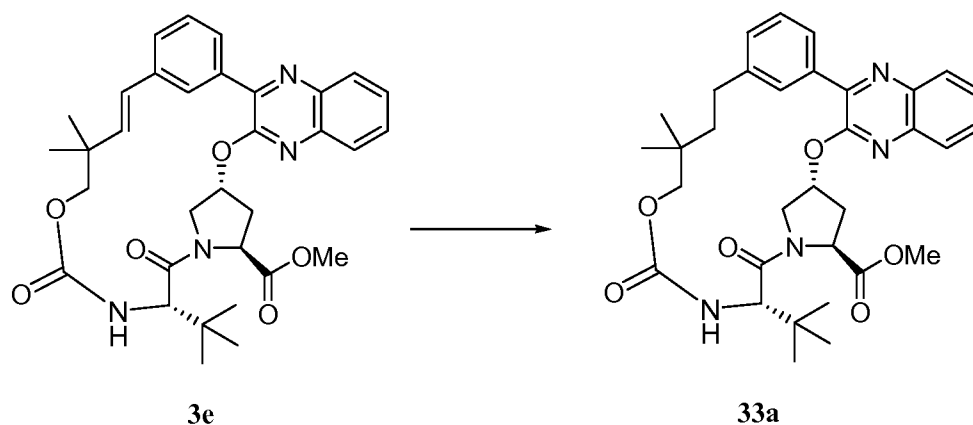
Example 32. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$ , $R' = CF_2H$, $G =$ 

This compound was prepared by the same procedures as described in Example 2 or Example

5. MS (ESI): m/z 779.26 (M+H).

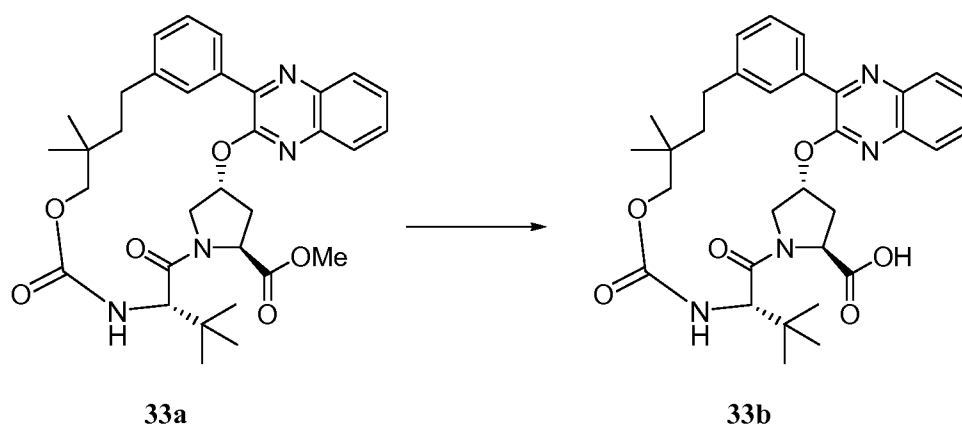
Example 33. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$ , $R' =$ , $G =$ 

Step 33A



A mixture of **3e** (1.52g, 2.59mmol), Pd-C (10% wt. 182mg) and EtOAc (38ml) was hydrogenated for 10h, filtered and concentrated. The residue was purified by silica gel flash chromatography using gradient elution (EtOAc/Hexane 0% to 25%) to yield compound **33a** (1.3g). MS (ESI): m/z 589.27 (M+H).

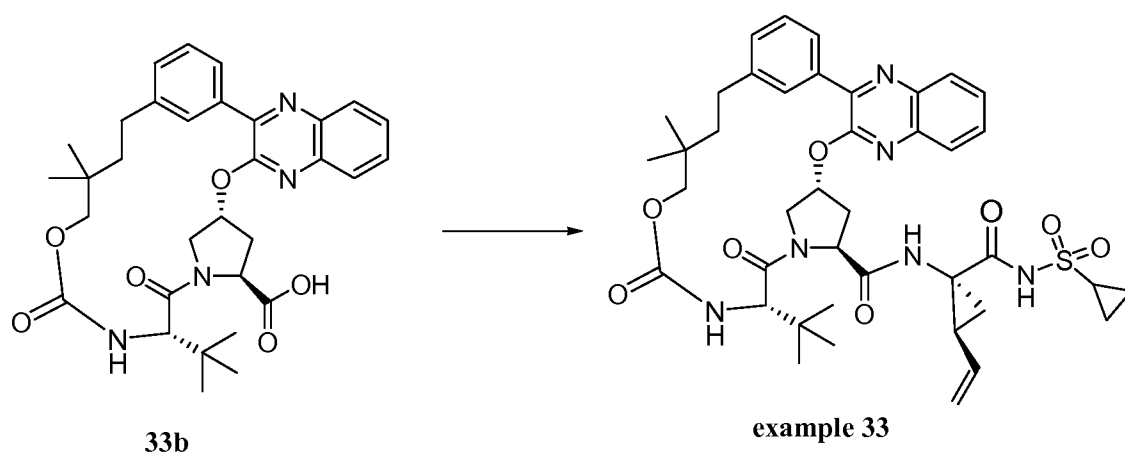
Step 33B



Compound **33b** was prepared from **33a** by the same procedures as described in Step3F of

5 Example 3. MS(ESI): m/z 575.15 (M+H).

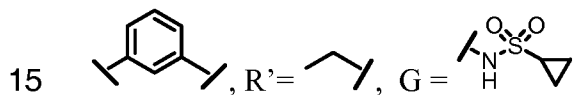
Step 33C



10

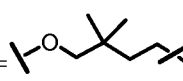
Compound of example 33 was prepared from **33b** by the same procedures as described in Example 3. MS (ESI): m/z 778.39 (M+H).

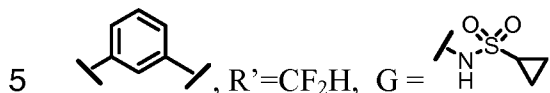
Example 34. Compound of Formula XV, wherein R = , M-L = , Ar =



This compound was prepared from **33b** by the same procedures as described in Example 4.

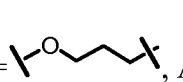
MS (ESI): m/z 789.37 (M+H).

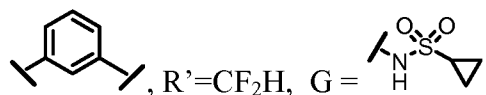
Example 35. Compound of Formula XV, wherein R = , M-L = , Ar =



This compound was prepared from **33b** by the same procedures as described in Example 5.

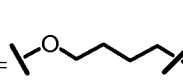
MS (ESI): m/z 811.26 (M+H).

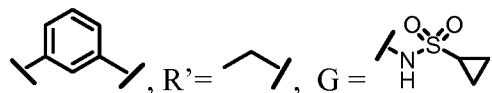
10 Example 36. Compound of Formula XV, wherein R = , M-L = , Ar =



This compound was prepared by the same procedures as described in Example 35. MS (ESI): m/z 769.35 (M+H).

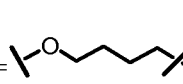
15

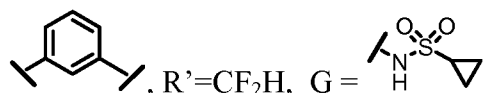
Example 37. Compound of Formula XV, wherein R = , M-L = , Ar =



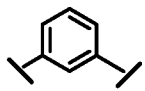
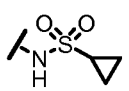
This compound was prepared by the same procedures as described in Example 34. MS (ESI):

20 m/z 761.62 (M+H).

Example 38. Compound of Formula XV, wherein R = , M-L = , Ar =

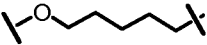
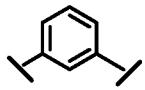
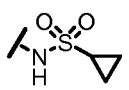


This compound was prepared by the same procedures as described in Example 35. MS (ESI): m/z 783.38 (M+H).

Example 39. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$ , $R' =$ , $G =$ 

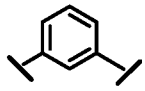
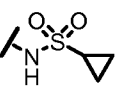
5

This compound was prepared by the same procedures as described in Example 33. MS (ESI): m/z 773.49 (M+H).

Example 40. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$ , $R' =$ , $G =$ 

10

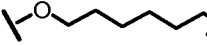
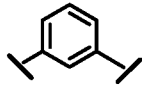
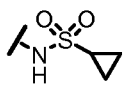
This compound was prepared by the same procedures as described in Example 34. MS (ESI): m/z 775.36 (M+H).

Example 41. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$ , $R' = CF_2H$, $G =$ 

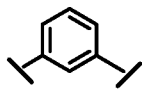
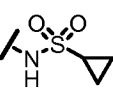
15

This compound was prepared by the same procedures as described in Example 35. MS (ESI): m/z 797.34 (M+H).

20

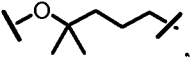
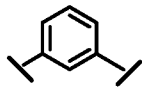
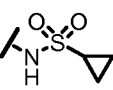
Example 42. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$ , $R' =$ , $G =$ 

This compound was prepared by the same procedures as described in Example 33. MS (ESI): m/z 787.41 (M+H).

Example 43. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$ , $R' =$ , $G =$ 

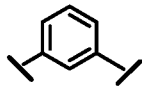
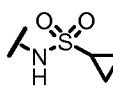
5

This compound was prepared by the same procedures as described in Example 34. MS (ESI): m/z 789.26 (M+H).

Example 44. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$ , $R' = CF_2H$, $G =$ 

10

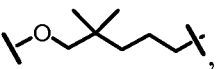
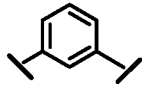
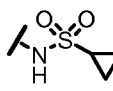
This compound was prepared by the same procedures as described in Example 35. MS (ESI): m/z 811.28 (M+H).

Example 45. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$ , $R' =$ , $G =$ 

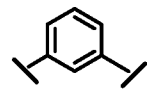
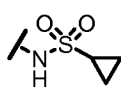
15

This compound was prepared by the same procedures as described in Example 33. MS (ESI): m/z 801.57 (M+H).

20

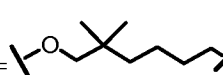
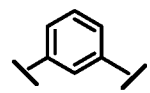
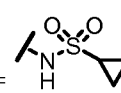
Example 46. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$ , $R' =$ , $G =$ 

This compound was prepared by the same procedures as described in Example 34. MS (ESI): m/z 803.57 (M+H).

Example 47. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$ , $R' = CF_2H$, $G =$ 

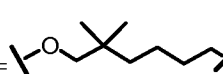
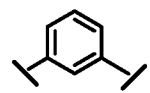
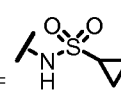
5

This compound was prepared by the same procedures as described in Example 35. MS (ESI): m/z 825.50 (M+H).

Example 48. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$ , $R' =$ , $G =$ 

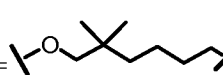
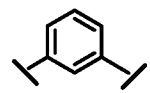
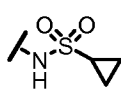
10

This compound was prepared by the same procedures as described in Example 33. MS (ESI): m/z 815.46 (M+H).

Example 49. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$ , $R' =$ , $G =$ 

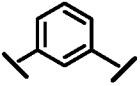
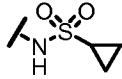
15

This compound was prepared by the same procedures as described in Example 34. MS (ESI): m/z 817.46 (M+H).

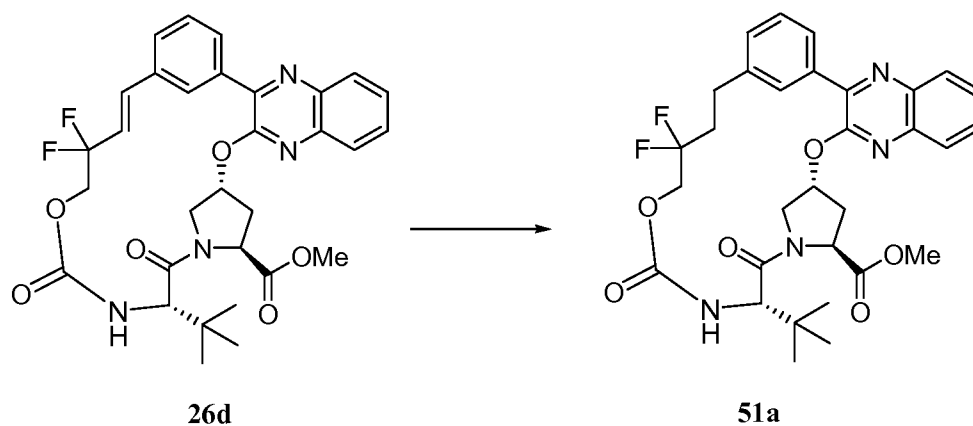
Example 50. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$ , $R' = CF_2H$, $G =$ 

20

This compound was prepared by the same procedures as described in Example 35. MS (ESI): m/z 839.46 (M+H).

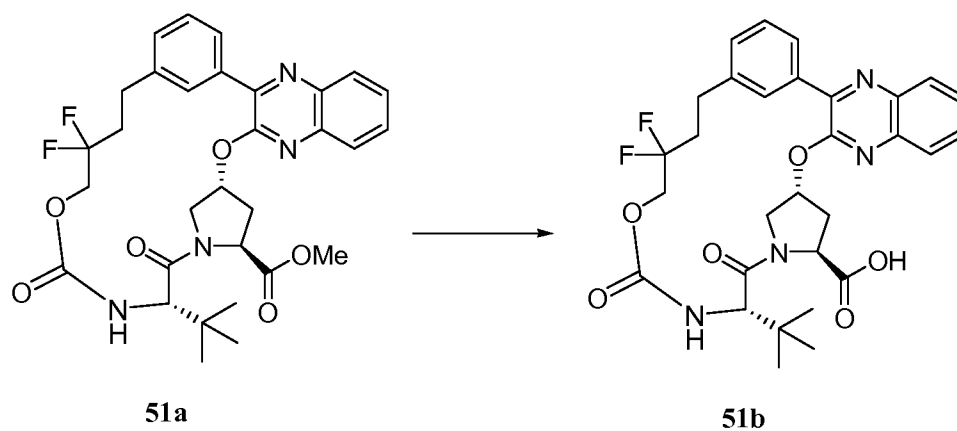
Example 51. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{C}(\text{F})_2 \text{---}$, $\text{Ar} =$ , $R' = \text{---} \text{CH}=\text{CH} \text{---}$, $G =$ 

5 Step 51A



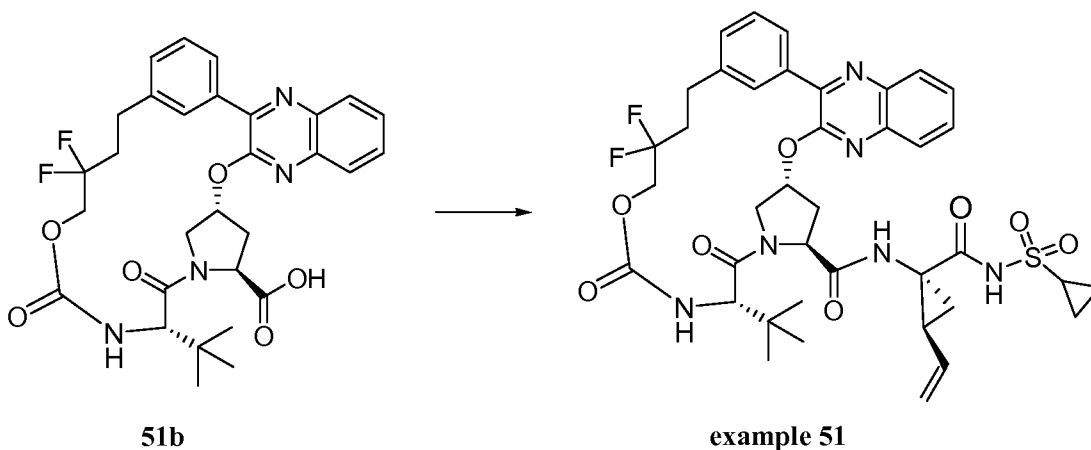
A mixture of **26d** (2.55g, 4.286mmol), Pd-C (10% wt. 255mg), DIPEA (1.5ml) and EtOAc (65ml) was hydrogenated for 4h, filtered and concentrated. The residue was purified by silica gel flash chromatography using gradient elution (EtOAc/Hexane 0% to 25%) to yield compound **51a** (1.83g). MS (ESI): m/z 597.05 ($M+H$).

Step 51B

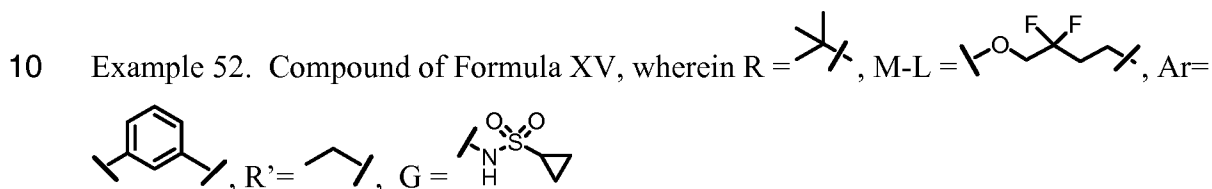


Compound **51b** was prepared from compound **51a** by the same procedure as described in Step3F of example 3. MS (ESI) m/z 583.04 (M+H).

Step 51C

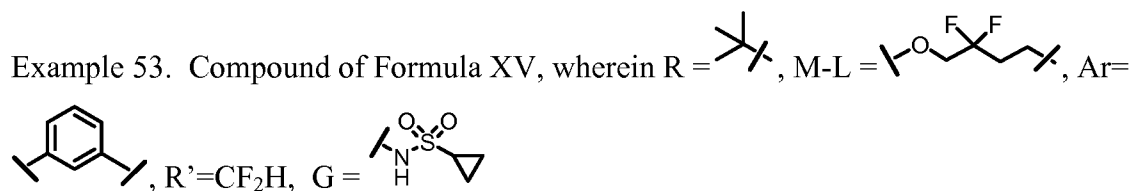


Compound of example 51 was prepared from **51b** by the same procedures as described in Example 3. MS (ESI): m/z 795.27 (M+H).



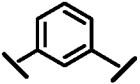
This compound was prepared from **51b** by the same procedures as described in Example 4. MS (ESI): m/z 797.43 (M+H).

15

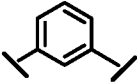
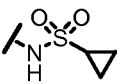


This compound was prepared from **51b** by the same procedures as described in Example 5.

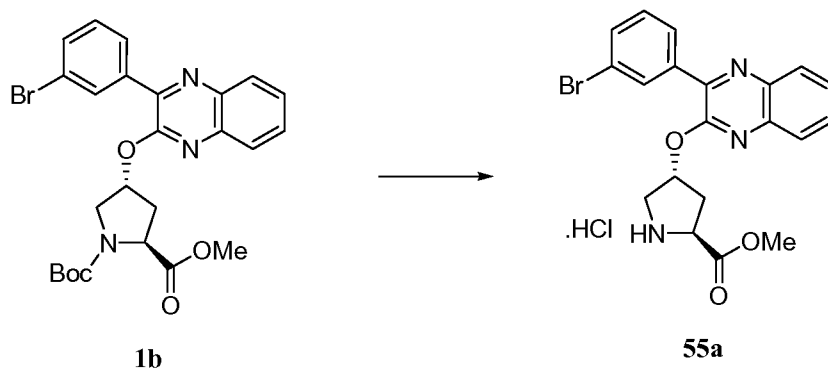
20 MS (ESI): m/z 819.43 (M+H).

Example 54. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_3 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{---}$, $\text{Ar} =$ , $R' = \text{CF}_2\text{H}$, $G = \text{OH}$

This compound was prepared by the same procedures as described in Example 1. MS (ESI):
 5 m/z 680.46 (M+H).

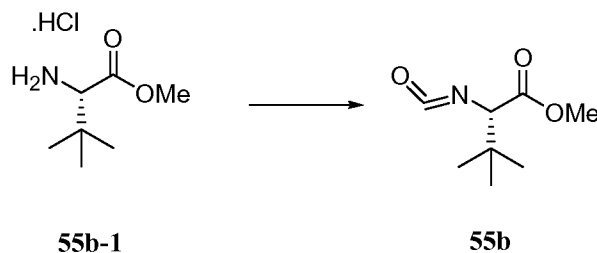
Example 55. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_3 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{C}(\text{CH}_3)_2 \text{CH}_2 \text{O} \text{---}$, $\text{Ar} =$ , $R' = \text{---} \text{CH}=\text{CH} \text{---}$, $G =$ 

10 Step 55A



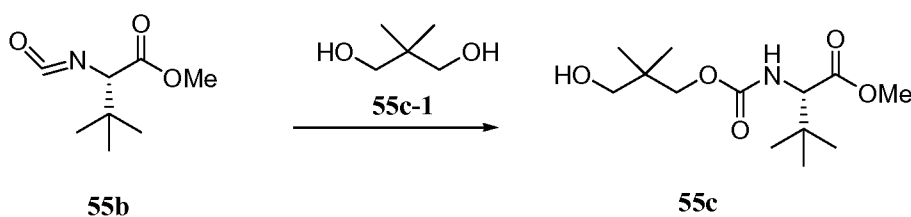
A solution of compound **1b** (1g, 1.9mmol) in dichloromethane (1ml) was treated with 4M HCl/dioxane (6ml, 24mmol). The resulting mixture was stirred at room temperature for 2
 15 hours, and concentrated in vacuo to dryness to afford HCl salt compound **55a** (100%).

Step 55B



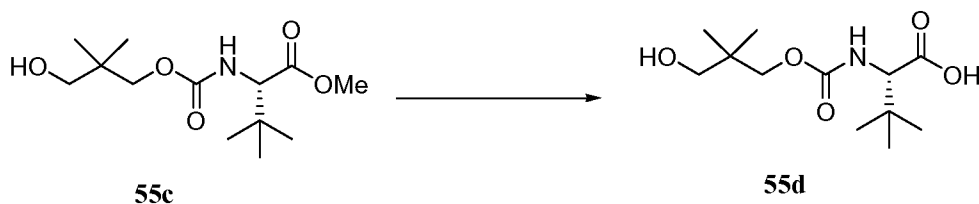
To a solution of compound **55b-1** (1.046g, 5.5mmol) in dichloromethane (30ml) at 0°C was added pyridine (2.23ml), followed by dropwise addition of phosgene solution (in toluene, 20% wt., 4.4ml, 8.3mmol). The mixture was stirred at 0°C for 2h, diluted with EtOAc, washed with 1N HCl, brine, dried (sodium sulfate) and concentrated to dryness to afford **55b** (0.95g).

Step 55C



To a solution of compound **55b** (0.228g, 1.33mmol) and **55c-1** (1.4g, 13.3mmol) in dichloromethane (10ml) - DMF (2ml) at rt was added DBU (0.3ml, 2.18mmol). The mixture was stirred at rt for 16h, diluted with EtOAc, washed with water, brine twice, 1N HCl, brine, dried (sodium sulfate) and concentrated. The residue was purified by silica gel flash chromatography using gradient elution (EtOAc/Hexane 0% to 30%) to yield compound **55c** (0.303g).

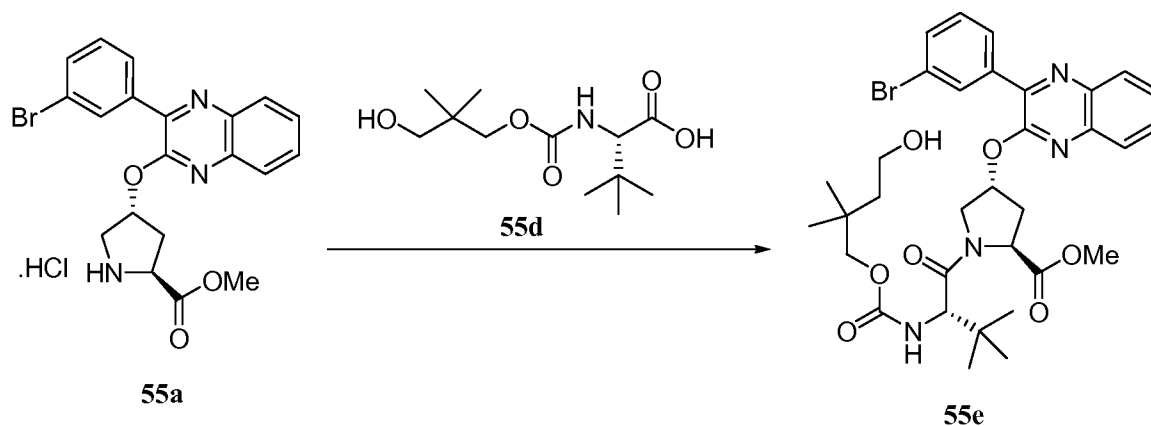
Step 55D



To a solution of compound **55c** (0.255g, 0.93mmol) in THF/MeOH (6ml/2.6ml) at 0°C was lithium hydroxide hydrate (0.195g, 4.6mmol), followed by water (2.6ml). The mixture was stirred at room temperature for 16h, placed at 0°C, 1N HCl was added dropwise until the mixture's pH = ~3. The mixture was extracted with EtOAc three times. the combined

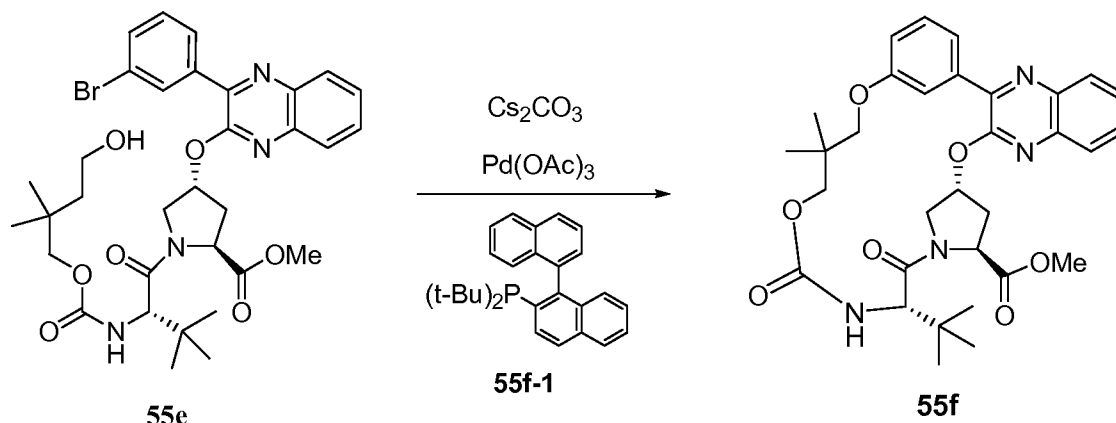
organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford **55d** (0.227g).

Step 55E

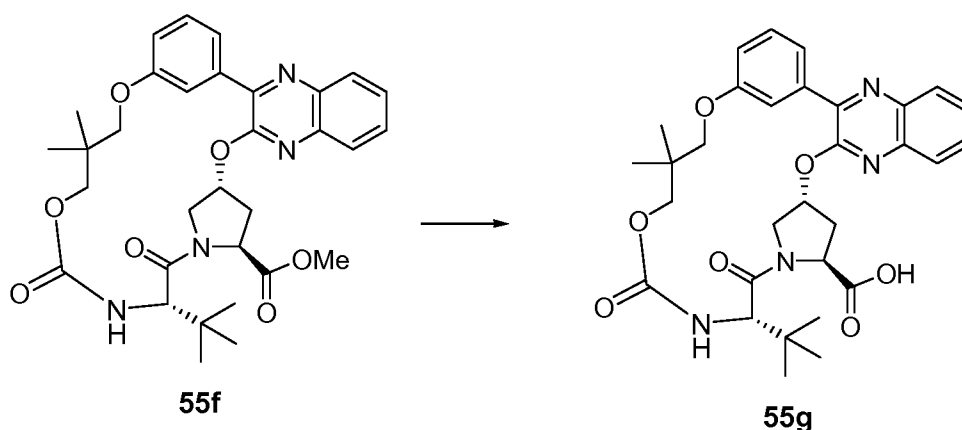


To a solution of compound **55a** (0.52g, 1.1mmol), **55d** (0.93mmol) and DIPEA (0.81ml, 5eq.) in DMF (8ml) at 0 °C was added in portions HATU (0.407g, 1.07mmol). The mixture was stirred at room temperature for 16h, diluted with EtOAc, washed with water once, brine four times. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc/Hexane 0% to 40%) to afford **55e** (0.328g). MS(ESI); m/z 671.32, 673.32 ($M+H$).

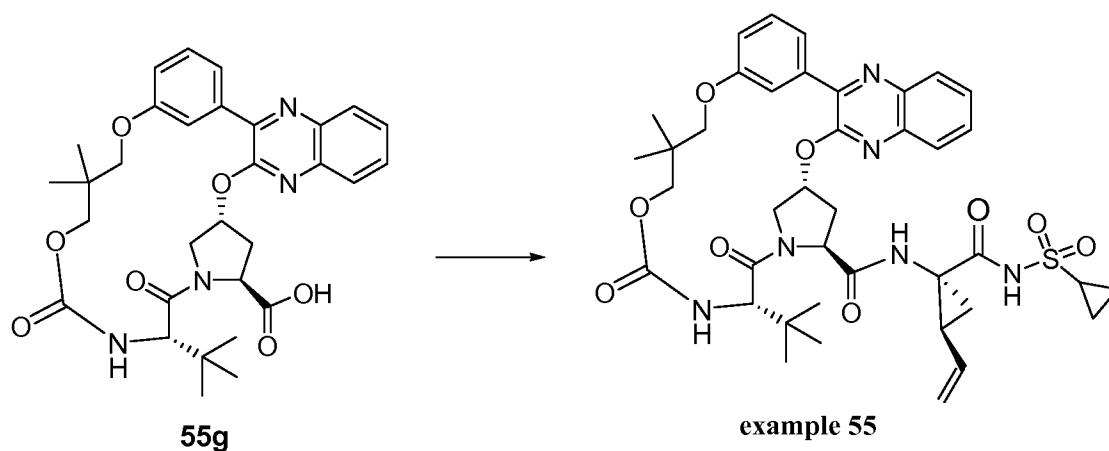
Step 55F



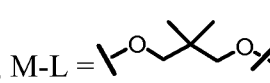
A mixture of compound **55e** (0.161g, 0.24mmol), cesium carbonate (0.156g, 0.48mmol) and toluene (10ml) was purged with nitrogen for 5min. Palladium acetate (11mg, 0.049mmol) and ligand **55f-1** (24mg, 0.06mmol) were added. The mixture was stirred at 80°C for 19h, cooled to rt, filtered, washed with EtOAc and concentrated. The residue was purified by silica gel chromatography (EtOAc/Hexane 0% to 25%) to afford **55f** (0.035g). MS(ESI); m/z 591.61(M+H).

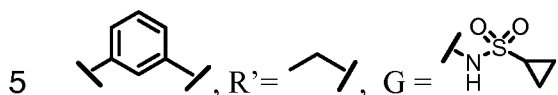
Step **55G**

Compound **55g** was prepared from compound **55f** by the same procedure as described in Step3F of example 3. MS(ESI): m/z 577.55 (M+H).

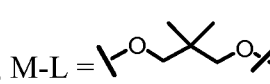
Step **55H**

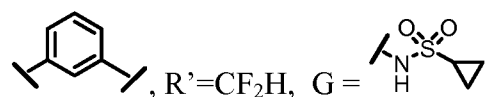
Compound of example 55 was prepared from **55g** by the same procedures as described in Example 3. MS (ESI): m/z 789.34 (M+H).

Example 56. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$

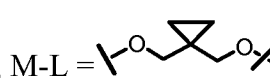


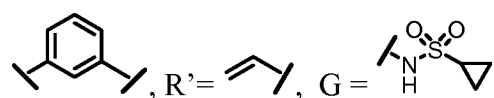
This compound was prepared from **55g** by the same procedures as described in Example 4. MS (ESI): m/z 790.92 (M+H).

Example 57. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$

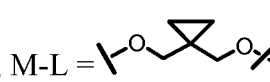


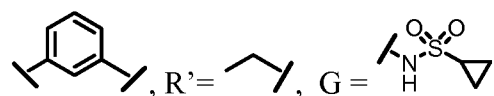
This compound was prepared from **55g** by the same procedures as described in Example 5. MS (ESI): m/z 813.74 (M+H).

Example 58. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$

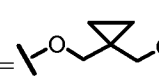


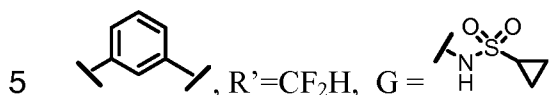
This compound was prepared by the same procedures as described in Example 55. MS (ESI): m/z 787.20 (M+H).

Example 59. Compound of Formula XV, wherein $R =$ , $M-L =$ , $Ar =$

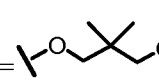


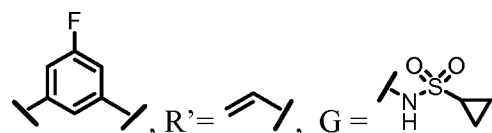
This compound was prepared by the same procedures as described in Example 56. MS (ESI): m/z 789.22 (M+H).

Example 60. Compound of Formula XV, wherein R = , M-L = , Ar =

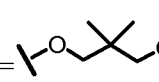


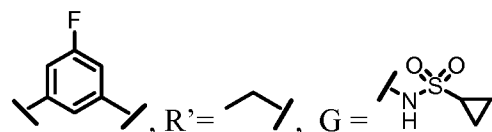
This compound was prepared by the same procedures as described in Example 57. MS (ESI): m/z 811.59 (M+H).

Example 61. Compound of Formula XV, wherein R = , M-L = , Ar =



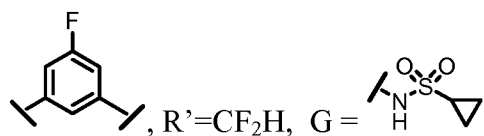
This compound was prepared by the same procedures as described in Example 55. MS (ESI): m/z 807.17 (M+H).

Example 62. Compound of Formula XV, wherein R = , M-L = , Ar =



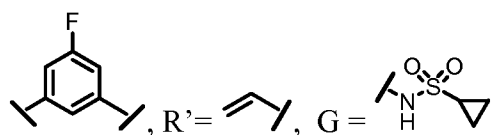
This compound was prepared by the same procedures as described in Example 56. MS (ESI): m/z 809.10 (M+H).

Example 63. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $\text{Ar} =$



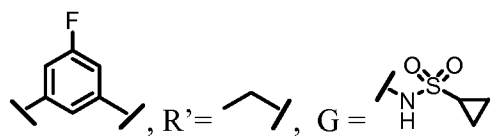
This compound was prepared by the same procedures as described in Example 57. MS (ESI):
 5 m/z 831.24 ($M+H$).

Example 64. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{Cyclopropyl} \text{---}$, $\text{Ar} =$



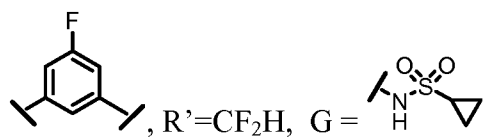
10 This compound was prepared by the same procedures as described in Example 55. MS (ESI):
 m/z 805.14 ($M+H$).

Example 65. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{Cyclopropyl} \text{---}$, $\text{Ar} =$

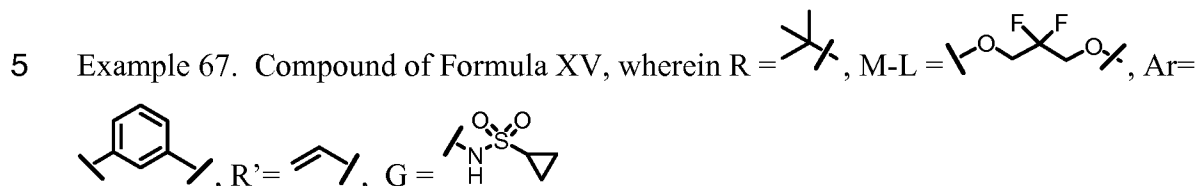


15 This compound was prepared by the same procedures as described in Example 56. MS (ESI):
 m/z 807.03 ($M+H$).

20 Example 66. Compound of Formula XV, wherein $R = \text{---} \text{C}(\text{CH}_3)_2 \text{---}$, $M-L = \text{---} \text{O} \text{---} \text{Cyclopropyl} \text{---}$, $\text{Ar} =$

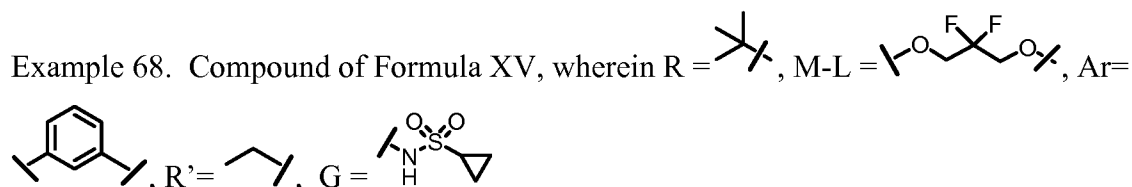


This compound was prepared by the same procedures as described in Example 57. MS (ESI): m/z 828.97 (M+H).



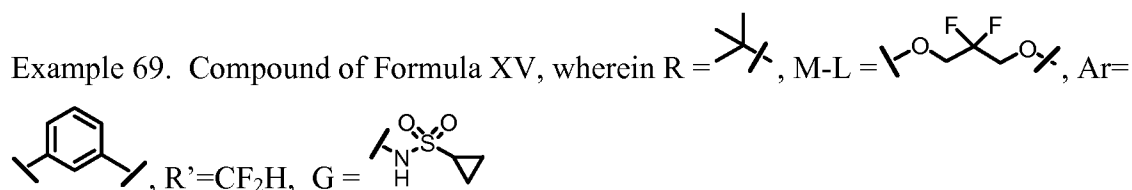
This compound was prepared by the same procedures as described in Example 55. MS (ESI): m/z 797.11 (M+H).

10



This compound was prepared by the same procedures as described in Example 56. MS (ESI): m/z 799.06 (M+H).

15



20 This compound was prepared by the same procedures as described in Example 57. MS (ESI): m/z 821.54 (M+H).

Examples 70 to 1506, compounds of Formula XV in Table 1, are made following the procedures described in Examples 1 to 69 and the Synthetic Methods section.

Examples 1507 to 1554, compounds of Formula XVI in Table 2, are made following the procedures described in Examples 1 to 69 and the Synthetic Methods section.

Examples 1555 to 1586, compounds of Formula XVII in Table 3, are made following the procedures described in Examples 1 to 69 and the Synthetic Methods section.

The compounds of the present invention exhibit potent inhibitory properties against the HCV NS3 protease. The following examples describe assays in which the compounds of the present invention can be tested for anti-HCV effects.

Example 1587. NS3/NS4a Protease Enzyme Assay

HCV protease activity and inhibition is assayed using an internally quenched fluorogenic substrate. A DABCYL and an EDANS group are attached to opposite ends of a short peptide. Quenching of the EDANS fluorescence by the DABCYL group is relieved upon proteolytic cleavage. Fluorescence is measured with a Molecular Devices Fluoromax (or equivalent) using an excitation wavelength of 355 nm and an emission wavelength of 485 nm.

The assay is run in Corning white half-area 96-well plates (VWR 29444-312 [Corning 3693]) with full-length NS3 HCV protease 1b tethered with NS4A cofactor (final enzyme concentration 1 to 15 nM). The assay buffer is complemented with 10 μ M NS4A cofactor Pep 4A (Anaspec 25336 or in-house, MW 1424.8). RET S1 (Ac-Asp-Glu-Asp(EDANS)-Glu-Glu-Abu-[COO]Ala-Ser-Lys-(DABCYL)-NH₂, AnaSpec 22991, MW 1548.6) is used as the fluorogenic peptide substrate. The assay buffer contains 50 mM Hepes at pH 7.5, 30 mM NaCl and 10 mM BME. The enzyme reaction is followed over a 30 minutes time course at room temperature in the absence and presence of inhibitors.

The peptide inhibitors HCV Inh 1 (Anaspec 25345, MW 796.8) Ac-Asp-Glu-Met-Glu-Glu-Cys-OH, [-20⁰C] and HCV Inh 2 (Anaspec 25346, MW 913.1) Ac-Asp-Glu-Dif-Cha-Cys-OH, are used as reference compounds.

IC50 values are calculated using XLFit in ActivityBase (IDBS) using equation 205:
 $y=A+((B-A)/(1+((C/x)^D)))$.

Example 1588 - Cell-Based Replicon Assay

5 Quantification of HCV replicon RNA (HCV Cell Based Assay) is accomplished using the Huh 11-7 cell line (Lohmann, et al Science 285:110-113, 1999). Cells are seeded at 4×10^3 cells/well in 96 well plates and fed media containing DMEM (high glucose), 10% fetal calf serum, penicillin-streptomycin and non-essential amino acids. Cells are incubated in a 7.5% CO₂ incubator at 37 °C. At the end of the incubation period, total RNA is
10 extracted and purified from cells using Ambion RNAqueous 96 Kit (Catalog No. AM1812). To amplify the HCV RNA so that sufficient material can be detected by an HCV specific probe (below), primers specific for HCV (below) mediate both the reverse transcription of the HCV RNA and the amplification of the cDNA by polymerase chain reaction (PCR) using the TaqMan One-Step RT-PCR Master Mix Kit (Applied Biosystems catalog no. 4309169).
15 The nucleotide sequences of the RT-PCR primers, which are located in the NS5B region of the HCV genome, are the following:

HCV Forward primer "RBNS5bfor"

5'GCTGCGGCCTGTCTGAGCT (SEQ ID NO: 1):

HCV Reverse primer "RBNS5Brev"

20 5'CAAGGTCGTCTCCGCATAC (SEQ ID NO 2).

Detection of the RT-PCR product is accomplished using the Applied Biosystems (ABI) Prism 7500 Sequence Detection System (SDS) that detects the fluorescence that is emitted when the probe, which is labeled with a fluorescence reporter dye and a quencher dye, is degraded during the PCR reaction. The increase in the amount of fluorescence is
25 measured during each cycle of PCR and reflects the increasing amount of RT-PCR product. Specifically, quantification is based on the threshold cycle, where the amplification plot crosses a defined fluorescence threshold. Comparison of the threshold cycles of the sample with a known standard provides a highly sensitive measure of relative template concentration in different samples (ABI User Bulletin #2 December 11, 1997). The data is analyzed using
30 the ABI SDS program version 1.7. The relative template concentration can be converted to

RNA copy numbers by employing a standard curve of HCV RNA standards with known copy number (ABI User Bulletin #2 December 11, 1997).

The RT-PCR product was detected using the following labeled probe:

5 5' FAM-CGAAGCTCCAGGACTGCACGATGCT-TAMRA (SEQ ID NO: 3)

FAM= Fluorescence reporter dye.

TAMRA:=Quencher dye.

10 The RT reaction is performed at 48 °C for 30 minutes followed by PCR. Thermal
cycler parameters used for the PCR reaction on the ABI Prism 7500 Sequence Detection
System are: one cycle at 95 °C, 10 minutes followed by 40 cycles each of which include one
incubation at 95 °C for 15 seconds and a second incubation for 60 °C for 1 minute.

15 To normalize the data to an internal control molecule within the cellular RNA, RT-
PCR is performed on the cellular messenger RNA glyceraldehyde-3-phosphate
dehydrogenase (GAPDH). The GAPDH copy number is very stable in the cell lines used.
GAPDH RT-PCR is performed on the same RNA sample from which the HCV copy number
is determined. The GAPDH primers and probes are contained in the ABI Pre-Developed
TaqMan Assay Kit (catalog no. 4310884E). The ratio of HCV/GAPDH RNA is used to
20 calculate the activity of compounds evaluated for inhibition of HCV RNA replication.

Activity of compounds as inhibitors of HCV replication (Cell based Assay) in
replicon containing Huh-7 cell lines.

25 The effect of a specific anti-viral compound on HCV replicon RNA levels in Huh-11-
7 cells is determined by comparing the amount of HCV RNA normalized to GAPDH (e.g.
the ratio of HCV/GAPDH) in the cells exposed to compound versus cells exposed to the
DMSO vehicle (negative control). Specifically, cells are seeded at 4×10^3 cells/well in a 96
well plate and are incubated either with: 1) media containing 1% DMSO (0% inhibition
30 control), or 2) media/1%DMSO containing a fixed concentration of compound. 96 well

plates as described above are then incubated at 37 °C for 4 days (EC50 determination).

Percent inhibition is defined as:

$$\% \text{ Inhibition} = 100 - 100 * S / C1$$

where

- 5 S= the ratio of HCV RNA copy number/GAPDH RNA copy number in the sample;
 C1= the ratio of HCV RNA copy number/GAPDH RNA copy number in the 0%
inhibition control (media/1%DMSO).

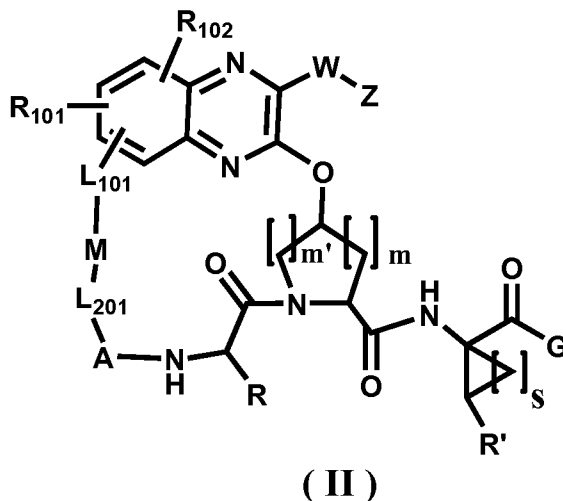
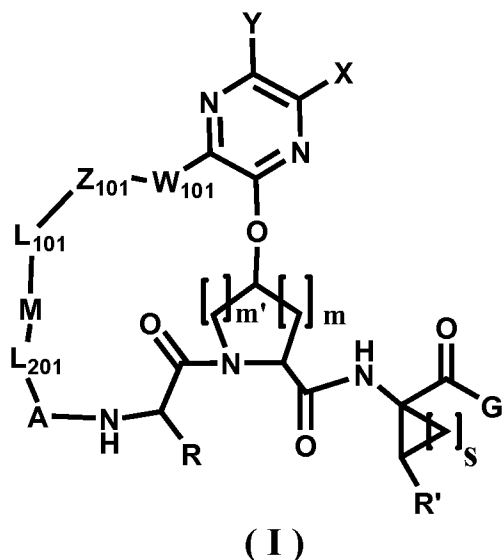
- 10 The dose-response curve of the inhibitor is generated by adding compound in serial,
three-fold dilutions over three logs to wells starting with the highest concentration of a
specific compound at 1.5 uM and ending with the lowest concentration of 0.23 nM. Further
dilution series (500 nM to 0.08 nM for example) is performed if the EC50 value is not
positioned well on the curve. EC50 is determined with the IDBS Activity Base program “XL
Fit” using a 4-paramater, non-linear regression fit (model # 205 in version 4.2.1, build 16).

15

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

WHAT IS CLAIMED:

1. A compound of Formula I or II:



5 wherein

A is absent or selected from $-(C=O)-$, $-S(O)_2$, $-C=N-OR_1$ or $-C(=N-CN)$;

10 L_{201} is absent or selected from $-C_1-C_8$ alkylene, $-C_2-C_8$ alkenylene, or $-C_2-C_8$ alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkylene, substituted $-C_2-C_8$ alkenylene, or substituted $-C_2-C_8$ alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkylene, or substituted $-C_3-C_{12}$ cycloalkylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkenylene, or substituted $-C_3-$
 15 C_{12} cycloalkenylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N;

M is absent or selected from O, S, SO, SO_2 or NR_1 ; wherein R_1 is selected at each occurrence from the group consisting of:

- 20 (i) hydrogen;
- (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;

- (iii) heterocycloalkyl or substituted heterocycloalkyl;
- (iv) $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;

L_{101} is absent or selected from $-C_1-C_8$ alkylene, $-C_2-C_8$ alkenylene, or $-C_2-C_8$ alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkylene, substituted $-C_2-C_8$ alkenylene, or substituted $-C_2-C_8$ alkynylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkylene, or substituted $-C_3-C_{12}$ cycloalkylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkenylene, or substituted $-C_3-C_{12}$ cycloalkenylene each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N;

Z_{101} is absent or selected from aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

W_{101} is absent or selected from $-O-$, $-S-$, $-NR_1-$, $-C(O)-$ or $-C(O)NR_1-$;

X and Y taken together with the carbon atoms to which they are attached to form a carbocyclic moiety or a heterocyclic moiety selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, or substituted heterocyclic;

or X and Y together form a C_2-C_8 -alkylene group or a C_2-C_8 -heteroalkylene group;

R_{101} and R_{102} are independently selected from the group consisting of:

- (i) hydrogen, halogen, CN, CF₃, N₃, NO₂, OR₁, SR₁, SO₂R₂, -NHS(O)₂-R₂, -NH(SO₂)NR₃R₄, NR₃R₄, CO₂R₁, COR₁, CONR₁R₂, N(R₁)COR₂;
- (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (iii) heterocycloalkyl or substituted heterocycloalkyl;
- (iv) -C₁-C₈ alkyl, -C₂-C₈ alkenyl, or -C₂-C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted -C₁-C₈ alkyl, substituted -C₂-C₈ alkenyl, or substituted -C₂-C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C₃-C₁₂ cycloalkyl, or substituted -C₃-C₁₂ cycloalkyl; -C₃-C₁₂ cycloalkenyl, or substituted -C₃-C₁₂ cycloalkenyl;

R and R' are each independently selected from the group consisting of:

- (i) -C₁-C₈ alkyl, -C₂-C₈ alkenyl, or -C₂-C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted -C₁-C₈ alkyl, substituted -C₂-C₈ alkenyl, or substituted -C₂-C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C₃-C₁₂ cycloalkyl, or substituted -C₃-C₁₂ cycloalkyl; -C₄-C₁₂ alkylcycloalkyl, or substituted -C₄-C₁₂ alkylcycloalkyl; -C₃-C₁₂ cycloalkenyl, or substituted -C₃-C₁₂ cycloalkenyl; -C₄-C₁₂ alkylcycloalkenyl, or substituted -C₄-C₁₂ alkylcycloalkenyl;
- (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (iii) heterocycloalkyl or substituted heterocycloalkyl;
- (iv) hydrogen; deuterium;

G is selected from -OH, -NHS(O)₂-R₂, -NH(SO₂)NR₃R₄, and NR₃R₄;

R₂ is selected from:

- (i) aryl; substituted aryl; heteroaryl; substituted heteroaryl
- (ii) heterocycloalkyl; substituted heterocycloalkyl;
- (iii) -C₁-C₈ alkyl, -C₂-C₈ alkenyl, or -C₂-C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N, substituted -C₁-C₈ alkyl, substituted

–C₂–C₈ alkenyl, or substituted –C₂–C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; –C₃–C₁₂ cycloalkyl, or substituted –C₃–C₁₂ cycloalkyl; –C₃–C₁₂ cycloalkenyl, or substituted –C₃–C₁₂ cycloalkenyl; heterocyclic; substituted heterocyclic;

5

R₃ and R₄ are independently selected from:

- (i) hydrogen;
- (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (iii) heterocycloalkyl or substituted heterocycloalkyl;
- (iv) –C₁–C₈ alkyl, –C₂–C₈ alkenyl, or –C₂–C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted –C₁–C₈ alkyl, substituted –C₂–C₈ alkenyl, or substituted –C₂–C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; –C₃–C₁₂ cycloalkyl, or substituted –C₃–C₁₂ cycloalkyl; –C₃–C₁₂ cycloalkenyl, or substituted –C₃–C₁₂ cycloalkenyl; heterocyclic, or substituted heterocyclic;

10

15

alternatively, R₃ and R₄ are taken together with the nitrogen they are attached to form a heterocyclic or substituted heterocyclic;

Z is selected from the groups consisting of:

- (i) hydrogen;
- (ii) CN;
- (iii) N₃;
- (iv) halogen;
- (v) –NH–N=CHR₁;
- (vi) aryl, substituted aryl;
- (vii) heteroaryl, substituted heteroaryl;
- (viii) –C₃–C₁₂ cycloalkyl, substituted –C₃–C₁₂ cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl;

20

25

- (ix) $-C_1-C_6$ alkyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;
- (x) $-C_2-C_6$ alkenyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;
- (xi) $-C_2-C_6$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

W is absent, or selected from alkylene, alkenylene, alkynylene, $-O-$, $-S-$, $-NR_1-$, $-C(O)NR_1-$, or $-C(O)-$;

m is 0, 1, 2 or 3;

m' is 0, 1, 2 or 3; and

s is 1, 2, 3 or 4.

2. A compound according to claim 1 wherein:

M is absent or selected from O or NR_1 ;

Z_{101} is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

W_{101} is absent, or selected from $-O-$, $-S-$, $-NH-$, $-N(Me)-$, $-C(O)NH-$, or $-$

$C(O)N(Me)-$;

X and Y taken together with the carbon atoms to which they are attached to form a cyclic moiety which selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, or substituted heterocyclic;

R₁₀₁ and R₁₀₂ are independently selected from the group consisting of:

- (i) hydrogen, halogen, CN, CF₃, NO₂, OR₁, SR₁, -NHS(O)₂-R₂, -NH(SO₂)NR₃R₄, NR₃R₄, CO₂R₁, COR₁, CONR₁R₂, N(R₁)COR₂;
- 5 (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (iii) heterocycloalkyl or substituted heterocycloalkyl;
- (iv) -C₁-C₈ alkyl, -C₂-C₈ alkenyl, or -C₂-C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted -C₁-C₈ alkyl, substituted -C₂-C₈ alkenyl, or substituted -C₂-C₈ alkynyl each containing 0, 1, 2, or 3
- 10 heteroatoms selected from O, S or N; -C₃-C₁₂ cycloalkyl, or substituted -C₃-C₁₂ cycloalkyl; -C₃-C₁₂ cycloalkenyl, or substituted -C₃-C₁₂ cycloalkenyl;

R₃ and R₄ are independently selected from:

- (i) hydrogen;
- 15 (ii) aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- (iii) heterocycloalkyl or substituted heterocycloalkyl;
- (iv) -C₁-C₈ alkyl, -C₂-C₈ alkenyl, or -C₂-C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted -C₁-C₈ alkyl, substituted -C₂-C₈ alkenyl, or substituted -C₂-C₈ alkynyl each containing 0, 1, 2, or 3
- 20 heteroatoms selected from O, S or N; -C₃-C₁₂ cycloalkyl, or substituted -C₃-C₁₂ cycloalkyl; -C₃-C₁₂ cycloalkenyl, or substituted -C₃-C₁₂ cycloalkenyl; heterocyclic, or substituted heterocyclic;

W is absent, or selected from alkylene, alkenylene, alkynylene, -O-, -S-,
 25 -NH-, -N(Me)-, -C(O)NH-, or -C(O)N(Me)-;

m = 0, 1, or 2;

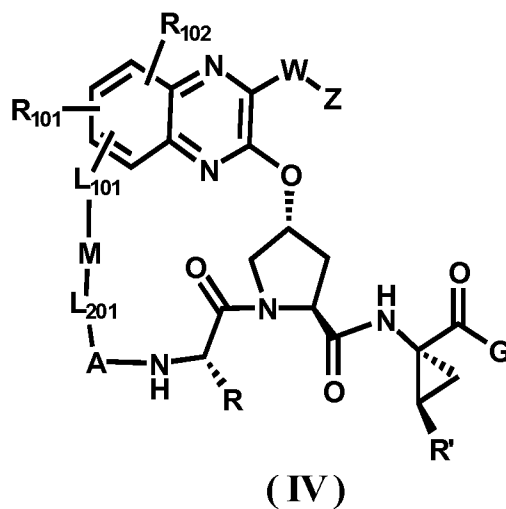
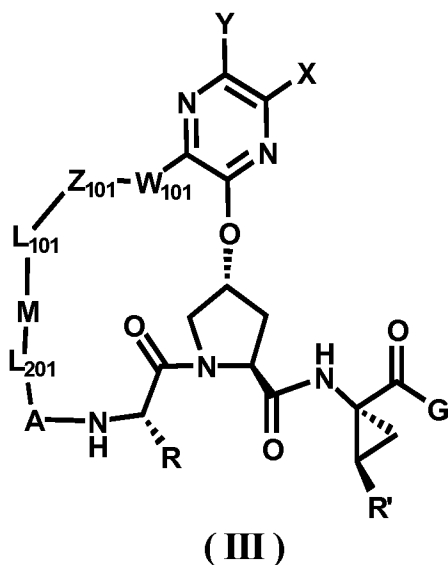
m' = 1 or 2; and

s is 1.

3. The compound of claim 1, wherein R' is $-\text{CHQ}_1\text{Q}_2$, wherein Q_1 and Q_2 are independently selected from F, Cl and Br.

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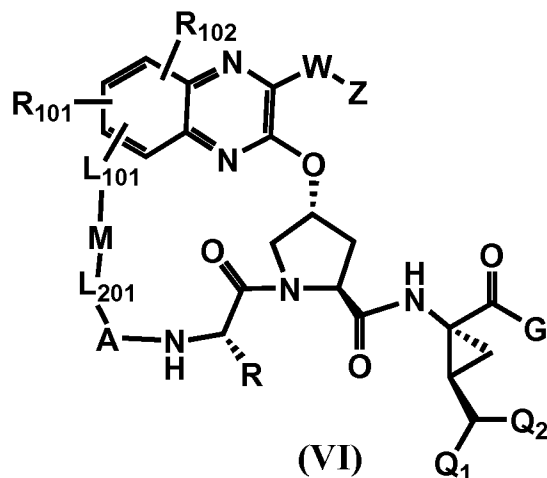
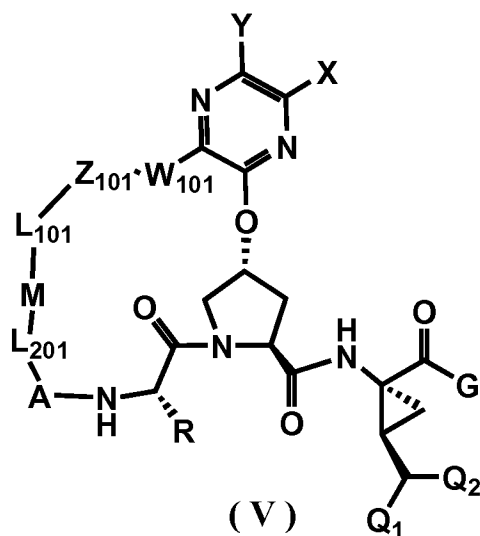
4. The compound of claim 1, wherein the compound is of Formula III or IV:



or a pharmaceutically acceptable salt, ester or prodrug thereof, where R, R', A, L₂₀₁, M, L₁₀₁, Z₁₀₁, W₁₀₁, X, Y, R₁₀₁, R₁₀₂, W, Z and G are as previously defined in claim 1.

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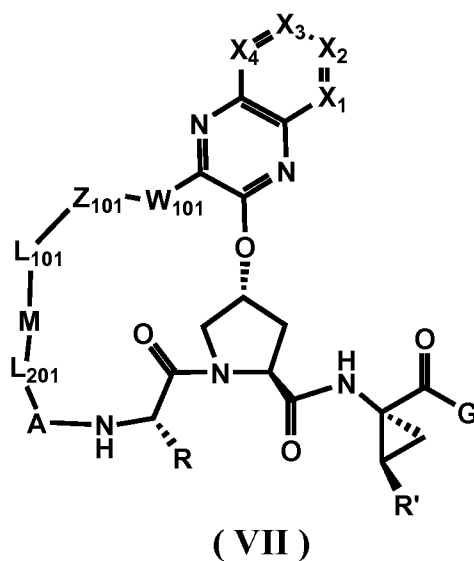
5. The compound of claim 1, wherein the compound is of Formula V or VI:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein Q_1 and Q_2 are each independently selected from F, Cl and Br, and R, A, L_{201} , M, L_{101} , Z_{101} , W_{101} , X, Y, R_{101} , R_{102} , W, Z and G are as previously defined in claim 1.

5 a.

6. The compound of claim 1, wherein the compound is of Formula VII:



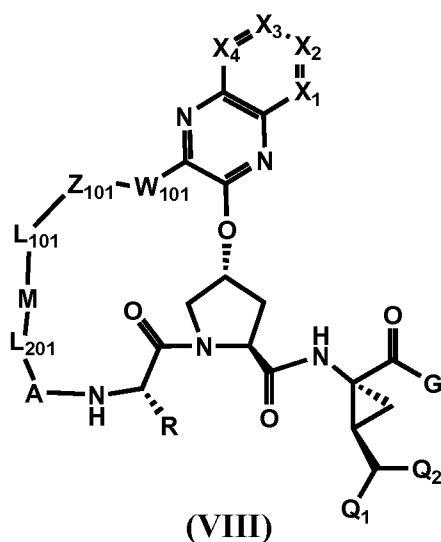
or a pharmaceutically acceptable salt, ester or prodrug thereof, where X_1 - X_4 are independently selected from $-CR_5$ and N, wherein:

R_5 is independently selected from:

- i. hydrogen; halogen; -NO₂; -CN; N₃; CF₃;
- ii. -M-R₄, M is O, S, NH;
- iii. NR₃R₄;
- iv. -C₁-C₈ alkyl, -C₂-C₈ alkenyl, or -C₂-C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted -C₁-C₈ alkyl, substituted -C₂-C₈ alkenyl, or substituted -C₂-C₈ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; -C₃-C₁₂ cycloalkyl, or substituted -C₃-C₁₂ cycloalkyl; -C₃-C₁₂ cycloalkenyl, or substituted -C₃-C₁₂ cycloalkenyl;
- v. aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- vi. heterocycloalkyl or substituted heterocycloalkyl; and

R₃, R₄, R, R', A, L₂₀₁, M, L₁₀₁, Z₁₀₁, W₁₀₁ and G are as previously defined in claim 1.

7. The compound of claim 1, wherein the compound is of Formula VIII:



or a pharmaceutically acceptable salt, ester or prodrug thereof, where X₁-X₄ are independently selected from -CR₅ and N, wherein:

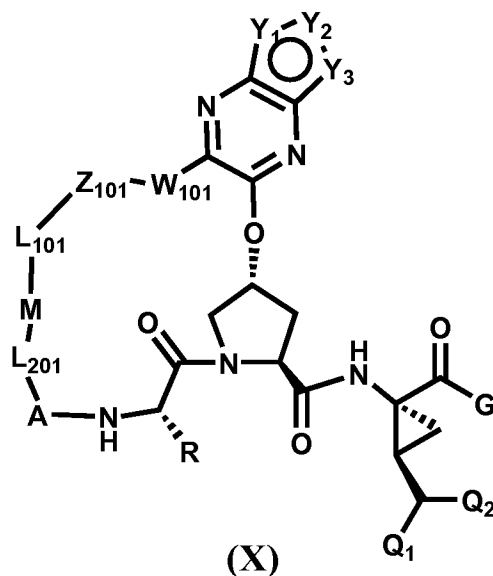
R₅ is independently selected from:

- i. hydrogen; halogen; -NO₂; -CN; N₃; CF₃;

- ii. $-M-R_4$, M is O, S, NH;
- iii. NR_3R_4 ;
- iv. $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;
- v. aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- vi. heterocycloalkyl or substituted heterocycloalkyl; and

R_3 , R_4 , R, R' , A, L_{201} , M, L_{101} , Z_{101} , W_{101} and G are as previously defined in claim 1.

9. The compound of claim 1, wherein the compound is of Formula X:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

Y_1 , Y_2 and Y_3 are independently selected from CR_5 , N, NR_5 , S and O;

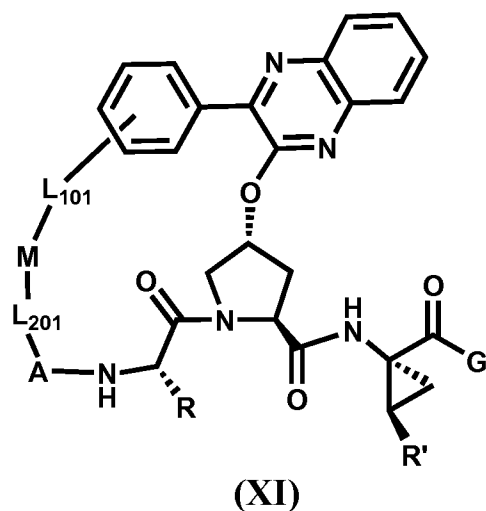
R_5 is independently selected from:

- i. hydrogen; halogen; $-NO_2$; $-CN$; N_3 ; CF_3 ;
- ii. $-M-R_4$, M is O, S, NH;
- iii. NR_3R_4 ;

- iv. $-C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; substituted $-C_1-C_8$ alkyl, substituted $-C_2-C_8$ alkenyl, or substituted $-C_2-C_8$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; $-C_3-C_{12}$ cycloalkyl, or substituted $-C_3-C_{12}$ cycloalkyl; $-C_3-C_{12}$ cycloalkenyl, or substituted $-C_3-C_{12}$ cycloalkenyl;
- v. aryl; substituted aryl; heteroaryl; substituted heteroaryl;
- vi. heterocycloalkyl or substituted heterocycloalkyl;

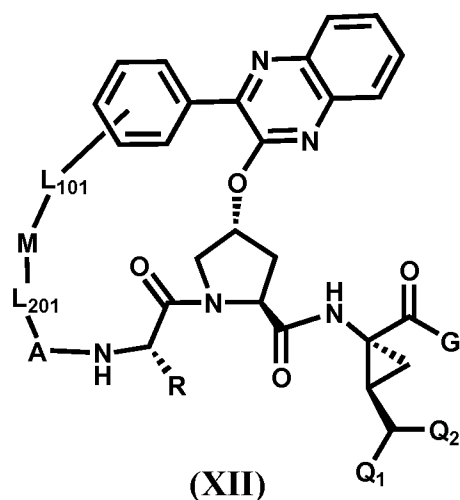
10 Q₁ and Q₂ are each independently fluorine, chlorine or bromine; and
R₃, R₄, R, A, L₂₀₁, M, L₁₀₁, Z₁₀₁, W₁₀₁ and G are as previously defined in claim 1.

10. The compound of claim 1, wherein the compound is of Formula XI:



15 or a pharmaceutically acceptable salt, ester or prodrug thereof, where R, R', A, L₂₀₁, M, L₁₀₁ and G are as previously defined in claim 1.

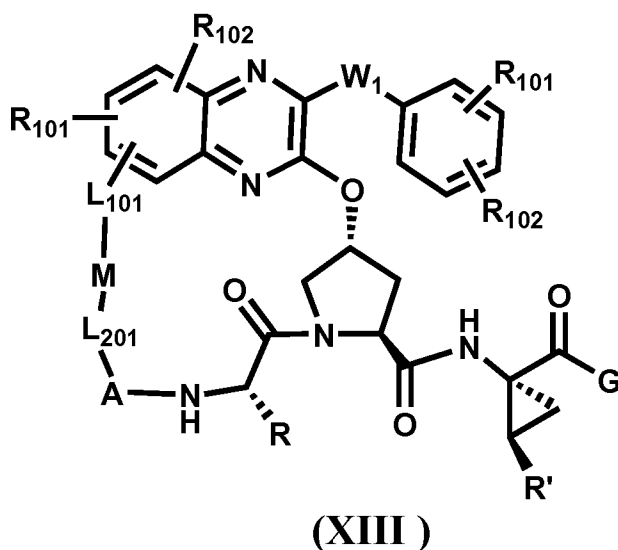
11. The compound of claim 1, wherein the compound is of Formula XII:



or a pharmaceutically acceptable salt, ester or prodrug thereof, where Q_1 and Q_2 are independently fluorine, chlorine or bromine and R, A, L_{201} , M, L_{101} and G are as previously defined in claim 1.

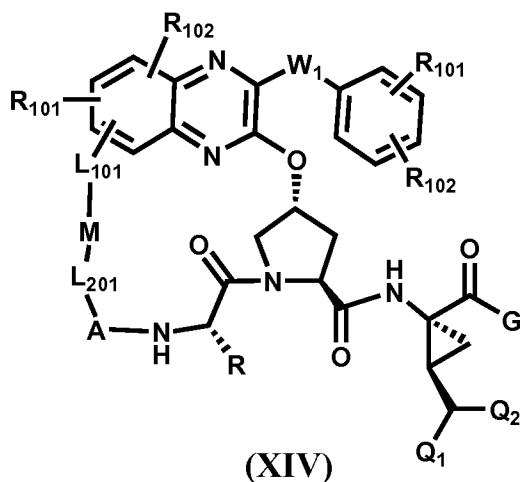
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12. The compound of claim 1, wherein the compound is of Formula XIII:



10 or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein W_1 is absent or selected from C_1 - C_4 alkylene, C_2 - C_4 alkenylene, and C_2 - C_4 alkynylene; and R, R' , A, L_{201} , M, L_{101} , R_{101} , R_{102} and G are as previously defined in claim 1.

13. The compound of claim 1, wherein the compound is of Formula XIV:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein

W_1 is absent or selected from C_1 - C_4 alkylene, C_2 - C_4 alkenylene, and C_2 - C_4 alkynylene;

5 Q_1 and Q_2 are independently fluorine, chlorine or bromine; and

R , A , L_{201} , M , L_{101} , R_{101} , R_{102} and G are as previously defined in claim 1.

14. A compound according to claim 1 as set forth in Table 1 herein.

10

15. A compound according to claim 1 which is selected from compounds of Formula XVI wherein R , L -Ar, R' and G are delineated for each example in Table 2:

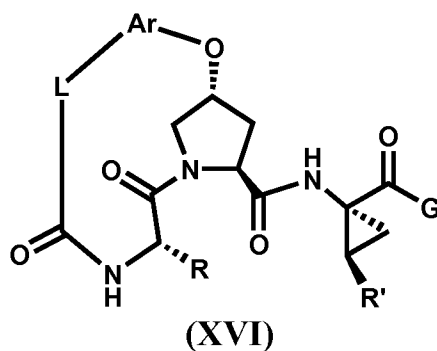
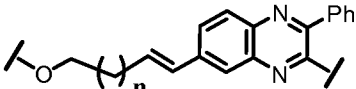
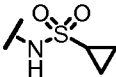
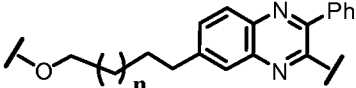
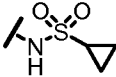
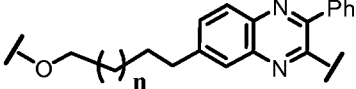
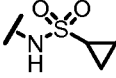
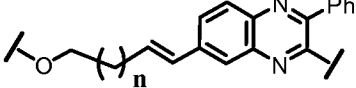
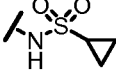
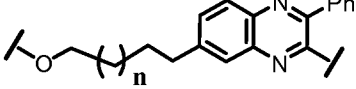
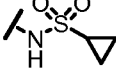
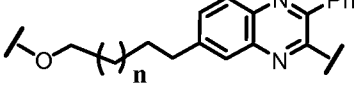
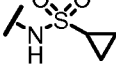
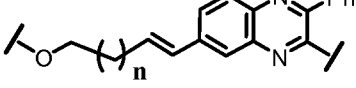
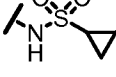
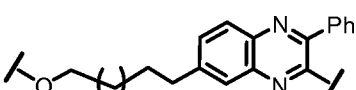
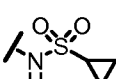
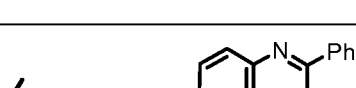
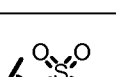
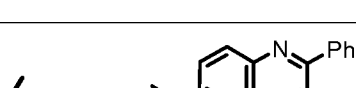
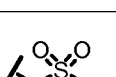
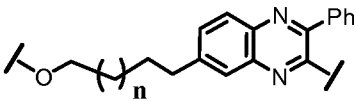
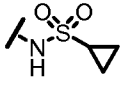
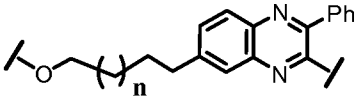
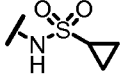
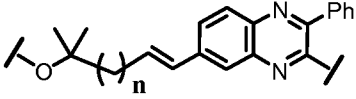
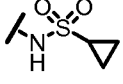
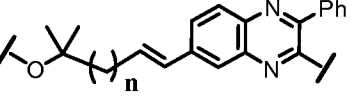
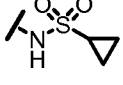
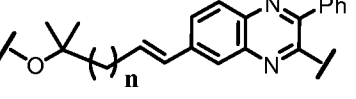
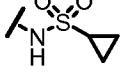
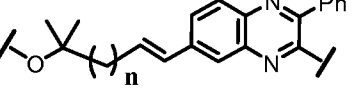
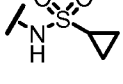
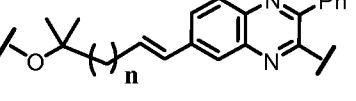
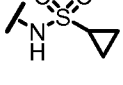
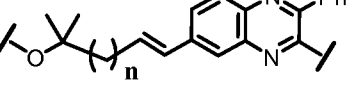
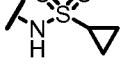
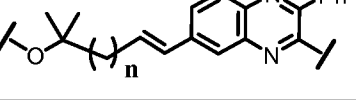
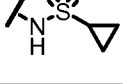
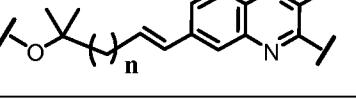
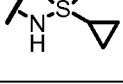
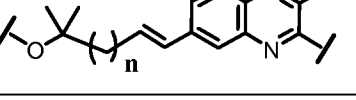
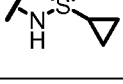
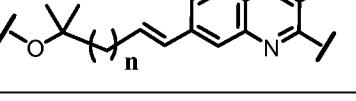
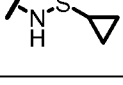
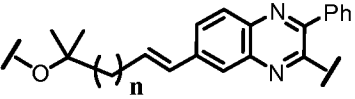
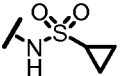
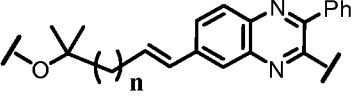
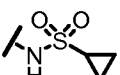
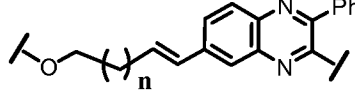
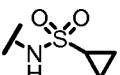
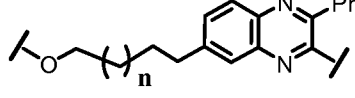
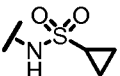
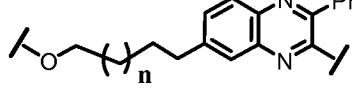
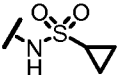
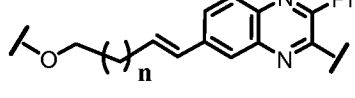
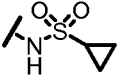
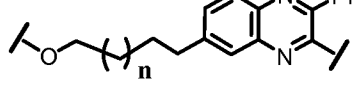
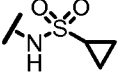
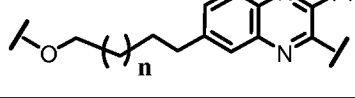
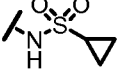
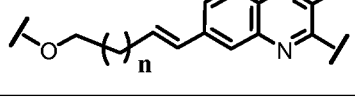
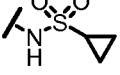
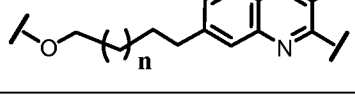
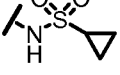
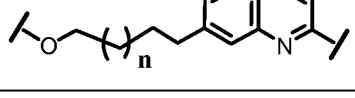
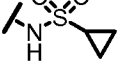
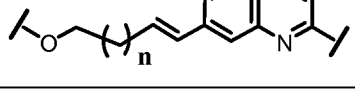
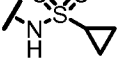
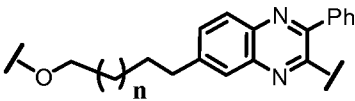
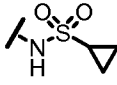
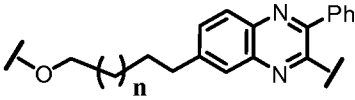
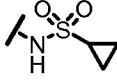
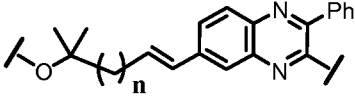
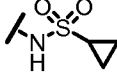
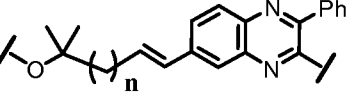
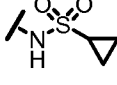
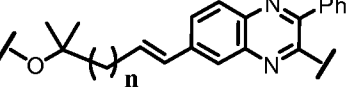
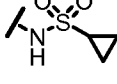
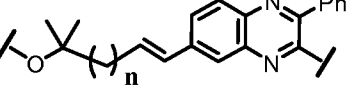
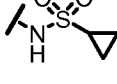
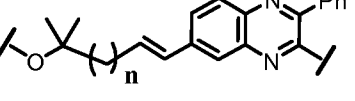
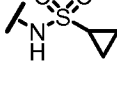
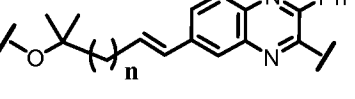
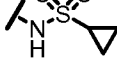
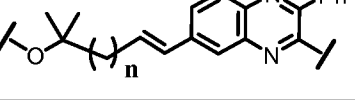
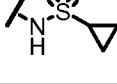
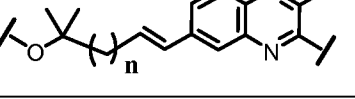
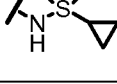
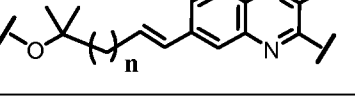
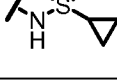
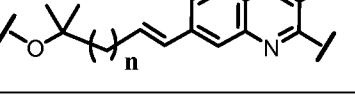
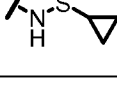


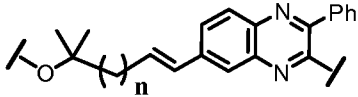
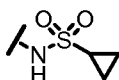
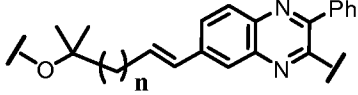
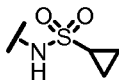
TABLE 2

Example #	R	L-Ar	n	R'	G
1507.			4		
1508.			4		
1509.			4		
1510.			3		
1511.			3		
1512.			3		
1513.			2		
1514.			2		
1515.			2		
1516.			1		

1517.			1		
1518.			1		
1519.			4		
1520.			4		
1521.			4		
1522.			3		
1523.			3		
1524.			3		
1525.			2		
1526.			2		
1527.			2		
1528.			1		

1529.			1		
1530.			1		
1531.			4		
1532.			4		
1533.			4		
1534.			3		
1535.			3		
1536.			3		
1537.			2		
1538.			2		
1539.			2		
1540.			1		

1541.			1		
1542.			1		
1543.			4		
1544.			4		
1545.			4		
1546.			3		
1547.			3		
1548.			3		
1549.			2		
1550.			2		
1551.			2		
1552.			1		

1553.			1		
1554.			1		

16. A compound according to claim 1 which is selected from compounds of Formula XVII
 5 wherein R, L-Ar, and G are delineated for each example in Table 3:

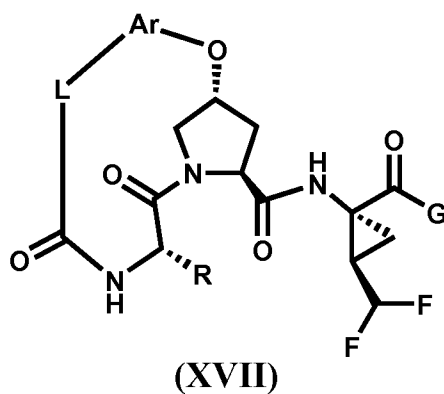
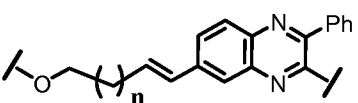
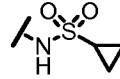
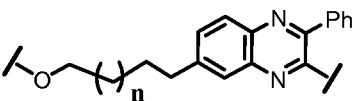
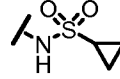
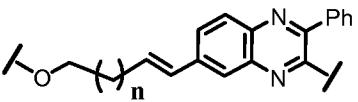
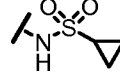
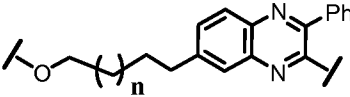
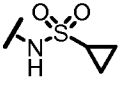
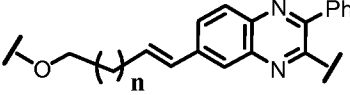
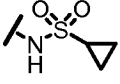
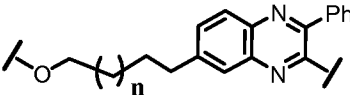
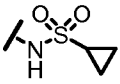
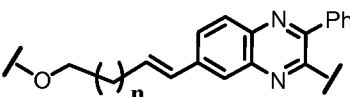
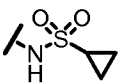
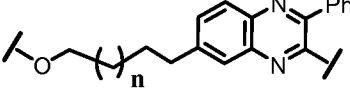
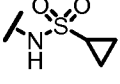
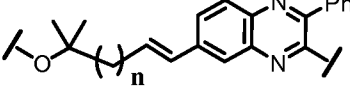
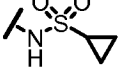
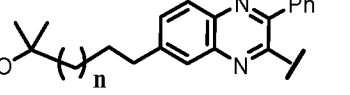
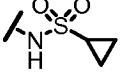
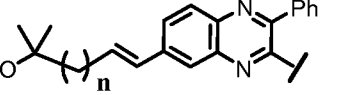
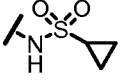
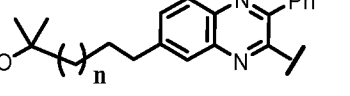
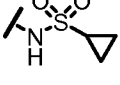
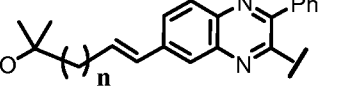
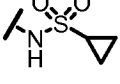
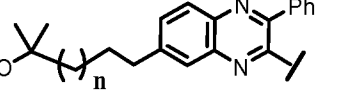
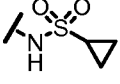
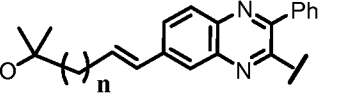
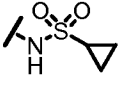
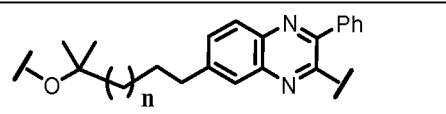
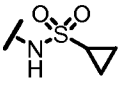
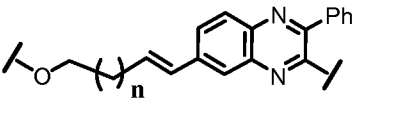
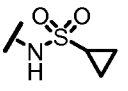
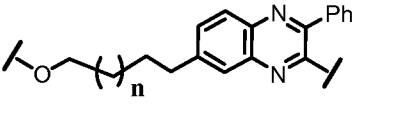
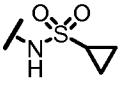
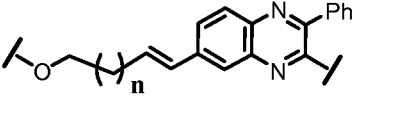
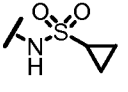
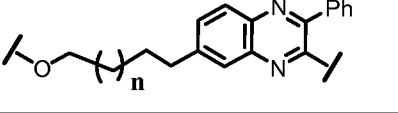
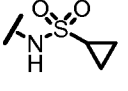
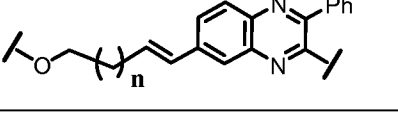
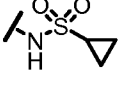
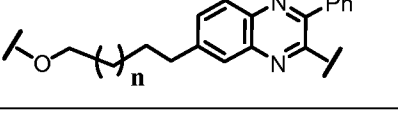
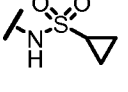
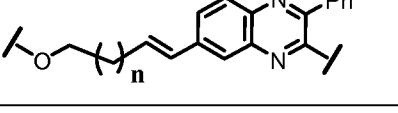
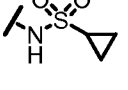
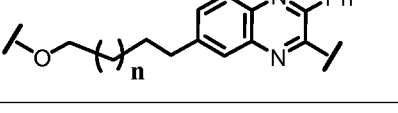
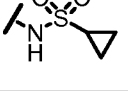
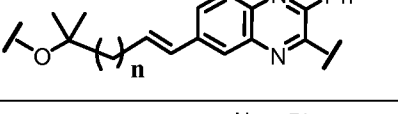
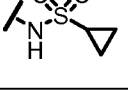
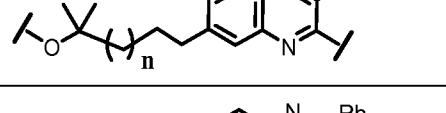
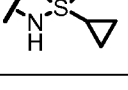
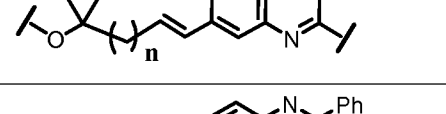
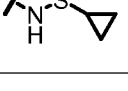
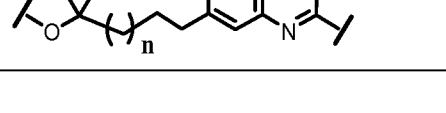
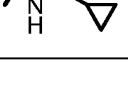
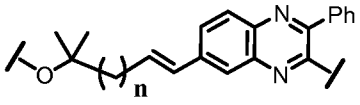
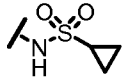
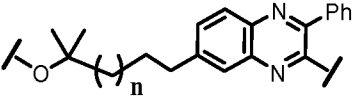
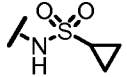
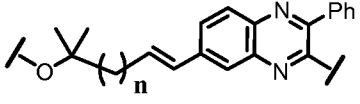
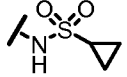
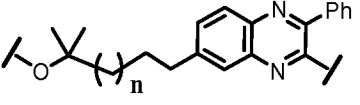
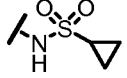


TABLE 3

Example#	R	L-Ar	n	G
1555.			4	
1556.			4	
1557.			3	

1558.			3	
1559.			2	
1560.			2	
1561.			1	
1562.			1	
1563.			4	
1564.			4	
1565.			3	
1566.			3	
1567.			2	
1568.			2	
1569.			1	

1570.			1	
1571.			4	
1572.			4	
1573.			3	
1574.			3	
1575.			2	
1576.			2	
1577.			1	
1578.			1	
1579.			4	
1580.			4	
1581.			3	
1582.			3	

1583.			2	
1584.			2	
1585.			1	
1586.			1	

17. A pharmaceutical composition comprising an inhibitory amount of a compound according to claim 1 or a pharmaceutically acceptable salt, ester, or prodrug thereof, in combination with a pharmaceutically acceptable carrier or excipient.

5

18. A method of treating a viral infection in a subject, comprising administering to the subject an inhibitory amount of a pharmaceutical composition according to claim 17.

19. The method according to claim 18, wherein the viral infection is hepatitis C virus.

10

20. A method of inhibiting the replication of hepatitis C virus, the method comprising supplying a hepatitis C viral NS3 protease inhibitory amount of the pharmaceutical composition of claim 17.

15

21. The method of claim 18 further comprising administering concurrently an additional anti-hepatitis C virus agent.

22. The method of claim 19, wherein said additional anti-hepatitis C virus agent is selected from the group consisting of α -interferon, β -interferon, ribavarin, and adamantine.

20

23. The method of claim 20, wherein said additional anti-hepatitis C virus agent is an inhibitor of hepatitis C virus helicase, polymerase, metalloprotease, or IRES.

24. The pharmaceutical composition of claim 17, further comprising another anti-HCV agent.
- 5 25. The pharmaceutical composition of claim 17, further comprising an agent selected from interferon, ribavirin, amantadine, another HCV protease inhibitor, an HCV polymerase inhibitor, an HCV helicase inhibitor, or an internal ribosome entry site inhibitor.
26. The pharmaceutical composition of claim 17, further comprising pegylated interferon.
- 10 27. The pharmaceutical composition of claim 17, further comprising another anti-viral, anti-bacterial, anti-fungal or anti-cancer agent, or an immune modulator.
- 15 28. The composition of claim 17, further comprising a cytochrome P450 monooxygenase inhibitor or a pharmaceutically acceptable salt thereof.
29. The composition of claim 28, wherein the cytochrome P450 monooxygenase inhibitor is ritonavir.
- 20 30. A method of co-administering to a patient in need of anti-hepatitis C viral treatment comprising a cytochrome P450 monooxygenase inhibitor or a pharmaceutically acceptable salt thereof and a compound as set forth in claim 1 or a pharmaceutically acceptable salt thereof.