

HEPATITIS C VIRUS INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No.
5 61/028,277 filed February 13, 2008.

The present disclosure is generally directed to antiviral compounds, and more specifically directed to compounds which can inhibit the function of the NS5A protein encoded by Hepatitis C virus (HCV), compositions comprising such compounds, and methods for inhibiting the function of the NS5A protein.

10 HCV is a major human pathogen, infecting an estimated 170 million persons worldwide - roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma.

Presently, the most effective HCV therapy employs a combination of alpha-
15 interferon and ribavirin, leading to sustained efficacy in 40% of patients. Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy. However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus,
20 there is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection.

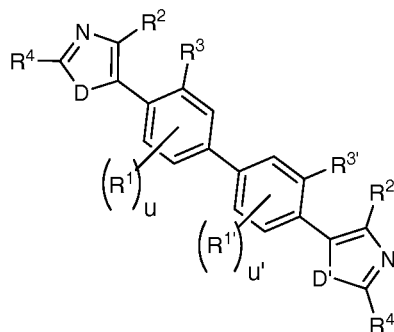
HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All
25 members of the Flaviviridae family have enveloped virions that contain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

Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. At least six major genotypes have been
30 characterized, and more than 50 subtypes have been described. The major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the possible effect of genotypes on pathogenesis and therapy.

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

Compounds useful for treating HCV-infected patients are desired which selectively inhibit HCV viral replication. In particular, compounds which are effective to inhibit the function of the NS5A protein are desired. The HCV NS5A protein is described, for example, in Tan, S.-L., Katzel, M.G. *Virology* 2001, 284, 1-12; and in Park, K.-J.; Choi, S.-H, *J. Biological Chemistry* 2003.

In a first aspect the present disclosure provides a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein

u and u' are independently 0, 1, 2, or 3;

D and D' are each independently selected from NR⁵, O, and S; wherein each R⁵ is independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, hydroxy, (NR^aR^b)carbonyl, and
5 trialkylsilylalkoxyalkyl;

each R¹ and R^{1'} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

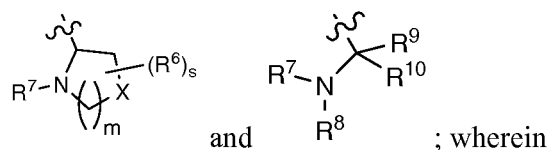
R² is selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl; and
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R³ is selected from hydrogen, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl; or

R² and R³, together with the carbon atoms to which they are attached, form a five- to eight-membered aromatic or non-aromatic ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the five- to eight-membered ring is optionally substituted with one, two, or three substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylsulfonyl, aryl, arylalkyl, arylsulfonyl, carboxy, formyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, oxo, and
20 spirocycle;

R^{2'} and R^{3'}, together with the carbon atoms to which they are attached, form a five- to eight-membered aromatic or non-aromatic ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the five- to eight-membered ring is optionally substituted with one, two, or three substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylsulfonyl, aryl, arylalkyl, arylsulfonyl, carboxy, formyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, (NR^aR^b)carbonyl, oxo, and
25 spirocycle;

30 R⁴ and R^{4'} are each independently selected from



; wherein

each m is independently 0, 1, or 2;

each s is independently 0, 1, 2, 3, or 4;

each X is independently selected from O, S, S(O), SO₂, CH₂, CHR⁶, and
 5 C(R⁶)₂; provided that when n is 0, X is selected from CH₂, CHR⁶, and C(R⁶)₂;

each R⁶ is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and -NR^aR^b, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

10 each R⁷ is independently selected from hydrogen and R¹¹-C(O)-, and R¹¹-C(S)-;

R⁸ is selected from hydrogen and alkyl;

R⁹ and R¹⁰ are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and (NR^aR^b)alkyl; or,

15 R⁹ and R¹⁰, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from NR^z, O, and S; wherein R^z is selected from hydrogen and alkyl; and each R¹¹ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocycliloxyalkyl, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

In a first embodiment of the first aspect the present disclosure provides a
 25 compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein D and D' are each NR⁵. In a second embodiment of the first aspect each R⁵ is independently selected from hydrogen and hydroxy.

In a third embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein u
 30 and u' are each 0.

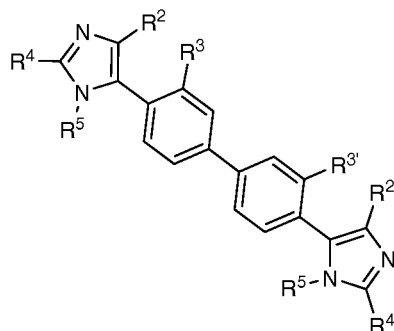
In a fourth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from hydrogen and haloalkyl.

In a fifth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from hydrogen and halo.

In a sixth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 , together with the carbon atoms to which they are attached, form a six- or seven-membered carbocyclic ring.

In a seventh embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein $R^{2'}$ and $R^{3'}$, together with the carbon atoms to which they are attached, form a six- to eight-membered ring optionally containing one heteroatom selected from oxygen, nitrogen, and sulfur; wherein the ring is optionally substituted with one or two alkyl groups.

In a second aspect the present disclosure provides a compound of Formula (II)



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(II),

or a pharmaceutically acceptable salt thereof, wherein

R^2 is selected from hydrogen and haloalkyl; and

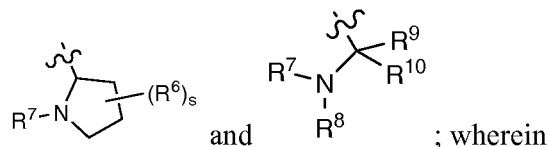
R^3 is selected from hydrogen and halo; or

R^2 and R^3 , together with the carbon atoms to which they are attached, form a five- or six-membered aromatic or non-aromatic carbocyclic ring;

$R^{2'}$ and $R^{3'}$, together with the carbon atoms to which they are attached, form a six- to eight-membered aromatic or non-aromatic ring optionally containing one

heteroatom selected from oxygen, nitrogen, and sulfur; wherein the ring is optionally substituted with one or two alkyl groups;

R^4 and $R^{4'}$ are each independently selected from



5 each s is 0 or 2;

each R^6 is independently selected from alkyl and halo, wherein the alkyl forms a fused three-membered ring with an adjacent carbon atom;

each R^7 is independently selected from hydrogen and $R^{11}-C(O)-$;

R^8 is selected from hydrogen and alkyl;

10 R^9 and R^{10} are each independently selected from hydrogen and alkyl; and

each R^{11} is independently selected from alkyl, arylalkoxy, arylalkyl, and $(NR^cR^d)alkyl$.

In a third aspect the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In a first embodiment of the third aspect the composition comprises one or two additional compounds having anti-HCV activity. In a second embodiment at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

In a fourth embodiment the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and one or two additional compounds having anti-HCV activity, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

In a fifth embodiment the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof,

a pharmaceutically acceptable carrier, and one or two additional compounds having anti-HCV activity, wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV
5 assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

In a fourth aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt
10 thereof. In a first embodiment of the fourth aspect the method further comprises administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In a second embodiment at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment the interferon is
15 selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

In a fourth embodiment of the fourth aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a
20 pharmaceutically acceptable salt thereof and one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA,
25 anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

In a fifth embodiment of the fourth aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a
30 pharmaceutically acceptable salt thereof and one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein wherein at least one of the additional compounds is effective to inhibit the function of a target selected from

HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B portein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

Other embodiments of the present disclosure may comprise suitable combinations of two or more of embodiments and/or aspects disclosed herein.

Yet other embodiments and aspects of the disclosure will be apparent according to the description provided below.

The compounds of the present disclosure also exist as tautomers; therefore the present disclosure also encompasses all tautomeric forms.

The description of the present disclosure herein should be construed in congruity with the laws and principals of chemical bonding.

It should be understood that the compounds encompassed by the present disclosure are those that are suitably stable for use as pharmaceutical agent.

It is intended that the definition of any substituent or variable (e.g., R^1 , R^2 , R^5 , R^6 , etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. For example, when u is 2, each of the two R^1 groups may be the same or different.

All patents, patent applications, and literature references cited in the specification are herein incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

As used in the present specification, the following terms have the meanings indicated:

As used herein, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise.

Unless stated otherwise, all aryl, cycloalkyl, and heterocyclyl groups of the present disclosure may be substituted as described in each of their respective definitions. For example, the aryl part of an arylalkyl group may be substituted as described in the definition of the term ‘aryl’.

The term “alkenyl,” as used herein, refers to a straight or branched chain group of two to six carbon atoms containing at least one carbon-carbon double bond.

The term “alkenyloxy,” as used herein, refers to an alkenyl group attached to the parent molecular moiety through an oxygen atom.

The term “alkenyloxycarbonyl,” as used herein, refers to an alkenyloxy group attached to the parent molecular moiety through a carbonyl group.

The term “alkoxy,” as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

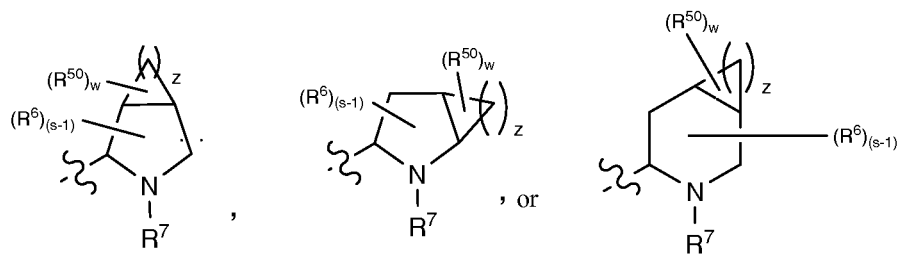
5 The term “alkoxyalkyl,” as used herein, refers to an alkyl group substituted with one, two, or three alkoxy groups.

The term “alkoxyalkylcarbonyl,” as used herein, refers to an alkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

10 The term “alkoxycarbonyl,” as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

The term “alkoxycarbonylalkyl,” as used herein, refers to an alkyl group substituted with one, two, or three alkoxycarbonyl groups.

15 The term “alkyl,” as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to six carbon atoms. In the compounds of the present disclosure, when m is 1 or 2; X is CHR^6 , and R^6 is alkyl, each alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom to provide one of the structures shown below:



20 where z is 1, 2, 3, or 4, w is 0, 1, or 2, and R^{50} is alkyl. When w is 2, the two R^{50} alkyl groups may be the same or different.

The term “alkylcarbonyl,” as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

The term “alkylcarbonylalkyl,” as used herein, refers to an alkyl group substituted with one, two, or three alkylcarbonyl groups.

25 The term “alkylcarbonyloxy,” as used herein, refers to an alkylcarbonyl group attached to the parent molecular moiety through an oxygen atom.

The term “alkylsulfanyl,” as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfur atom.

The term “alkylsulfonyl,” as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group.

The term “aryl,” as used herein, refers to a phenyl group, or a bicyclic fused ring system wherein one or both of the rings is a phenyl group. Bicyclic fused ring systems consist of a phenyl group fused to a four- to six-membered aromatic or non-
5 aromatic carbocyclic ring. The aryl groups of the present disclosure can be attached to the parent molecular moiety through any substitutable carbon atom in the group. Representative examples of aryl groups include, but are not limited to, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. The aryl groups of the present
10 disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^xR^y$, $(NR^xR^y)alkyl$, oxo, and $-P(O)OR_2$, wherein
15 each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three
20 substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term “arylalkenyl,” as used herein, refers to an alkenyl group substituted with one, two, or three aryl groups.

The term “arylalkoxy,” as used herein, refers to an aryl group attached to the
25 parent molecular moiety through an alkoxy group.

The term “arylalkoxyalkyl,” as used herein, refers to an alkyl group substituted with one, two, or three arylalkoxy groups.

The term “arylalkoxyalkylcarbonyl,” as used herein, refers to an arylalkoxyalkyl group attached to the parent molecular moiety through a carbonyl
30 group.

The term “arylalkoxycarbonyl,” as used herein, refers to an arylalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "arylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryl groups. The alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, and $-NR^cR^d$,
5 wherein the heterocyclyl is further optionally substituted with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstituted arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^xR^y$.

The term "arylalkylcarbonyl," as used herein, refers to an arylalkyl group
10 attached to the parent molecular moiety through a carbonyl group.

The term "arylcarbonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a carbonyl group.

The term "aryloxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an oxygen atom.

15 The term "aryloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryloxy groups.

The term "aryloxycarbonyl," as used herein, refers to an aryloxy group attached to the parent molecular moiety through a carbonyl group.

The term "arylsulfonyl," as used herein, refers to an aryl group attached to the
20 parent molecular moiety through a sulfonyl group.

The terms "Cap" and "cap" as used herein, refer to the group which is placed on the nitrogen atom of the terminal nitrogen-containing ring, i.e., the pyrrolidine rings of the compound of Formula (I). It should be understood that "Cap" or "cap" can refer to the reagent used to append the group to the terminal nitrogen-containing
25 ring or to the fragment in the final product, i.e., "Cap-51" or "The Cap-51 fragment found in Example 5".

The term "carbonyl," as used herein, refers to $-C(O)-$.

The term "carboxy," as used herein, refers to $-CO_2H$.

The term "cyano," as used herein, refers to $-CN$.

30 The term "cycloalkyl," as used herein, refers to a saturated monocyclic, hydrocarbon ring system having three to seven carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. The cycloalkyl groups of the present

disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, nitro, and $-NR^xR^y$, wherein the aryl and the heterocyclyl are further optionally substituted with one, two, or three substituents
5 independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

The term “(cycloalkyl)alkenyl,” as used herein, refers to an alkenyl group substituted with one, two, or three cycloalkyl groups.

The term “(cycloalkyl)alkyl,” as used herein, refers to an alkyl group
10 substituted with one, two, or three cycloalkyl groups. The alkyl part of the (cycloalkyl)alkyl is further optionally substituted with one or two groups independently selected from hydroxy and $-NR^cR^d$.

The term “cycloalkyloxy,” as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through an oxygen atom.

15 The term “cycloalkyloxyalkyl,” as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyloxy groups.

The term “cycloalkylsulfonyl,” as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through a sulfonyl group.

The term “formyl,” as used herein, refers to $-CHO$.

20 The terms “halo” and “halogen,” as used herein, refer to F, Cl, Br, or I.

The term “haloalkoxy,” as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term “haloalkoxycarbonyl,” as used herein, refers to a haloalkoxy group attached to the parent molecular moiety through a carbonyl group.

25 The term “haloalkyl,” as used herein, refers to an alkyl group substituted by one, two, three, or four halogen atoms.

The term “heterocyclyl,” as used herein, refers to a four-, five-, six-, or seven-membered ring containing one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur. The four-membered ring has zero double
30 bonds, the five-membered ring has zero to two double bonds, and the six- and seven-membered rings have zero to three double bonds. The term “heterocyclyl” also includes bicyclic groups in which the heterocyclyl ring is fused to another monocyclic heterocyclyl group, or a four- to six-membered aromatic or non-aromatic

carbocyclic ring; as well as bridged bicyclic groups such as 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-yl, and 2-azabicyclo[2.2.2]oc-3-yl. The heterocyclyl groups of the present disclosure can be attached to the parent molecular moiety through any carbon atom or nitrogen atom in the group. Examples of heterocyclyl groups include, but are not limited to, benzothienyl, furyl, imidazolyl, indolyl, indolyl, isothiazolyl, isoxazolyl, morpholyl, oxazolyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrrolopyridinyl, pyrrolyl, thiazolyl, thienyl, thiomorpholyl, 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-yl, and 2-azabicyclo[2.2.2]oc-3-yl. The heterocyclyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -NR^xR^y, (NR^xR^y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term “heterocyclylalkenyl,” as used herein, refers to an alkenyl group substituted with one, two, or three heterocyclyl groups.

The term “heterocyclylalkoxy,” as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an alkoxy group.

The term “heterocyclylalkoxycarbonyl,” as used herein, refers to a heterocyclylalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term “heterocyclylalkyl,” as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyl groups. The alkyl part of the heterocyclylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, aryl, halo, haloalkoxy, haloalkyl, hydroxy, and -NR^cR^d, wherein the aryl is further optionally substituted with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl,

unsubstituted arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^xR^y$.

The term "heterocyclylalkylcarbonyl," as used herein, refers to a heterocyclylalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclylcarbonyl," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclyloxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an oxygen atom.

The term "heterocyclyloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyloxy groups.

The term "heterocyclyloxycarbonyl," as used herein, refers to a heterocyclyloxy group attached to the parent molecular moiety through a carbonyl group.

The term "hydroxy," as used herein, refers to $-OH$.

The term "hydroxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three hydroxy groups.

The term "hydroxyalkylcarbonyl," as used herein, refers to a hydroxyalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "nitro," as used herein, refers to $-NO_2$.

The term " $-NR^aR^b$," as used herein, refers to two groups, R^a and R^b , which are attached to the parent molecular moiety through a nitrogen atom. R^a and R^b are independently selected from hydrogen, alkenyl, and alkyl.

The term " (NR^aR^b) alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^aR^b$ groups.

The term " (NR^aR^b) carbonyl," as used herein, refers to an $-NR^aR^b$ group attached to the parent molecular moiety through a carbonyl group.

The term " $-NR^cR^d$," as used herein, refers to two groups, R^c and R^d , which are attached to the parent molecular moiety through a nitrogen atom. R^c and R^d are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl,

heterocyclalkoxycarbonyl, heterocyclalkyl, heterocyclalkylcarbonyl, heterocyclcarbonyl, heterocyclloxycarbonyl, hydroxyalkylcarbonyl, (NR^cR^f)alkyl, (NR^cR^f)alkylcarbonyl, (NR^cR^f)carbonyl, (NR^cR^f)sulfonyl, -C(NCN)OR', and -C(NCN)NR^xR^y, wherein R' is selected from alkyl and unsubstituted phenyl, and
5 wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclalkyl, and the heterocyclalkylcarbonyl are further optionally substituted with one -NR^cR^f group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocycl, and the heterocycl part of the heterocyclalkoxycarbonyl, the
10 heterocyclalkyl, the heterocyclalkylcarbonyl, the heterocyclcarbonyl, and the heterocyclloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "(NR^cR^d)alkenyl," as used herein, refers to an alkenyl group
15 substituted with one, two, or three -NR^cR^d groups.

The term "(NR^cR^d)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three -NR^cR^d groups. The alkyl part of the (NR^cR^d)alkyl is further optionally substituted with one or two additional groups selected from alkoxy, alkoxyalkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylalkoxyalkylcarbonyl,
20 carboxy, heterocycl, heterocyclcarbonyl, hydroxy, and (NR^cR^f)carbonyl; wherein the heterocycl is further optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "(NR^cR^d)carbonyl," as used herein, refers to an -NR^cR^d group
25 attached to the parent molecular moiety through a carbonyl group.

The term "-NR^cR^f," as used herein, refers to two groups, R^c and R^f, which are attached to the parent molecular moiety through a nitrogen atom. R^c and R^f are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cycloalkyl)alkyl, unsubstituted
30 heterocycl, unsubstituted heterocyclalkyl, (NR^xR^y)alkyl, and (NR^xR^y)carbonyl.

The term "(NR^cR^f)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three -NR^cR^f groups.

The term “(NR^eR^f)alkylcarbonyl,” as used herein, refers to an (NR^eR^f)alkyl group attached to the parent molecular moiety through a carbonyl group.

The term “(NR^eR^f)carbonyl,” as used herein, refers to an -NR^eR^f group attached to the parent molecular moiety through a carbonyl group.

5 The term “(NR^eR^f)sulfonyl,” as used herein, refers to an -NR^eR^f group attached to the parent molecular moiety through a sulfonyl group.

The term “-NR^xR^y,” as used herein, refers to two groups, R^x and R^y, which are attached to the parent molecular moiety through a nitrogen atom. R^x and R^y are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, 10 unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and (NR^{x'}R^{y'})carbonyl, wherein R^{x'} and R^{y'} are independently selected from hydrogen and alkyl.

The term “(NR^xR^y)alkyl,” as used herein, refers to an alkyl group substituted with one, two, or three -NR^xR^y groups.

15 The term “(NR^xR^y)carbonyl,” as used herein, refers to an -NR^xR^y group attached to the parent molecular moiety through a carbonyl group.

The term “oxo,” as used herein, refers to =O.

The term “sulfonyl,” as used herein, refers to -SO₂-.

The term “trialkylsilyl,” as used herein, refers to -SiR₃, wherein R is alkyl.

20 The R groups may be the same or different.

The term “trialkylsilylalkyl,” as used herein, refers to an alkyl group substituted with one, two, or three trialkylsilyl groups.

The term “trialkylsilylalkoxy,” as used herein, refers to a trialkylsilylalkyl group attached to the parent molecular moiety through an oxygen atom.

25 The term “trialkylsilylalkoxyalkyl,” as used herein, refers to an alkyl group substituted with one, two, or three trialkylsilylalkoxy groups.

Asymmetric centers exist in the compounds of the present disclosure. These centers are designated by the symbols “R” or “S”, depending on the configuration of substituents around the chiral carbon atom. It should be understood that the 30 disclosure encompasses all stereochemical isomeric forms, or mixtures thereof, which possess the ability to inhibit NS5A. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products

followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, or direct separation of enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art.

Certain compounds of the present disclosure may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present disclosure includes each conformational isomer of these compounds and mixtures thereof.

The term "compounds of the present disclosure", and equivalent expressions, are meant to embrace compounds of Formula (I), and pharmaceutically acceptable enantiomers, diastereomers, and salts thereof. Similarly, references to intermediates are meant to embrace their salts where the context so permits.

The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; digluconate, dihydrobromide, dihydrochloride, dihydroiodide, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can

be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

When it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula (I), as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the disclosure further provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of formula (I) or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "therapeutically effective amount," as used herein, refers to the total amount of each active component that is sufficient to show a meaningful patient benefit, e.g., a reduction in viral load. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously. The compounds of formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the present

disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "pharmaceutically acceptable," as used herein,
5 refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

10 Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Dosage levels of between about 0.01 and about 250 milligram per kilogram ("mg/kg") body weight per day, preferably between about 0.05 and about 100 mg/kg body weight per day of the compounds of the present disclosure are typical in a monotherapy for the prevention
15 and treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending on the
20 condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Treatment may be
25 initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

30 When the compositions of this disclosure comprise a combination of a compound of the present disclosure and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent are usually present at dosage levels of between about 10 to 150%, and more preferably between about 10

and 80% of the dosage normally administered in a monotherapy regimen.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral
5 (including subcutaneous, intracutaneous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, intravenous, or intradermal injections or infusions) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). Oral administration or administration by injection are
10 preferred.

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

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

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to
25 the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate, or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture.
30 Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, and the like. Lubricants used in these dosage forms include sodium oleate, sodium chloride, and

the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, betonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitable comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginat, gelating, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as betonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present disclosure can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners, or saccharin or other artificial sweeteners, and the like can also be added.

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

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

The compounds of formula (I) and pharmaceutically acceptable salts thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include
10 polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters,
15 polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

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

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

25 Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

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

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers, or insufflators.

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

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

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

The term "patient" includes both human and other mammals.

The term "treating" refers to: (i) preventing a disease, disorder or condition from occurring in a patient that may be predisposed to the disease, disorder, and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder, or condition, i.e., arresting its development; and (iii) relieving the disease, disorder, or condition, i.e., causing regression of the disease, disorder, and/or condition.

The compounds of the present disclosure can also be administered with a cyclosporin, for example, cyclosporin A. Cyclosporin A has been shown to be active against HCV in clinical trials (*Hepatology* 2003, 38, 1282; *Biochem. Biophys. Res. Commun.* 2004, 313, 42; *J. Gastroenterol.* 2003, 38, 567).

Table 1 below lists some illustrative examples of compounds that can be administered with the compounds of this disclosure. The compounds of the disclosure can be administered with other anti-HCV activity compounds in

combination therapy, either jointly or separately, or by combining the compounds into a composition.

Table 1

<i>Brand Name</i>	<i>Physiological Class</i>	<i>Type of Inhibitor or Target</i>	<i>Source Company</i>
NIM811		Cyclophilin Inhibitor	Novartis
Zadaxin		Immunomodulator	Sciclone
Suvus		Methylene blue	Bioenvision
Actilon (CPG10101)		TLR9 agonist	Coley
Batabulin (T67)	Anticancer	β -tubulin inhibitor	Tularik Inc., South San Francisco, CA
ISIS 14803	Antiviral	antisense	ISIS Pharmaceutical s Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceutical s Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	HCV Inhibitor	Achillion / Gilead
Pyrazolopyrimidine compounds and salts From WO-2005047288 26 May 2005	Antiviral	HCV Inhibitors	Arrow Therapeutics Ltd.
Levovirin	Antiviral	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceutical s Inc., Cambridge, MA

<i>Brand Name</i>	<i>Physiological Class</i>	<i>Type of Inhibitor or Target</i>	<i>Source Company</i>
XTL-6865 (XTL-002)	Antiviral	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Isreal
Telaprevir (VX-950, LY-570310)	Antiviral	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN
HCV-796	Antiviral	NS5B Replicase Inhibitor	Wyeth / Viropharma
NM-283	Antiviral	NS5B Replicase Inhibitor	Idenix / Novartis
GL-59728	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
GL-60667	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
2'C MeA	Antiviral	NS5B Replicase Inhibitor	Gilead
PSI 6130	Antiviral	NS5B Replicase Inhibitor	Roche
R1626	Antiviral	NS5B Replicase Inhibitor	Roche
2'C Methyl adenosine	Antiviral	NS5B Replicase Inhibitor	Merck
JTK-003	Antiviral	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Levovirin	Antiviral	ribavirin	ICN Pharmaceuticals, Costa Mesa, CA

<i>Brand Name</i>	<i>Physiological Class</i>	<i>Type of Inhibitor or Target</i>	<i>Source Company</i>
Ribavirin	Antiviral	ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Viramidine	Antiviral	Ribavirin Prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
SCH 503034	Antiviral	serine protease inhibitor	Schering Plough
Zadazim	Immune modulator	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Immunomodulator	immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
CellCept	Immunosuppressant	HCV IgG immunosuppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Civacir	Immunosuppressant	HCV IgG immunosuppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL

<i>Brand Name</i>	<i>Physiological Class</i>	<i>Type of Inhibitor or Target</i>	<i>Source Company</i>
Albuferon - α	Interferon	albumin IFN- α 2b	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferon	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferon	IFN- ω	Intarcia Therapeutics
IFN- β and EMZ701	Interferon	IFN- β and EMZ701	Transition Therapeutics Inc., Ontario, Canada
Rebif	Interferon	IFN- β 1a	Serono, Geneva, Switzerland
Roferon A	Interferon	IFN- α 2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Intron A	Interferon	IFN- α 2b	Schering-Plough Corporation, Kenilworth, NJ
Intron A and Zadaxin	Interferon	IFN- α 2b/ α 1-thymosin	RegeneRx Biopharmaceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Rebetron	Interferon	IFN- α 2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ

<i>Brand Name</i>	<i>Physiological Class</i>	<i>Type of Inhibitor or Target</i>	<i>Source Company</i>
Actimmune	Interferon	INF- γ	InterMune Inc., Brisbane, CA
Interferon- β	Interferon	Interferon- β -1a	Serono
Multiferon	Interferon	Long lasting IFN	Viragen/Valentis
Wellferon	Interferon	lymphoblastoid IFN- α n1	GlaxoSmithKline plc, Uxbridge, UK
Omniferon	Interferon	natural IFN- α	Viragen Inc., Plantation, FL
Pegasys	Interferon	PEGylated IFN- α 2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ceplene	Interferon	PEGylated IFN- α 2a/ immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys and Ribavirin	Interferon	PEGylated IFN- α 2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
PEG-Intron	Interferon	PEGylated IFN- α 2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	Interferon	PEGylated IFN- α 2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Liver protection	antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA

<i>Brand Name</i>	<i>Physiological Class</i>	<i>Type of Inhibitor or Target</i>	<i>Source Company</i>
IDN-6556	Liver protection	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	serine protease inhibitor	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	NS5B Replicase Inhibitor	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys

The compounds of the present disclosure may also be used as laboratory reagents. Compounds may be instrumental in providing research tools for designing of viral replication assays, validation of animal assay systems and structural biology studies to further enhance knowledge of the HCV disease mechanisms. Further, the compounds of the present disclosure are useful in establishing or determining the binding site of other antiviral compounds, for example, by competitive inhibition.

The compounds of this disclosure may also be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials, e.g., blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection or transfusion apparatuses and materials.

This disclosure is intended to encompass compounds having formula (I) when prepared by synthetic processes or by metabolic processes including those occurring in the human or animal body (*in vivo*) or processes occurring *in vitro*.

The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows: TFA for trifluoroacetic acid; Ph for phenyl; tBu or t-Bu for tert-butyl; DMSO for dimethylsulfoxide; DMF for N,N-dimethylformamide; EtOH for ethanol; Boc or BOC for tert-butoxycarbonyl; THF for tetrahydrofuran; Et₂O for diethyl ether; Et for ethyl; MeOH for methanol; EtOAc and EtOAC for ethyl acetate; RT for room temperature or retention time

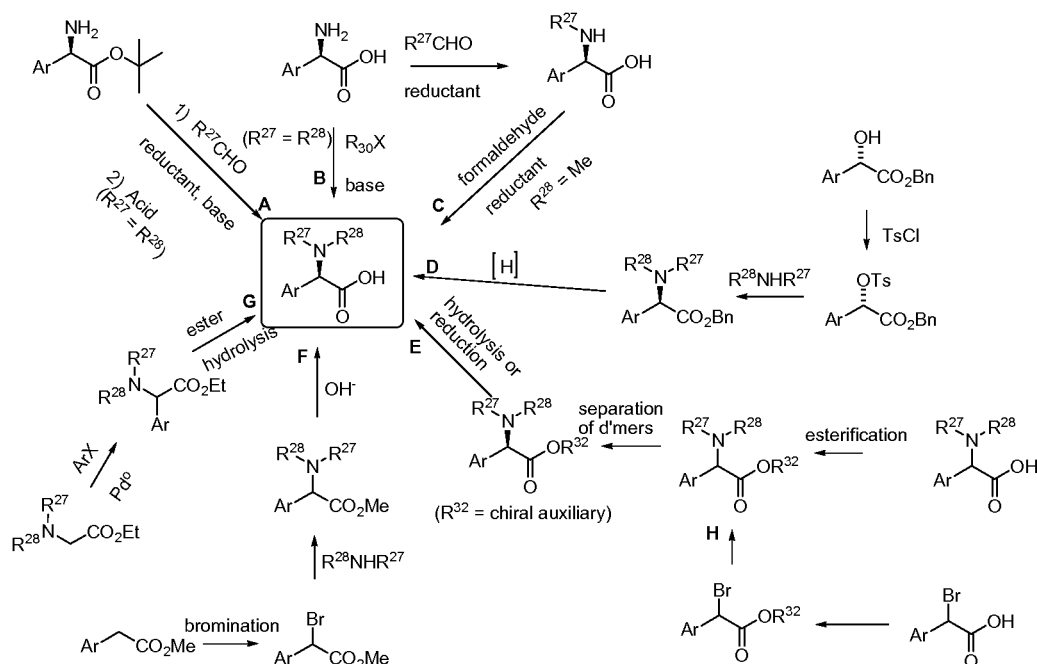
(context will dictate); R_t or t_R for retention time; h for hours; sat'd for saturated; PCC for pyridinium chlorochromate; TBDPS for tert-butyldiphenylsilyl; DMAP for 4-dimethylaminopyridine; TBAF for tetrabutylammonium fluoride; Et_3N or TEA for triethylamine; min for minutes; OAc for acetate; Cbz for carbobenzyloxy; SEM for 2-trimethylsilylethoxymethoxy; AIBN for azobisisobutyronitrile; HATU for O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; DDQ for 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; dppf for 1,1'-bis(diphenylphosphino)ferrocene; and iPr_2NEt or DIPEA or DIEA for diisopropylethylamine.

10 The compounds and processes of the present disclosure will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the present disclosure may be prepared. Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art. It will be
15 readily apparent to one of ordinary skill in the art that the compounds defined above can be synthesized by substitution of the appropriate reactants and agents in the syntheses shown below. It will also be readily apparent to one skilled in the art that the selective protection and deprotection steps, as well as the order of the steps themselves, can be carried out in varying order, depending on the nature of the
20 variables to successfully complete the syntheses below. The variables are as defined above unless otherwise noted below.

Scheme 1: Substituted Phenylglycine Derivatives

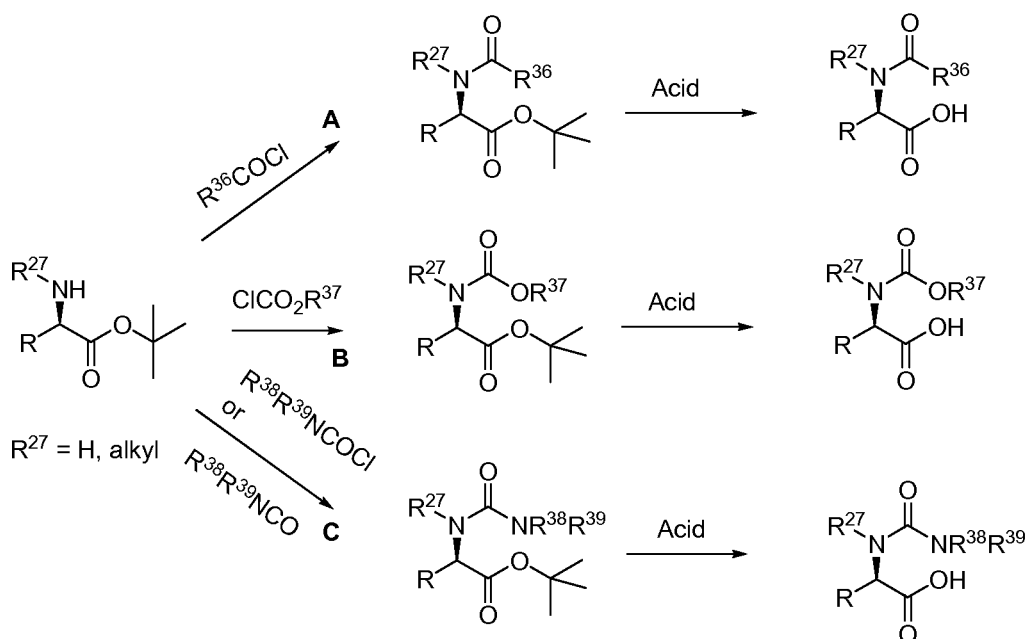
Substituted phenylglycine derivatives can be prepared by a number of methods shown below. Phenylglycine t-butyl ester can be reductively alkylated
25 (pathway A) with an appropriate aldehyde and a reductant such as sodium cyanoborohydride in acidic medium. Hydrolysis of the t-butyl ester can be accomplished with strong acid such as HCl or trifluoroacetic acid. Alternatively, phenylglycine can be alkylated with an alkyl halide such as ethyl iodide and a base such as sodium bicarbonate or potassium carbonate (pathway B). Pathway C
30 illustrates reductive alkylation of phenylglycine as in pathway A followed by a second reductive alkylation with an alternate aldehyde such as formaldehyde in the presence of a reducing agent and acid. Pathway D illustrates the synthesis of substituted phenylglycines *via* the corresponding mandelic acid analogs. Conversion

of the secondary alcohol to a competent leaving group can be accomplished with p-toluensulfonyl chloride. Displacement of the tosylate group with an appropriate amine followed by reductive removal of the benzyl ester can provide substituted phenylglycine derivatives. In pathway E a racemic substituted phenylglycine derivative is resolved by esterification with an enantiomerically pure chiral auxiliary such as but not limited to (+)-1-phenylethanol, (-)-1-phenylethanol, an Evan's oxazolidinone, or enantiomerically pure pantolactone. Separation of the diastereomers is accomplished *via* chromatography (silica gel, HPLC, crystallization, etc) followed by removal of the chiral auxiliary providing enantiomerically pure phenylglycine derivatives. Pathway H illustrates a synthetic sequence which intersects with pathway E wherein the aforementioned chiral auxiliary is installed prior to amine addition. Alternatively, an ester of an arylacetic acid can be brominated with a source of bromonium ion such as bromine, N-bromosuccinimide, or CBr₄. The resultant benzylic bromide can be displaced with a variety of mono- or disubstituted amines in the presence of a tertiary amine base such as triethylamine or Hunig's base. Hydrolysis of the methyl ester *via* treatment with lithium hydroxide at low temperature or 6N HCl at elevated temperature provides the substituted phenylglycine derivatives. Another method is shown in pathway G. Glycine analogs can be derivatized with a variety of aryl halides in the presence of a source of palladium (0) such as palladium bis(tributylphosphine) and base such as potassium phosphate. The resultant ester can then be hydrolyzed by treatment with base or acid. It should be understood that other well known methods to prepare phenylglycine derivatives exist in the art and can be amended to provide the desired compounds in this description. It should also be understood that the final phenylglycine derivatives can be purified to enantiomeric purity greater than 98%ee *via* preparative HPLC.



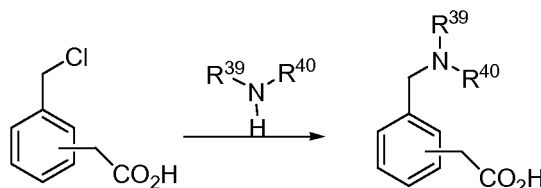
Scheme 2: Acylated Amino Acid Derivatives

In another embodiment of the present disclosure, acylated phenylglycine derivatives may be prepared as illustrated below. Phenylglycine derivatives wherein the carboxylic acid is protected as an easily removed ester, may be acylated with an acid chloride in the presence of a base such as triethylamine to provide the corresponding amides (pathway A). Pathway B illustrates the acylation of the starting phenylglycine derivative with an appropriate chloroformate while pathway C shows reaction with an appropriate isocyanate or carbamoyl chloride. Each of the three intermediates shown in pathways A – C may be deprotected by methods known by those skilled in the art (ie; treatment of the t-butyl ester with strong base such as HCl or trifluoroacetic acid).



Scheme 3

Amino-substituted phenylacetic acids may be prepared by treatment of a chloromethylphenylacetic acid with an excess of an amine.



5

Compound analysis conditions

Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters Micromass ZQ MS system. It should be noted that retention times may vary slightly between machines. The LC conditions employed in determining the retention time (RT) were:

Additional LC conditions applicable to the current section, unless noted otherwise.

Cond.-MS-W1

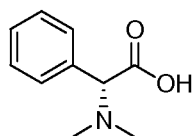
Column = XTERRA 3.0 X 50 mm S7

	Start %B	= 0
	Final %B	= 100
	Gradient time	= 2 min
	Stop time	= 3 min
5	Flow Rate	= 5 mL/min
	Wavelength	= 220 nm
	Solvent A	= 0.1% TFA in 10% methanol/90% H ₂ O
	Solvent B	= 0.1% TFA in 90% methanol/10% H ₂ O
10	<i>Cond.-MS-W2</i>	
	Column	= XTERRA 3.0 X 50 mm S7
	Start %B	= 0
	Final %B	= 100
	Gradient time	= 3 min
15	Stop time	= 4 min
	Flow Rate	= 4 mL/min
	Wavelength	= 220 nm
	Solvent A	= 0.1% TFA in 10% methanol/90% H ₂ O
	Solvent B	= 0.1% TFA in 90% methanol/10% H ₂ O
20	<i>Cond.-MS-W5</i>	
	Column	= XTERRA 3.0 X 50 mm S7
	Start %B	= 0
	Final %B	= 30
25	Gradient time	= 2 min
	Stop time	= 3 min
	Flow Rate	= 5 mL/min
	Wavelength	= 220 nm
	Solvent A	= 0.1% TFA in 10% methanol/90% H ₂ O
30	Solvent B	= 0.1% TFA in 90% methanol/10% H ₂ O
	<i>Cond.-D1</i>	
	Column	= XTERRA C18 3.0 X 50 mm S7

	Start %B	= 0
	Final %B	= 100
	Gradient time	= 3 min
	Stop time	= 4 min
5	Flow Rate	= 4 mL/min
	Wavelength	= 220 nm
	Solvent A	= 0.1% TFA in 10% methanol/90%H ₂ O
	Solvent B	= 0.1% TFA in 90% methanol/10% H ₂ O
10	<i>Cond.-D2</i>	
	Column	= Phenomenex-Luna 4.6 X 50 mm S10
	Start %B	= 0
	Final %B	= 100
	Gradient time	= 3 min
15	Stop time	= 4 min
	Flow Rate	= 4 mL/min
	Wavelength	= 220 nm
	Solvent A	= 0.1% TFA in 10% methanol/90%H ₂ O
	Solvent B	= 0.1% TFA in 90% methanol/10% H ₂ O
20	<i>Cond.-M3</i>	
	Column	= XTERRA C18 3.0 X 50 mm S7
	Start %B	= 0
	Final %B	= 40
25	Gradient time	= 2 min
	Stop time	= 3 min
	Flow Rate	= 5 mL/min
	Wavelength	= 220 nm
	Solvent A	= 0.1% TFA in 10% methanol/90%H ₂ O
30	Solvent B	= 0.1% TFA in 90% methanol/10% H ₂ O
	Condition I	
	Column	= Phenomenex-Luna 3.0 X 50 mm S10

- Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
- 5 Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90% H₂O
Solvent B = 0.1% TFA in 90% methanol/10% H₂O
- 10 Condition II
Column = Phenomenex-Luna 4.6 X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
- 15 Stop time = 3 min
Flow Rate = 5 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90% H₂O
Solvent B = 0.1% TFA in 90% methanol/10% H₂O
- 20 Condition III
Column = XTERRA C18 3.0 x 50mm S7
Start %B = 0
Final %B = 100
- 25 Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90% H₂O
- 30 Solvent B = 0.1% TFA in 90% methanol/10% H₂O

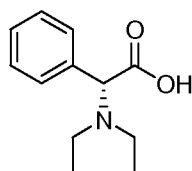
Cap-1



A suspension of 10% Pd/C (2.0g) in methanol (10 mL) was added to a mixture of (R)-2-phenylglycine (10g, 66.2 mmol), formaldehyde (33 mL of 37% wt. in water), 1N HCl (30 mL) and methanol (30 mL), and exposed to H₂ (60 psi) for 3 hours. The reaction mixture was filtered through diatomaceous earth (Celite[®]), and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol to provide the HCl salt of Cap-1 as a white needle (4.0 g). Optical rotation: -117.1° [c=9.95 mg/mL in H₂O; λ=589 nm]. ¹H NMR (DMSO-d₆, δ=2.5 ppm, 500 MHz): δ 7.43-7.34 (m, 5H), 4.14 (s, 1H), 2.43 (s, 6H); LC (Cond. I): RT=0.25; LC/MS: Anal. Calcd. for [M+H]⁺ C₁₀H₁₄NO₂ 180.10; found 180.17; HRMS: Anal. Calcd. for [M+H]⁺ C₁₀H₁₄NO₂ 180.1025; found 180.1017.

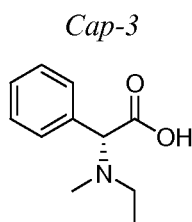
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Cap-2



NaBH₃CN (6.22g, 94 mmol) was added in portions over a few minutes to a cooled (ice/water) mixture of (R)-2-Phenylglycine (6.02 g, 39.8 mmol) and methanol (100 mL), and stirred for 5 minutes. Acetaldehyde (10 mL) was added dropwise over 10 minutes and stirring was continued at the same cooled temperature for 45 minutes and at ambient temperature for ~6.5 hours. The reaction mixture was cooled back with ice-water bath, treated with water (3 mL) and then quenched with a dropwise addition of concentrated HCl over ~45 minutes until the pH of the mixture was ~ 1.5 – 2.0. The cooling bath was removed and the stirring was continued while adding concentrated HCl in order to maintain the pH of the mixture around 1.5-2.0. The reaction mixture was stirred overnight, filtered to remove the white suspension, and the filtrate was concentrated *in vacuo*. The crude material was recrystallized from ethanol to afford the HCl salt of Cap-2 as a shining white solid in two crops (crop-1:

4.16 g; crop-2: 2.19 g). ^1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz): 10.44 (1.00, br s, 1H), 7.66 (m, 2H), 7.51 (m, 3H), 5.30 (s, 1H), 3.15 (br m, 2H), 2.98 (br m, 2H), 1.20 (app br s, 6H). Crop-1: $[\alpha]^{25}_{\text{D}}$ -102.21° (c=0.357, H₂O); crop-2: $[\alpha]^{25}_{\text{D}}$ -99.7° (c=0.357, H₂O). LC (Cond. I): RT=0.43 min; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ C₁₂H₁₈NO₂: 208.13; found 208.26.

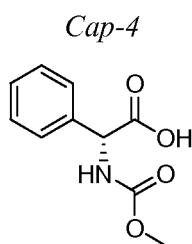


Acetaldehyde (5.0 mL, 89.1 mmol) and a suspension of 10% Pd/C (720 mg) in methanol/H₂O (4mL/1 mL) was sequentially added to a cooled (~ 15 °C) mixture of (R)-2-phenylglycine (3.096g, 20.48 mmol), 1N HCl (30 mL) and methanol (40 mL). The cooling bath was removed and the reaction mixture was stirred under a balloon of H₂ for 17 hours. An additional acetaldehyde (10 mL, 178.2 mmol) was added and stirring continued under H₂ atmosphere for 24 hours [Note: the supply of H₂ was replenished as needed throughout the reaction]. The reaction mixture was filtered through diatomaceous earth (Celite[®]), and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol to provide the HCl salt of (R)-2-(ethylamino)-2-phenylacetic acid as a shining white solid (2.846g). ^1H NMR (DMSO- d_6 , δ =2.5 ppm, 400 MHz): δ 14.15 (br s, 1H), 9.55 (br s, 2H), 7.55-7.48 (m, 5H), 2.88 (br m, 1H), 2.73 (br m, 1H), 1.20 (app t, J =7.2, 3H). LC (Cond. I): RT=0.39 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ C₁₀H₁₄NO₂: 180.10; found 180.18.

A suspension of 10% Pd/C (536 mg) in methanol/H₂O (3 mL/1 mL) was added to a mixture of (R)-2-(ethylamino)-2-phenylacetic acid/HCl (1.492g, 6.918 mmol), formaldehyde (20 mL of 37% wt. in water), 1N HCl (20 mL) and methanol (23 mL). The reaction mixture was stirred under a balloon of H₂ for ~72 hours, where the H₂ supply was replenished as needed. The reaction mixture was filtered through diatomaceous earth (Celite[®]) and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol (50 mL) to provide the HCl salt of Cap-3 as a white solid (985 mg). ^1H NMR (DMSO- d_6 , δ =2.5 ppm, 400

MHz): δ 10.48 (br s, 1H), 7.59-7.51 (m, 5H), 5.26 (s, 1H), 3.08 (app br s, 2H), 2.65 (br s, 3H), 1.24 (br m, 3H). LC (Cond. I): RT=0.39 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; found 194.18; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.1180; found 194.1181.

5



$ClCO_2Me$ (3.2 mL, 41.4 mmol) was added dropwise to a cooled (ice/water) THF (410 mL) semi-solution of (R)-*tert*-butyl 2-amino-2-phenylacetate/HCl (9.877 g, 40.52 mmol) and diisopropylethylamine (14.2 mL, 81.52 mmol) over 6 min, and stirred at similar temperature for 5.5 hours. The volatile component was removed *in vacuo*, and the residue was partitioned between water (100 mL) and ethyl acetate (200 mL). The organic layer was washed with 1N HCl (25 mL) and saturated $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant colorless oil was triturated from hexanes, filtered and washed with hexanes (100 mL) to provide (R)-*tert*-butyl 2-(methoxycarbonylamino)-2-phenylacetate as a white solid (7.7 g). 1H NMR ($DMSO-d_6$, δ =2.5 ppm, 400 MHz): 7.98 (d, J =8.0, 1H), 7.37-7.29 (m, 5H), 5.09 (d, J =8, 1H), 3.56 (s, 3H), 1.33 (s, 9H). LC (Cond. I): RT=1.53 min; ~90 % homogeneity index; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{14}H_{19}NNaO_4$: 288.12; found 288.15.

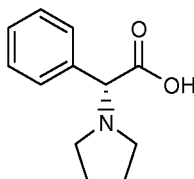
TFA (16 mL) was added dropwise to a cooled (ice/water) CH_2Cl_2 (160 mL) solution of the above product over 7 minutes, and the cooling bath was removed and the reaction mixture was stirred for 20 hours. Since the deprotection was still not complete, an additional TFA (1.0 mL) was added and stirring continued for an additional 2 hours. The volatile component was removed *in vacuo*, and the resulting oil residue was treated with diethyl ether (15 mL) and hexanes (12 mL) to provide a precipitate. The precipitate was filtered and washed with diethyl ether/hexanes (~1:3 ratio; 30 mL) and dried *in vacuo* to provide Cap-4 as a fluffy white solid (5.57 g). Optical rotation: -176.9° [c =3.7 mg/mL in H_2O ; λ =589 nm]. 1H NMR ($DMSO-d_6$,

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$\delta=2.5$ ppm, 400 MHz): δ 12.84 (br s, 1H), 7.96 (d, $J=8.3$, 1H), 7.41-7.29 (m, 5H), 5.14 (d, $J=8.3$, 1H), 3.55 (s, 3H). LC (Cond. I): RT=1.01 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ C₁₀H₁₂NO₄ 210.08; found 210.17; HRMS: Anal. Calcd. for $[M+H]^+$ C₁₀H₁₂NO₄ 210.0766; found 210.0756.

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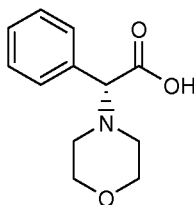
Cap-5



A mixture of (R)- 2-phenylglycine (1.0 g, 6.62 mmol), 1,4-dibromobutane (1.57 g, 7.27 mmol) and Na₂CO₃ (2.10 g, 19.8 mmol) in ethanol (40 mL) was heated at 100 °C for 21 hours. The reaction mixture was cooled to ambient temperature and filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethanol and acidified with 1N HCl to pH 3-4, and the volatile component was removed *in vacuo*. The resulting crude material was purified by a reverse phase HPLC (water/methanol/TFA) to provide the TFA salt of Cap-5 as a semi-viscous white foam (1.0 g). ¹H NMR (DMSO-d₆, $\delta=2.5$, 500 MHz) δ 10.68 (br s, 1H), 7.51 (m, 5H), 5.23 (s, 1H), 3.34 (app br s, 2H), 3.05 (app br s, 2H), 1.95 (app br s, 4H); RT=0.30 minutes (Cond. I); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ C₁₂H₁₆NO₂: 206.12; found 206.25.

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Cap-6

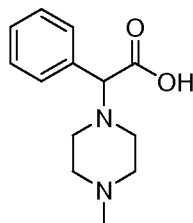


The TFA salt of Cap-6 was synthesized from (R)-2-phenylglycine and 1-bromo-2-(2-bromoethoxy)ethane by using the method of preparation of Cap-5. ¹H NMR (DMSO-d₆, $\delta=2.5$, 500 MHz) δ 12.20 (br s, 1H), 7.50 (m, 5H), 4.92 (s, 1H), 3.78 (app br s, 4H), 3.08 (app br s, 2H), 2.81 (app br s, 2H); RT=0.32 minutes (Cond. I).

25

D; >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.11; found 222.20;
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.1130; found 222.1121.

Cap-7



Cap-7a: enantiomer-1
Cap-7b: enantiomer-2

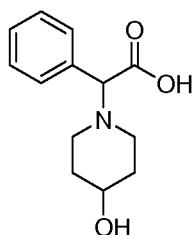
5 A CH_2Cl_2 (200 mL) solution of p-toluenesulfonyl chloride (8.65 g, 45.4 mmol) was added dropwise to a cooled ($-5\text{ }^{\circ}C$) CH_2Cl_2 (200 mL) solution of (S)-benzyl 2-hydroxy-2-phenylacetate (10.0 g, 41.3 mmol), triethylamine (5.75 mL, 41.3 mmol) and 4-dimethylaminopyridine (0.504 g, 4.13 mmol), while maintaining the
10 temperature between $-5\text{ }^{\circ}C$ and $0\text{ }^{\circ}C$. The reaction was stirred at $0\text{ }^{\circ}C$ for 9 hours, and then stored in a freezer ($-25\text{ }^{\circ}C$) for 14 hours. It was allowed to thaw to ambient temperature and washed with water (200 mL), 1N HCl (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide benzyl 2-phenyl-2-(tosyloxy)acetate as a viscous oil which solidified upon standing (16.5 g). The chiral
15 integrity of the product was not checked and that product was used for the next step without further purification. 1H NMR ($DMSO-d_6$, $\delta=2.5$, 500 MHz) δ 7.78 (d, $J=8.6$, 2H), 7.43-7.29 (m, 10H), 7.20 (m, 2H), 6.12 (s, 1H), 5.16 (d, $J=12.5$, 1H), 5.10 (d, $J=12.5$, 1H), 2.39 (s, 3H). RT=3.00 (Cond. III); >90% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{22}H_{20}NaO_5S$: 419.09; found 419.04.

20 A THF (75 mL) solution of benzyl 2-phenyl-2-(tosyloxy)acetate (6.0 g, 15.1 mmol), 1-methylpiperazine (3.36 mL, 30.3 mmol) and N,N-diisopropylethylamine (13.2 mL, 75.8 mmol) was heated at $65\text{ }^{\circ}C$ for 7 hours. The reaction was allowed to cool to ambient temperature and the volatile component was removed *in vacuo*. The residue was partitioned between ethylacetate and water, and the organic layer was
25 washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by flash chromatography (silica gel, ethyl acetate) to provide benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate as an orangish-brown viscous oil (4.56 g). Chiral HPLC analysis (Chiralcel OD-H) indicated that the sample is a mixture of enantiomers in a 38.2 to 58.7 ratio. The separation of the

enantiomers were effected as follow: the product was dissolved in 120 mL of ethanol/heptane (1:1) and injected (5 mL/injection) on chiral HPLC column (Chiracel OJ, 5 cm ID x 50 cm L, 20 μ m) eluting with 85:15 Heptane/ethanol at 75 mL/min, and monitored at 220 nm. Enantiomer-1 (1.474 g) and enantiomer-2 (2.2149 g) were
5 retrieved as viscous oil. ^1H NMR (CDCl_3 , δ =7.26, 500 MHz) 7.44-7.40 (m, 2H), 7.33-7.24 (m, 6H), 7.21-7.16 (m, 2H), 5.13 (d, J =12.5, 1H), 5.08 (d, J =12.5, 1H), 4.02 (s, 1H), 2.65-2.38 (app br s, 8H), 2.25 (s, 3H). RT=2.10 (Cond. III); >98% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_2$: 325.19; found 325.20.

10 A methanol (10 mL) solution of either enantiomer of benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate (1.0 g, 3.1 mmol) was added to a suspension of 10% Pd/C (120 mg) in methanol (5.0 mL). The reaction mixture was exposed to a balloon of hydrogen, under a careful monitoring, for <50 minutes. Immediately after the completion of the reaction, the catalyst was filtered through diatomaceous earth
15 (Celite[®]) and the filtrate was concentrated *in vacuo* to provide Cap-7, contaminated with phenylacetic acid as a tan foam (867.6 mg; mass is above the theoretical yield). The product was used for the next step without further purification. ^1H NMR ($\text{DMSO}-d_6$, δ =2.5, 500 MHz) δ 7.44-7.37 (m, 2H), 7.37-7.24 (m, 3H), 3.92 (s, 1H), 2.63-2.48 (app. br s, 2H), 2.48-2.32 (m, 6H), 2.19 (s, 3H); RT=0.31 (Cond. II);
20 >90% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_2$: 235.14; found 235.15; HRMS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_2$: 235.1447; found 235.1440.

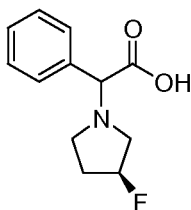
The synthesis of Cap-8 and Cap-9 was conducted according to the synthesis of Cap-7 by using appropriate amines for the $\text{S}_\text{N}2$ displacement step (i.e., 4-
25 hydroxypiperidine for Cap-8 and (S)-3-fluoropyrrolidine for Cap-9) and modified conditions for the separation of the respective stereoisomeric intermediates, as described below.

Cap-8

8a: enantiomer-1
8b: enantiomer-2

The enantiomeric separation of the intermediate benzyl 2-(4-hydroxypiperidin-1-yl)-2-phenyl acetate was effected by employing the following conditions: the compound (500 mg) was dissolved in ethanol/heptane (5 mL/45 mL). The resulting solution was injected (5 mL/injection) on a chiral HPLC column (Chiracel OJ, 2 cm ID x 25 cm L, 10 μ m) eluting with 80:20 heptane/ethanol at 10 mL/min, monitored at 220 nm, to provide 186.3 mg of enantiomer-1 and 209.1 mg of enantiomer-2 as light-yellow viscous oils. These benzyl ester was hydrogenolysed according to the preparation of Cap-7 to provide Cap-8: ^1H NMR (DMSO- d_6 , δ =2.5, 500 MHz) 7.40 (d, J =7, 2H), 7.28-7.20 (m, 3H), 3.78 (s 1H), 3.46 (m, 1H), 2.93 (m, 1H), 2.62 (m, 1H), 2.20 (m, 2H), 1.70 (m, 2H), 1.42 (m, 2H). RT=0.28 (Cond. II); >98% homogeneity index; LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{18}\text{NO}_3$: 236.13; found 236.07; HRMS: Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{18}\text{NO}_3$: 236.1287; found 236.1283.

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Cap-9

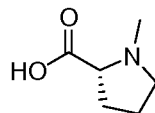
9a: diastereomer-1
9b: diastereomer-2

The diastereomeric separation of the intermediate benzyl 2-((S)-3-fluoropyrrolidin-1-yl)-2-phenylacetate was effected by employing the following conditions: the ester (220 mg) was separated on a chiral HPLC column (Chiracel OJ-H, 0.46 cm ID x 25 cm L, 5 μ m) eluting with 95% CO_2 / 5% methanol with 0.1% TFA, at 10 bar pressure, 70 mL/min flow rate, and a temperature of 35 $^\circ\text{C}$. The HPLC elute for the respective stereoisomers was concentrated, and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with an aqueous medium (10 mL water + 1 mL saturated NaHCO_3 solution). The organic phase was dried (MgSO_4), filtered, and

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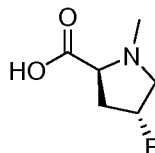
concentrated *in vacuo* to provide 92.5 mg of fraction-1 and 59.6 mg of fraction-2. These benzyl esters were hydrogenolysed according to the preparation of Cap-7 to prepare Caps 9a and 9b. Cap-9a (diastereomer-1; the sample is a TFA salt as a result of purification on a reverse phase HPLC using H₂O/methanol/TFA solvent): ¹H NMR (DMSO-d₆, δ=2.5, 400 MHz) 7.55-7.48 (m, 5H), 5.38 (d of m, *J*=53.7, 1H), 5.09 (br s, 1H), 3.84-2.82 (br m, 4H), 2.31-2.09 (m, 2H). RT=0.42 (Cond. I); >95% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₁₂H₁₅FNO₂: 224.11; found 224.14; Cap-9b (diastereomer-2): ¹H NMR (DMSO-d₆, δ=2.5, 400 MHz) 7.43-7.21 (m, 5H), 5.19 (d of m, *J*=55.9, 1H), 3.97 (s, 1H), 2.95-2.43 (m, 4H), 2.19-1.78 (m, 2H). RT=0.44 (Cond. I); LC/MS: Anal. Calcd. for [M+H]⁺ C₁₂H₁₅FNO₂: 224.11; found 224.14.

Cap-10



To a solution of D-proline (2.0 g, 17 mmol) and formaldehyde (2.0 mL of 37% wt. in H₂O) in methanol (15 mL) was added a suspension of 10% Pd/C (500 mg) in methanol (5 mL). The mixture was stirred under a balloon of hydrogen for 23 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo* to provide Cap-10 as an off-white solid (2.15 g). ¹H NMR (DMSO-d₆, δ=2.5, 500 MHz) 3.42 (m, 1H), 3.37 (dd, *J*=9.4, 6.1, 1H), 2.85-2.78 (m, 1H), 2.66 (s, 3H), 2.21-2.13 (m, 1H), 1.93-1.84 (m, 2H), 1.75-1.66 (m, 1H). RT=0.28 (Cond. II); >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₆H₁₂NO₂: 130.09; found 129.96.

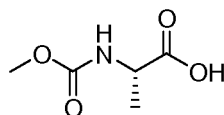
Cap-11



A mixture of (2S,4R)-4-fluoropyrrolidine-2-carboxylic acid (0.50 g, 3.8 mmol), formaldehyde (0.5 mL of 37% wt. in H₂O), 12 N HCl (0.25 mL) and 10%

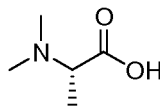
Pd/C (50 mg) in methanol (20 mL) was stirred under a balloon of hydrogen for 19 hours. The reaction mixture was filtered through diatomaceous earth (Celite[®]) and the filtrate was concentrated *in vacuo*. The residue was recrystallized from isopropanol to provide the HCl salt of Cap-11 as a white solid (337.7 mg). ¹H NMR (DMSO-d₆, δ=2.5, 500 MHz) 5.39 (d m, *J*=53.7, 1H), 4.30 (m, 1H), 3.90 (ddd, *J*=31.5, 13.5, 4.5, 1H), 3.33 (dd, *J*=25.6, 13.4, 1H), 2.85 (s, 3H), 2.60-2.51 (m, 1H), 2.39-2.26 (m, 1H). RT=0.28 (Cond. II); >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]⁺ C₆H₁₁FNO₂: 148.08; found 148.06.

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Cap-12 (same as cap 52)

L-Alanine (2.0 g, 22.5 mmol) was dissolved in 10% aqueous sodium carbonate solution (50 mL), and a THF (50 mL) solution of methyl chloroformate (4.0 mL) was added to it. The reaction mixture was stirred under ambient conditions for 4.5 hours and concentrated *in vacuo*. The resulting white solid was dissolved in water and acidified with 1N HCl to a pH ~ 2-3. The resulting solutions was extracted with ethyl acetate (3 x 100 mL), and the combined organic phase was dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide a colorless oil (2.58 g). 500 mg of this material was purified by a reverse phase HPLC (H₂O/methanol/TFA) to provide 150 mg of Cap-12 as a colorless oil. ¹H NMR (DMSO-d₆, δ=2.5, 500 MHz) 7.44 (d, *J*=7.3, 0.8H), 7.10 (br s, 0.2H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, *J*=7.3, 3H).

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Cap-13

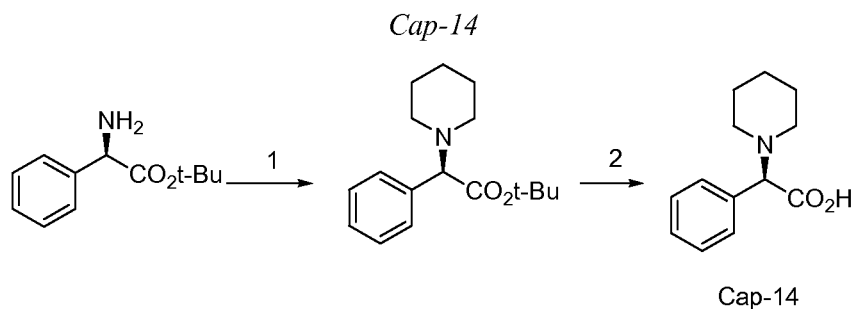
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A mixture of L-alanine (2.5 g, 28 mmol), formaldehyde (8.4 g, 37 wt. %), 1N HCl (30 mL) and 10% Pd/C (500 mg) in methanol (30 mL) was stirred under a hydrogen atmosphere (50 psi) for 5 hours. The reaction mixture was filtered through diatomaceous earth (Celite[®]) and the filtrate was concentrated *in vacuo* to provide the HCl salt of Cap-13 as an oil which solidified upon standing under vacuum (4.4 g; the

mass is above theoretical yield). The product was used without further purification.

^1H NMR (DMSO- d_6 , $\delta=2.5$, 500 MHz) δ 12.1 (br s, 1H), 4.06 (q, $J=7.4$, 1H), 2.76 (s, 6H), 1.46 (d, $J=7.3$, 3H).

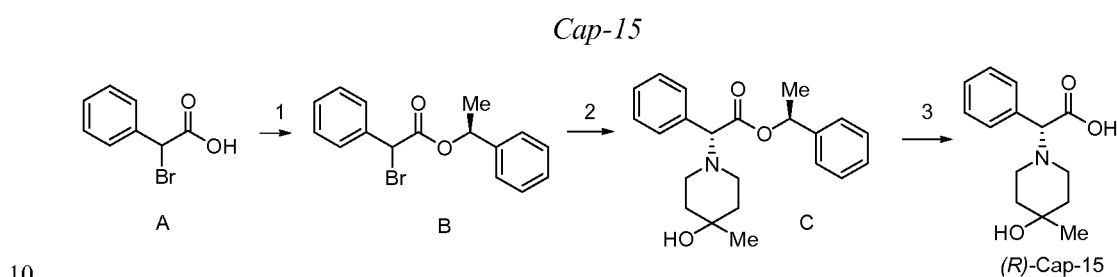
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Step 1: A mixture of (R)-(-)-D-phenylglycine tert-butyl ester (3.00 g, 12.3 mmol), NaBH_3CN (0.773 g, 12.3 mmol), KOH (0.690 g, 12.3 mmol) and acetic acid (0.352 mL, 6.15 mmol) were stirred in methanol at 0 °C. To this mixture was added glutaric dialdehyde (2.23 mL, 12.3 mmol) dropwise over 5 minutes. The reaction mixture was stirred as it was allowed to warm to ambient temperature and stirring was continued at the same temperature for 16 hours. The solvent was subsequently removed and the residue was partitioned with 10% aqueous NaOH and ethyl acetate. The organic phase was separated, dried (MgSO_4), filtered and concentrated to dryness to provide a clear oil. This material was purified by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN - H_2O -0.1% TFA) to give the intermediate ester (2.70 g, 56%) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 7.53-7.44 (m, 3H), 7.40-7.37 (m, 2H), 3.87 (d, $J=10.9$ Hz, 1H), 3.59 (d, $J=10.9$ Hz, 1H), 2.99 (t, $J=11.2$ Hz, 1H), 2.59 (t, $J=11.4$ Hz, 1H), 2.07-2.02 (m, 2H), 1.82 (d, $J=1.82$ Hz, 3H), 1.40 (s, 9H). LC/MS: Anal. Calcd. for $\text{C}_{17}\text{H}_{25}\text{NO}_2$: 275; found: 276 ($\text{M}+\text{H}$) $^+$.

Step 2: To a stirred solution of the intermediate ester (1.12g, 2.88mmol) in dichloromethane (10 mL) was added TFA (3 mL). The reaction mixture was stirred at ambient temperature for 4 hours and then it was concentrated to dryness to give a light yellow oil. The oil was purified using reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN - H_2O -0.1% TFA). The appropriate fractions were combined and concentrated to dryness *in vacuo*. The residue was then dissolved in a minimum amount of methanol and applied to applied to MCX LP

extraction cartridges (2 x 6 g). The cartridges were rinsed with methanol (40 mL) and then the desired compound was eluted using 2M ammonia in methanol (50 mL). Product-containing fractions were combined and concentrated and the residue was taken up in water. Lyophilization of this solution provided the title compound (0.492 g, 78%) as a light yellow solid. ^1H NMR (DMSO- d_6) δ 7.50 (s, 5H), 5.13 (s, 1H), 3.09 (br s, 2H), 2.92-2.89 (m, 2H), 1.74 (m, 4H), 1.48 (br s, 2H). LC/MS: Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}_2$: 219; found: 220 ($\text{M}+\text{H}$) $^+$.

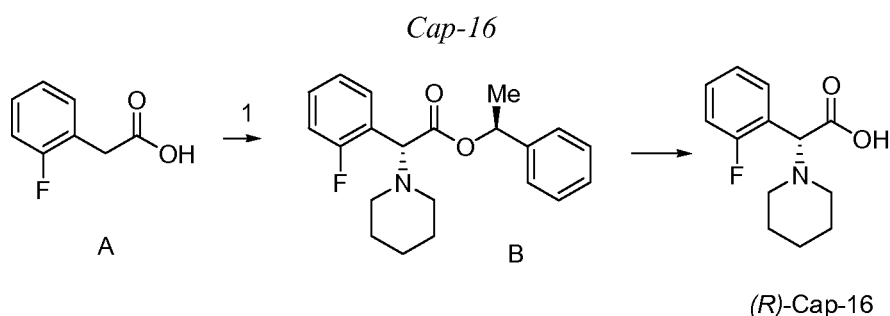


Step 1: (S)-1-Phenylethyl 2-bromo-2-phenylacetate: To a mixture of α -bromophenylacetic acid (10.75 g, 0.050 mol), (S)-(-)-1-phenylethanol (7.94 g, 0.065 mol) and DMAP (0.61 g, 5.0 mmol) in dry dichloromethane (100 mL) was added solid EDCI (12.46 g, 0.065 mol) all at once. The resulting solution was stirred at room temperature under Ar for 18 hours and then it was diluted with ethyl acetate, washed (H_2O x 2, brine), dried (Na_2SO_4), filtered, and concentrated to give a pale yellow oil. Flash chromatography (SiO_2 / hexane-ethyl acetate, 4:1) of this oil provided the title compound (11.64 g, 73%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.53-7.17 (m, 10H), 5.95 (q, $J=6.6$ Hz, 0.5H), 5.94 (q, $J=6.6$ Hz, 0.5H), 5.41 (s, 0.5H), 5.39 (s, 0.5H), 1.58 (d, $J=6.6$ Hz, 1.5H), 1.51 (d, $J=6.6$ Hz, 1.5H).

Step 2: (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)-2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (0.464 g, 1.45 mmol) in THF (8 mL) was added triethylamine (0.61 mL, 4.35 mmol), followed by tetrabutylammonium iodide (0.215 g, 0.58 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-methyl-4-hydroxypiperidine (0.251 g, 2.18 mmol) in THF (2 mL) was added. The mixture was stirred for 1 hour at room temperature and then it was heated at 55-60 $^\circ\text{C}$ (oil bath temperature) for 4 hours. The cooled reaction mixture was then diluted with ethyl acetate (30 mL), washed (H_2O x2, brine), dried (MgSO_4), filtered and concentrated.

The residue was purified by silica gel chromatography (0-60% ethyl acetate-hexane) to provide first the (S,R)-isomer of the title compound (0.306 g, 60%) as a white solid and then the corresponding (S,S)-isomer (0.120 g, 23%), also as a white solid. (S,R)-isomer: ^1H NMR (CD_3OD) δ 7.51-7.45 (m, 2H), 7.41-7.25 (m, 8H), 5.85 (q, $J=6.6$ Hz, 1H), 4.05 (s, 1H), 2.56-2.45 (m, 2H), 2.41-2.29 (m, 2H), 1.71-1.49 (m, 4H), 1.38 (d, $J=6.6$ Hz, 3H), 1.18 (s, 3H). LCMS: Anal. Calcd. for $\text{C}_{22}\text{H}_{27}\text{NO}_3$: 353; found: 354 ($\text{M}+\text{H}$) $^+$. (S,S)-isomer: ^1H NMR (CD_3OD) δ 7.41-7.30 (m, 5H), 7.20-7.14 (m, 3H), 7.06-7.00 (m, 2H), 5.85 (q, $J=6.6$ Hz, 1H), 4.06 (s, 1H), 2.70-2.60 (m, 1H), 2.51 (dt, $J=6.6, 3.3$ Hz, 1H), 2.44-2.31 (m, 2H), 1.75-1.65 (m, 1H), 1.65-1.54 (m, 3H), 1.50 (d, $J=6.8$ Hz, 3H), 1.20 (s, 3H). LCMS: Anal. Calcd. for $\text{C}_{22}\text{H}_{27}\text{NO}_3$: 353; found: 354 ($\text{M}+\text{H}$) $^+$.

Step 3: (R)-2-(4-Hydroxy-4-methylpiperidin-1-yl)-2-phenylacetic acid: To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)-2-phenylacetate (0.185 g, 0.52 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed *in vacuo* and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20 x 100mm; $\text{CH}_3\text{CN}-\text{H}_2\text{O}-0.1\%$ TFA) to give the title compound (as TFA salt) as a pale bluish solid (0.128 g, 98%). LCMS: Anal. Calcd. for $\text{C}_{14}\text{H}_{19}\text{NO}_3$: 249; found: 250 ($\text{M}+\text{H}$) $^+$.



Step 1: (S)-1-Phenylethyl 2-(2-fluorophenyl)acetate: A mixture of 2-fluorophenylacetic acid (5.45 g, 35.4 mmol), (S)-1-phenylethanol (5.62 g, 46.0 mmol), EDCI (8.82 g, 46.0 mmol) and DMAP (0.561 g, 4.60 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 12 hours. The solvent was then concentrated and the residue partitioned with H_2O -ethyl acetate. The phases were

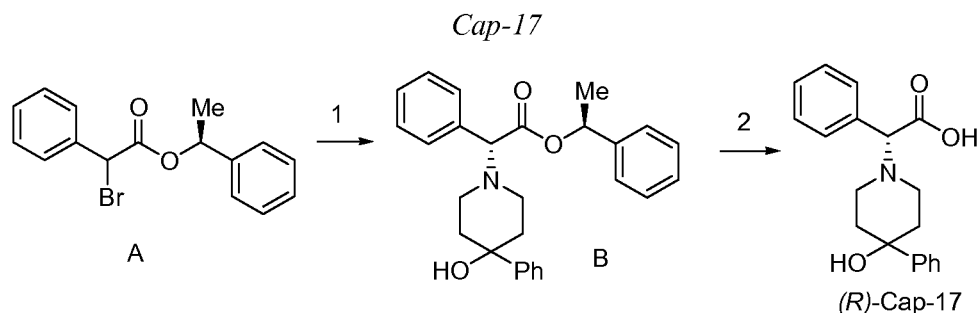
separated and the aqueous layer back-extracted with ethyl acetate (2x). The combined organic phases were washed (H₂O, brine), dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Biotage/ 0-20% ethyl acetate-hexane) to provide the title compound as a colorless oil (8.38 g, 92%). ¹H NMR (400 MHz, CD₃OD) δ 7.32-7.23 (m, 7H), 7.10-7.04 (m, 2), 5.85 (q, *J*=6.5 Hz, 1H), 3.71 (s, 2H), 1.48 (d, *J*=6.5 Hz, 3H).

Step 2: (R)-((S)-1-Phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate:
To a solution of (S)-1-phenylethyl 2-(2-fluorophenyl)acetate (5.00 g, 19.4 mmol) in THF (1200 mL) at 0 °C was added DBU (6.19 g, 40.7 mmol) and the solution was allowed to warm to room temperature while stirring for 30 minutes. The solution was then cooled to -78 °C and a solution of CBr₄ (13.5 g, 40.7 mmol) in THF (100 mL) was added and the mixture was allowed to warm to -10 °C and stirred at this temperature for 2 hours. The reaction mixture was quenched with saturated aq. NH₄Cl and the layers were separated. The aqueous layer was back-extracted with ethyl acetate (2x) and the combined organic phases were washed (H₂O, brine), dried (Na₂SO₄), filtered, and concentrated *in vacuo*. To the residue was added piperidine (5.73 mL, 58.1 mmol) and the solution was stirred at room temperature for 24 hours. The volatiles were then concentrated *in vacuo* and the residue was purified by silica gel chromatography (Biotage/ 0-30% diethyl ether-hexane) to provide a pure mixture of diastereomers (2:1 ratio by ¹H NMR) as a yellow oil (2.07 g, 31%), along with unreacted starting material (2.53 g, 51%). Further chromatography of the diastereomeric mixture (Biotage/ 0-10% diethyl ether-toluene) provided the title compound as a colorless oil (0.737 g, 11%). ¹H NMR (400 MHz, CD₃OD) δ 7.52 (ddd, *J*=9.4, 7.6, 1.8 Hz, 1H), 7.33 – 7.40 (m, 1), 7.23 – 7.23 (m, 4H), 7.02 – 7.23 (m, 4H), 5.86 (q, *J*=6.6 Hz, 1H), 4.45 (s, 1H), 2.39 – 2.45 (m, 4H), 1.52 – 1.58 (m, 4H), 1.40 – 1.42 (m, 1H), 1.38 (d, *J*=6.6 Hz, 3H). LCMS: Anal. Calcd. for C₂₁H₂₄FNO₂: 341; found: 342 (M+H)⁺.

Step 3: (R)-2-(2-fluorophenyl)-2-(piperidin-1-yl)acetic acid: A mixture of (R)-((S)-1-phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate (0.737 g, 2.16 mmol) and 20% Pd(OH)₂/C (0.070 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H₂ balloon) for 2 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite[®]), and concentrated

in vacuo. This provided the title compound as a colorless solid (0.503 g, 98%). ^1H NMR (400 MHz, CD_3OD) δ 7.65 (ddd, $J=9.1, 7.6, 1.5$ Hz, 1H), 7.47-7.53 (m, 1H), 7.21-7.30 (m, 2H), 3.07-3.13 (m, 4H), 1.84 (br s, 4H), 1.62 (br s, 2H). LCMS: Anal. Calcd. for $\text{C}_{13}\text{H}_{16}\text{FNO}_2$: 237; found: 238 ($\text{M}+\text{H}$) $^+$.

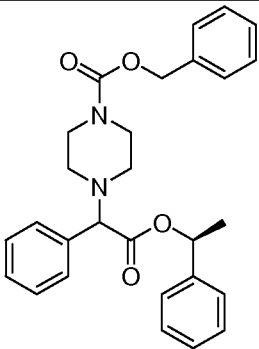
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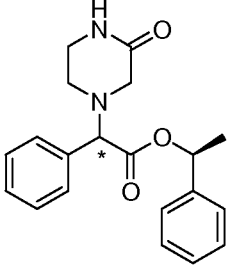
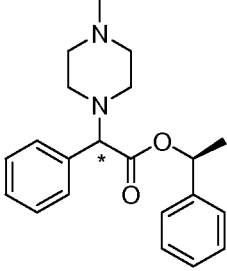
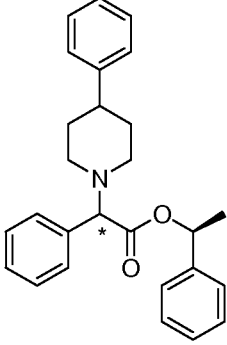


Step 1: (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)- 2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (1.50 g, 4.70 mmol) in THF (25 mL) was added triethylamine (1.31 mL, 9.42 mmol), followed by tetrabutylammonium iodide (0.347 g, 0.94 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-phenyl-4-hydroxypiperidine (1.00 g, 5.64 mmol) in THF (5 mL) was added. The mixture was stirred for 16 hours and then it was diluted with ethyl acetate (100 mL), washed (H_2O x2, brine), dried (MgSO_4), filtered and concentrated. The residue was purified on a silica gel column (0-60% ethyl acetate-hexane) to provide an approximately 2:1 mixture of diastereomers, as judged by ^1H NMR. Separation of these isomers was performed using supercritical fluid chromatography (Chiralcel OJ-H, 30 x 250mm; 20% ethanol in CO_2 at 35 $^\circ\text{C}$), to give first the (R)-isomer of the title compound (0.534 g, 27%) as a yellow oil and then the corresponding (S)-isomer (0.271 g, 14%), also as a yellow oil. (S,R)-isomer: ^1H NMR (400 MHz, CD_3OD) δ 7.55-7.47 (m, 4H), 7.44-7.25 (m, 10H), 7.25-7.17 (m, 1H), 5.88 (q, $J=6.6$ Hz, 1H), 4.12 (s, 1H), 2.82-2.72 (m, 1H), 2.64 (dt, $J=11.1, 2.5$ Hz, 1H), 2.58-2.52 (m, 1H), 2.40 (dt, $J=11.1, 2.5$ Hz, 1H), 2.20 (dt, $J=12.1, 4.6$ Hz, 1H), 2.10 (dt, $J=12.1, 4.6$ Hz, 1H), 1.72-1.57 (m, 2H), 1.53 (d, $J=6.5$ Hz, 3H). LCMS: Anal. Calcd. for $\text{C}_{27}\text{H}_{29}\text{NO}_3$: 415; found: 416 ($\text{M}+\text{H}$) $^+$; (S,S)-isomer: ^1H NMR (400 MHz, CD_3OD) δ 7.55-7.48 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.30 (m, 5H), 7.25-7.13 (m, 4H), 7.08-7.00 (m, 2H), 5.88 (q, $J=6.6$ Hz, 1H), 4.12 (s, 1H), 2.95-2.85 (m, 1H), 2.68 (dt, $J=11.1, 2.5$ Hz, 1H), 2.57-2.52 (m, 1H), 2.42 (dt, $J=11.1, 2.5$ Hz, 1H), 2.25 (dt, $J=12.1, 4.6$ Hz,

1H), 2.12 (dt, $J=12.1, 4.6$ Hz, 1H), 1.73 (dd, $J=13.6, 3.0$ Hz, 1H), 1.64 (dd, $J=13.6, 3.0$ Hz, 1H), 1.40 (d, $J=6.6$ Hz, 3H). LCMS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 (M+H)⁺.

5 The following esters were prepared in similar fashion:

<i>Intermediate-17a</i>		Diastereomer 1: ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.36 (d, $J=6.41$ Hz, 3H) 2.23-2.51 (m, 4H) 3.35 (s, 4H) 4.25 (s, 1H) 5.05 (s, 2H) 5.82 (d, $J=6.71$ Hz, 1H) 7.15-7.52 (m, 15H). LCMS: Anal. Calcd. for: $C_{28}H_{30}N_2O_4$ 458.22; Found: 459.44 (M+H)⁺. Diastereomer 2: ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.45 (d, $J=6.71$ Hz, 3H) 2.27-2.44 (m, 4H) 3.39 (s, 4H) 4.23 (s, 1H) 5.06 (s, 2H) 5.83 (d, $J=6.71$ Hz, 1H) 7.12 (dd, $J=6.41, 3.05$ Hz, 2H) 7.19-7.27 (m, 3H) 7.27-7.44 (m, 10H). LCMS: Anal. Calcd. for: $C_{28}H_{30}N_2O_4$ 458.22; Found: 459.44 (M+H)⁺.
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<i>Intermediate -17b</i>		Diastereomer 1: RT=11.76 minutes (Cond'n II); LCMS: Anal. Calcd. for: C₂₀H₂₂N₂O₃ 338.16 Found: 339.39 (M+H)⁺; Diastereomer 2: RT=10.05 minutes (Cond'n II); LCMS: Anal. Calcd. for: C₂₀H₂₂N₂O₃ 338.16; Found: 339.39 (M+H)⁺.
<i>Intermediate -17c</i>		Diastereomer 1: T_R=4.55 minutes (Cond'n I); LCMS: Anal. Calcd. for: C₂₁H₂₆N₂O₂ 338.20 Found: 339.45 (M+H)⁺; Diastereomer 2: T_R=6.00 minutes (Cond'n I); LCMS: Anal. Calcd. for: C₂₁H₂₆N₂O₂ 338.20 Found: 339.45 (M+H)⁺.
<i>Intermediate -17d</i>		Diastereomer 1: RT=7.19 minutes (Cond'n I); LCMS: Anal. Calcd. for: C₂₇H₂₉NO₂ 399.22 Found: 400.48 (M+H)⁺; Diastereomer 2: RT=9.76 minutes (Cond'n I); LCMS: Anal. Calcd. for: C₂₇H₂₉NO₂ 399.22 Found: 400.48 (M+H)⁺.

Chiral SFC Conditions for determining retention time

Condition I

Column: Chiralpak AD-H Column, 4.62x50 mm, 5 μ m

5 Solvents: 90% CO₂-10% methanol with 0.1%DEA

Temp: 35 °C

Pressure: 150 bar

Flow rate: 2.0 mL/min.

UV monitored @ 220 nm

10 Injection: 1.0 mg/3mL methanol

Condition II

Column: Chiralcel OD-H Column, 4.62x50 mm, 5 μ m

Solvents: 90% CO₂-10% methanol with 0.1%DEA

15 Temp: 35 °C

Pressure: 150 bar

Flow rate: 2.0 mL/min.

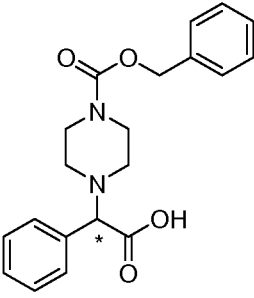
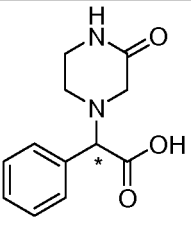
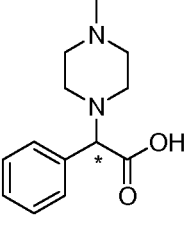
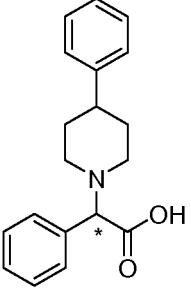
UV monitored @ 220 nm

Injection: 1.0 mg/mL methanol

20

Cap 17, Step 2; (R)-2-(4-Hydroxy-4-phenylpiperidin-1-yl)-2-phenylacetic acid: To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-2-phenylacetate (0.350 g, 0.84 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed *in vacuo* and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20 x 100mm; CH₃CN-H₂O-0.1% TFA) to give the title compound (as TFA salt) as a white solid (0.230 g, 88%). LCMS: Anal. Calcd. for C₁₉H₂₁NO₃: 311.15; found: 312 (M+H)⁺.

30 The following carboxylic acids were prepared in optically pure form in a similar fashion:

<i>Cap-17a</i>		RT=2.21 (Cond'n II); ¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 2.20-2.35 (m, 2H) 2.34-2.47 (m, 2H) 3.37 (s, 4H) 3.71 (s, 1H) 5.06 (s, 2H) 7.06-7.53 (m, 10H). LCMS: Anal. Calcd. for: C ₂₀ H ₂₂ N ₂ O ₄ 354.16; Found: 355.38 (M+H) ⁺ .
<i>Cap-17b</i>		RT=0.27 (Cond'n III); LCMS: Anal. Calcd. for: C ₁₂ H ₁₄ N ₂ O ₃ 234.10; Found: 235.22 (M+H) ⁺ .
<i>Cap-17c</i>		RT=0.48 (Cond'n II); LCMS: Anal. Calcd. for: C ₁₃ H ₁₈ N ₂ O ₂ 234.14; Found: 235.31 (M+H) ⁺ .
<i>Cap-17d</i>		RT=2.21 (Cond'n I); LCMS: Anal. Calcd. for: C ₁₉ H ₂₁ NO ₂ 295.16; Found: 296.33 (M+H) ⁺ .

LCMS Conditions for determining retention time

Condition I

5 Column: Phenomenex-Luna 4.6 X 50 mm S10

Start % B=0

Fianl % B=100

Gradient Time=4 min

Flow Rate=4 mL/min

Wavelength=220

Solvent A=10% methanol – 90% H₂O – 0.1% TFA

5 Solvent B=90% methanol – 10% H₂O – 0.1% TFA

Condition II

Column: Waters-Sunfire 4.6 X 50 mm S5

Start % B=0

10 Fianl % B=100

Gradient Time=2 min

Flow Rate=4 mL/min

Wavelength=220

Solvent A=10% methanol – 90% H₂O – 0.1% TFA

15 Solvent B=90% methanol – 10% H₂O – 0.1% TFA

Condition III

Column: Phenomenex 10 μ 3.0 X 50 mm

Start % B=0

20 Fianl % B=100

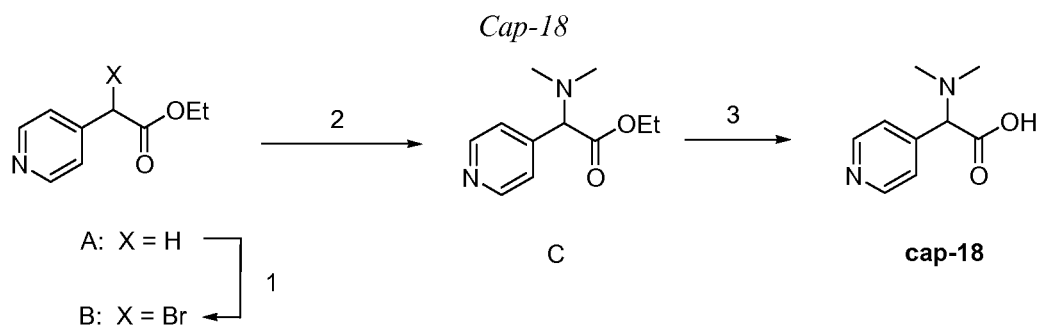
Gradient Time=2 min

Flow Rate=4 mL/min

Wavelength=220

Solvent A=10% methanol – 90% H₂O – 0.1% TFA

25 Solvent B=90% methanol – 10% H₂O – 0.1% TFA



Step 1; (R,S)-Ethyl 2-(4-pyridyl)-2-bromoacetate: To a solution of ethyl 4-pyridylacetate (1.00 g, 6.05 mmol) in dry THF (150 mL) at 0 °C under argon was added DBU (0.99 mL, 6.66 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes and then it was cooled to -78 °C. To this mixture was added CBr₄ (2.21 g, 6.66 mmol) and stirring was continued at -78 °C for 2 hours. The reaction mixture was then quenched with sat. aq. NH₄Cl and the phases were separated. The organic phase was washed (brine), dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting yellow oil was immediately purified by flash chromatography (SiO₂/ hexane-ethyl acetate, 1:1) to provide the title compound (1.40 g, 95%) as a somewhat unstable yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.62 (dd, *J*=4.6, 1.8 Hz, 2H), 7.45 (dd, *J*=4.6, 1.8 Hz, 2H), 5.24 (s, 1H), 4.21-4.29 (m, 2H), 1.28 (t, *J*=7.1 Hz, 3H). LCMS: Anal. Calcd. for C₉H₁₀BrNO₂: 242, 244; found: 243, 245 (M+H)⁺.

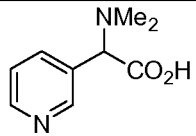
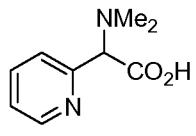
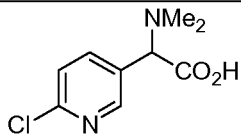
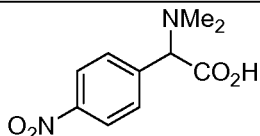
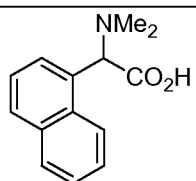
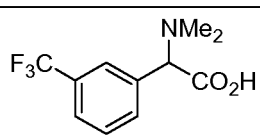
Step 2; (R,S)-Ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-bromoacetate (1.40 g, 8.48 mmol) in DMF (10 mL) at room temperature was added dimethylamine (2M in THF, 8.5 mL, 17.0 mmol). After completion of the reaction (as judged by thin layer chromatography) the volatiles were removed *in vacuo* and the residue was purified by flash chromatography (Biotage, 40+M SiO₂ column; 50%-100% ethyl acetate-hexane) to provide the title compound (0.539 g, 31%) as a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.58 (d, *J*=6.0 Hz, 2H), 7.36 (d, *J*=6.0 Hz, 2H), 4.17 (m, 2H), 3.92 (s, 1H), 2.27 (s, 6H), 1.22 (t, *J*=7.0 Hz). LCMS: Anal. Calcd. for C₁₁H₁₆N₂O₂: 208; found: 209 (M+H)⁺.

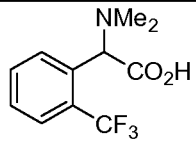
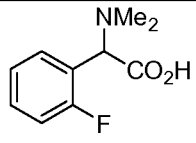
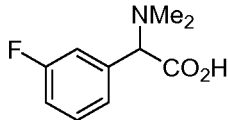
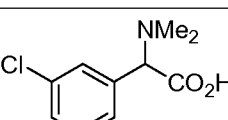
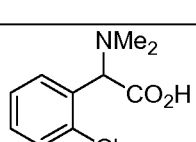
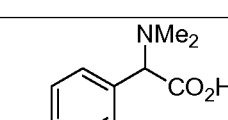
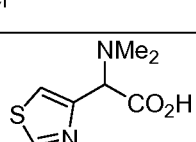
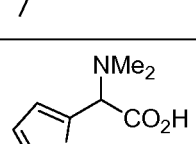
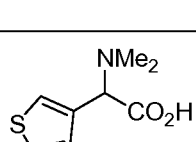
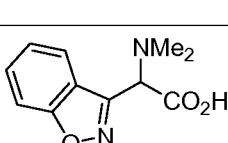
Step 3; (R,S)-2-(4-Pyridyl)-2-(N,N-dimethylamino)acetic acid: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate (0.200 g, 0.960 mmol) in

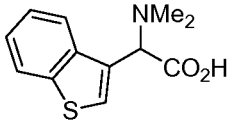
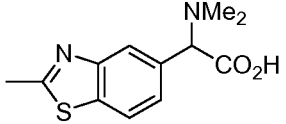
a mixture of THF-methanol-H₂O (1:1:1, 6 mL) was added powdered LiOH (0.120 g, 4.99 mmol) at room temperature. The solution was stirred for 3 hours and then it was acidified to pH 6 using 1N HCl. The aqueous phase was washed with ethyl acetate and then it was lyophilized to give the dihydrochloride of the title compound as a yellow solid (containing LiCl). The product was used as such in subsequent steps.

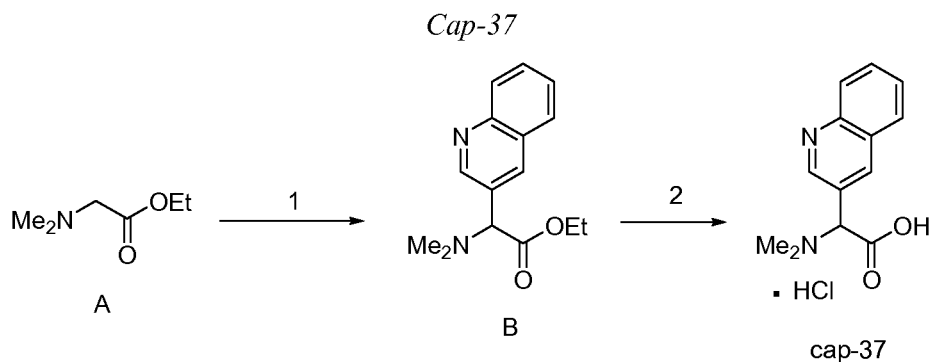
¹H NMR (400 MHz, DMSO-d₆) δ 8.49 (d, *J*=5.7 Hz, 2H), 7.34 (d, *J*=5.7 Hz, 2H), 3.56 (s, 1H), 2.21 (s, 6H).

The following examples were prepared in similar fashion using the method described above;

Cap-19		LCMS: Anal. Calcd. for C ₉ H ₁₂ N ₂ O ₂ : 180; found: 181 (M+H) ⁺ .
Cap-20		LCMS: no ionization. ¹ H NMR (400 MHz, CD ₃ OD) δ 8.55 (d, <i>J</i> =4.3 Hz, 1H), 7.84 (app t, <i>J</i> =5.3 Hz, 1H), 7.61 (d, <i>J</i> =7.8 Hz, 1H), 7.37 (app t, <i>J</i> =5.3 Hz, 1H), 4.35 (s, 1H), 2.60 (s, 6H).
Cap-21		LCMS: Anal. Calcd. for C ₉ H ₁₁ ClN ₂ O ₂ : 214, 216; found: 215, 217 (M+H) ⁺ .
Cap-22		LCMS: Anal. Calcd. for C ₁₀ H ₁₂ N ₂ O ₄ : 224; found: 225 (M+H) ⁺ .
Cap-23		LCMS: Anal. Calcd. for C ₁₄ H ₁₅ NO ₂ : 229; found: 230 (M+H) ⁺ .
Cap-24		LCMS: Anal. Calcd. for C ₁₁ H ₁₂ F ₃ NO ₂ : 247; found: 248 (M+H) ⁺ .

Cap-25		LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.
Cap-26		LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 197; found: 198 $(M+H)^+$.
Cap-27		LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 247; found: 248 $(M+H)^+$.
Cap-28		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.
Cap-29		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.
Cap-30		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.
Cap-31		LCMS: Anal. Calcd. for $C_8H_{12}N_2O_2S$: 200; found: 201 $(M+H)^+$.
Cap-32		LCMS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$.
Cap-33		LCMS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$.
Cap-34		LCMS: Anal. Calcd. for $C_{11}H_{12}N_2O_3$: 220; found: 221 $(M+H)^+$.

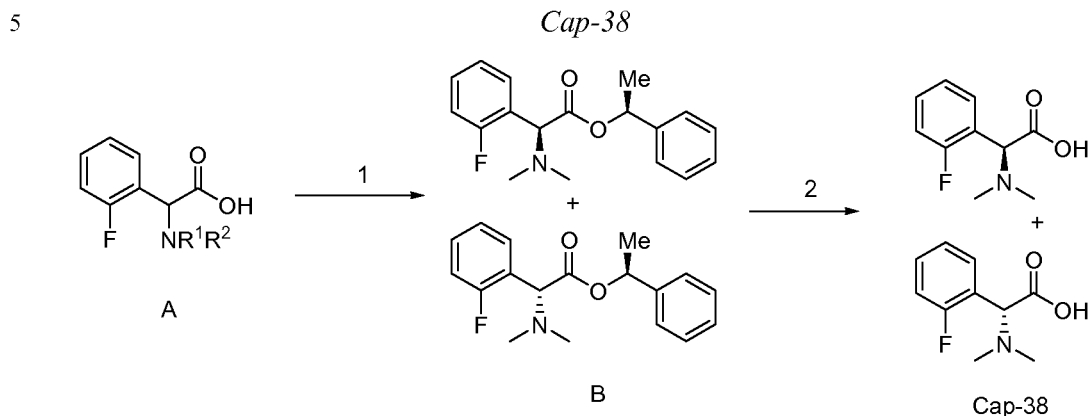
Cap-35		LCMS: Anal. Calcd. for C ₁₂ H ₁₃ NO ₂ S: 235; found: 236 (M+H) ⁺ .
Cap-36		LCMS: Anal. Calcd. for C ₁₂ H ₁₄ N ₂ O ₂ S: 250; found: 251 (M+H) ⁺ .



Step 1; (R,S)-Ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)-acetate: A mixture of ethyl N,N-dimethylaminoacetate (0.462 g, 3.54 mmol), K₃PO₄ (1.90 g, 8.95 mmol), Pd(t-Bu₃P)₂ (0.090 g, 0.176 mmol) and toluene (10 mL) was degassed with a stream of Ar bubbles for 15 minutes. The reaction mixture was then heated at 100 °C for 12 hours, after which it was cooled to room temperature and poured into H₂O. The mixture was extracted with ethyl acetate (2x) and the combined organic phases were washed (H₂O, brine), dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The residue was purified first by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH₃CN-H₂O-5 mM NH₄OAc) and then by flash chromatography (SiO₂/ hexane-ethyl acetate, 1:1) to provide the title compound (0.128 g, 17%) as an orange oil. ¹H NMR (400 MHz, CDCl₃) δ 8.90 (d, *J*=2.0 Hz, 1H), 8.32 (d, *J*=2.0 Hz, 1H), 8.03-8.01 (m, 2H), 7.77 (ddd, *J*=8.3, 6.8, 1.5 Hz, 1H), 7.62 (ddd, *J*=8.3, 6.8, 1.5 Hz, 1H), 4.35 (s, 1H), 4.13 (m, 2H), 2.22 (s, 6H), 1.15 (t, *J*=7.0 Hz, 3H). LCMS: Anal. Calcd. for C₁₅H₁₈N₂O₂: 258; found: 259 (M+H)⁺.

Step 2; (R,S) 2-(Quinolin-3-yl)-2-(N,N-dimethylamino)acetic acid: A mixture of (R,S)-ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)acetate (0.122 g, 0.472 mmol) and 6M HCl (3 mL) was heated at 100 °C for 12 hours. The solvent was removed *in vacuo* to provide the dihydrochloride of the title compound (0.169 g,

>100%) as a light yellow foam. The unpurified material was used in subsequent steps without further purification. LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_2$: 230; found: 231 ($M+H$)⁺.



Step 1; (R)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate and (S)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate: To a mixture of (RS)-2-(dimethylamino)-2-(2-fluorophenyl)acetic acid (2.60 g, 13.19 mmol), DMAP (0.209 g, 1.71 mmol) and (S)-1-phenylethanol (2.09 g, 17.15 mmol) in CH_2Cl_2 (40 mL) was added EDCI (3.29 g, 17.15 mmol) and the mixture was allowed to stir at room temperature for 12 hours. The solvent was then removed *in vacuo* and the residue partitioned with ethyl acetate- H_2O . The layers were separated, the aqueous layer was back-extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O , brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Biotage/ 0-50% diethyl ether-hexane). The resulting pure diastereomeric mixture was then separated by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O -0.1% TFA) to give first (S)-1-phenethyl (R)-2-(dimethylamino)-2-(2-fluorophenyl)acetate (0.501 g, 13%) and then (S)-1-phenethyl (S)-2-(dimethylamino)-2-(2-fluorophenyl)-acetate (0.727 g, 18%), both as their TFA salts.

(S,R)-isomer: 1H NMR (400 MHz, CD_3OD) δ 7.65-7.70 (m, 1H), 7.55-7.60 (ddd, $J=9.4, 8.1, 1.5$ Hz, 1H), 7.36-7.41 (m, 2H), 7.28-7.34 (m, 5H), 6.04 (q, $J=6.5$ Hz, 1H), 5.60 (s, 1H), 2.84 (s, 6H), 1.43 (d, $J=6.5$ Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 ($M+H$)⁺; (S,S)-isomer: 1H NMR (400 MHz, CD_3OD) δ 7.58-7.63 (m, 1H), 7.18-7.31 (m, 6H), 7.00 (dd, $J=8.5, 1.5$ Hz, 2H), 6.02 (q, $J=6.5$

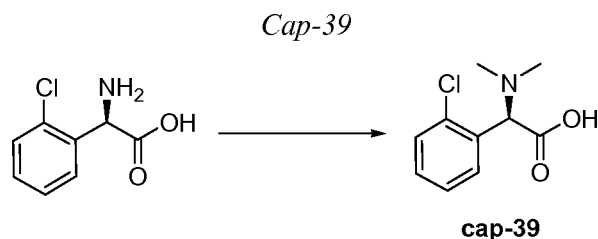
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Hz, 1H), 5.60 (s, 1H), 2.88 (s, 6H), 1.54 (d, $J=6.5$ Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 (M+H)⁺.

Step 2; (R)-2-(dimethylamino)-2-(2-fluorophenyl)acetic acid: A mixture of (R)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt (1.25 g, 3.01 mmol) and 20% Pd(OH)₂/C (0.125 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H₂ balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite[®]), and concentrated *in vacuo*. This gave the title compound as a colorless solid (0.503 g, 98%). ¹H NMR (400 MHz, CD₃OD) δ 7.53-7.63 (m, 2H), 7.33-7.38 (m, 2H), 5.36 (s, 1H), 2.86 (s, 6H). LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 197; found: 198 (M+H)⁺.

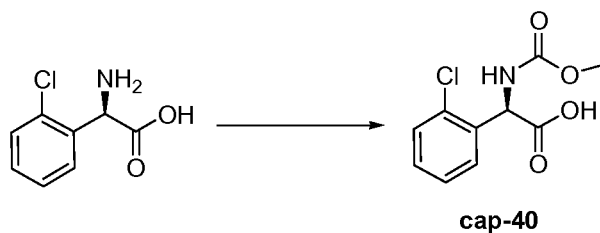
The S-isomer could be obtained from (S)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt in similar fashion.

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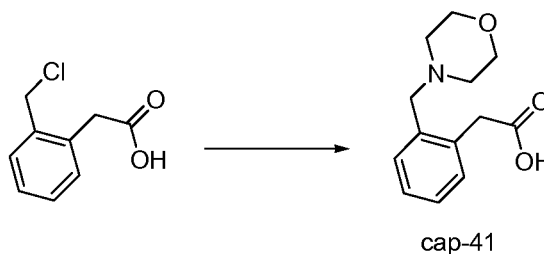
A mixture of (R)-2-(chlorophenyl)glycine (0.300 g, 1.62 mmol), formaldehyde (35% aqueous solution, 0.80 mL, 3.23 mmol) and 20% Pd(OH)₂/C (0.050 g) was hydrogenated at room temperature and atmospheric pressure (H₂ balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite[®]) and concentrated *in vacuo*. The residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH₃CN-H₂O-0.1% TFA) to give the TFA salt of the title compound (R)-2-(dimethylamino)-2-(2-chlorophenyl)acetic acid as a colorless oil (0.290 g, 55%). ¹H NMR (400 MHz, CD₃OD) δ 7.59-7.65 (m, 2H), 7.45-7.53 (m, 2H), 5.40 (s, 1H), 2.87 (s, 6H). LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 (M+H)⁺.

Cap-40



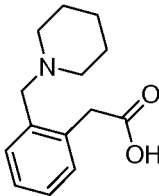
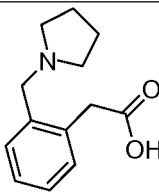
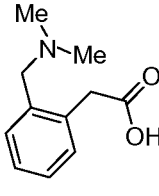
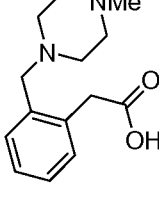
To an ice-cold solution of (R)-2-(2-chlorophenyl)glycine (1.00 g, 5.38 mmol) and NaOH (0.862 g, 21.6 mmol) in H_2O (5.5 mL) was added methyl chloroformate (1.00 mL, 13.5 mmol) dropwise. The mixture was allowed to stir at 0 °C for 1 hour and then it was acidified by the addition of conc. HCl (2.5 mL). The mixture was extracted with ethyl acetate (2x) and the combined organic phase was washed (H_2O , brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give the title compound (R)-2-(methoxycarbonylamino)-2-(2-chlorophenyl)acetic acid as a yellow-orange foam (1.31 g, 96%). ^1H NMR (400 MHz, CD_3OD) δ 7.39 – 7.43 (m, 2H), 7.29 – 7.31 (m, 2H), 5.69 (s, 1H), 3.65 (s, 3H). LCMS: Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{ClNO}_4$: 243; found: 244 ($\text{M}+\text{H}$) $^+$.

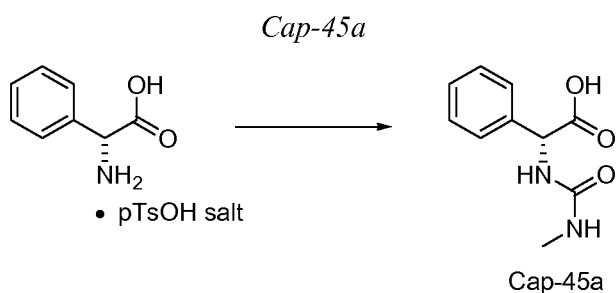
Cap-41



To a suspension of 2-(2-(chloromethyl)phenyl)acetic acid (2.00 g, 10.8 mmol) in THF (20 mL) was added morpholine (1.89 g, 21.7 mmol) and the solution was stirred at room temperature for 3 hours. The reaction mixture was then diluted with ethyl acetate and extracted with H_2O (2x). The aqueous phase was lyophilized and the residue was purified by silica gel chromatography (Biotage/ 0-10% methanol- CH_2Cl_2) to give the title compound 2-(2-(Morpholinomethyl)phenyl)acetic acid as a colorless solid (2.22 g, 87%). ^1H NMR (400 MHz, CD_3OD) δ 7.37-7.44 (m, 3H), 7.29-7.33 (m, 1H), 4.24 (s, 2H), 3.83 (br s, 4H), 3.68 (s, 2H), 3.14 (br s, 4H). LCMS: Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}_3$: 235; found: 236 ($\text{M}+\text{H}$) $^+$.

The following examples were similarly prepared using the method described for Cap-41:

Cap-42		LCMS: Anal. Calcd. for C ₁₄ H ₁₉ NO ₂ : 233; found: 234 (M+H) ⁺ .
Cap-43		LCMS: Anal. Calcd. for C ₁₃ H ₁₇ NO ₂ : 219; found: 220 (M+H) ⁺ .
Cap-44		LCMS: Anal. Calcd. for C ₁₁ H ₁₅ NO ₂ : 193; found: 194 (M+H) ⁺ .
Cap-45		LCMS: Anal. Calcd. for C ₁₄ H ₂₀ N ₂ O ₂ : 248; found: 249 (M+H) ⁺ .

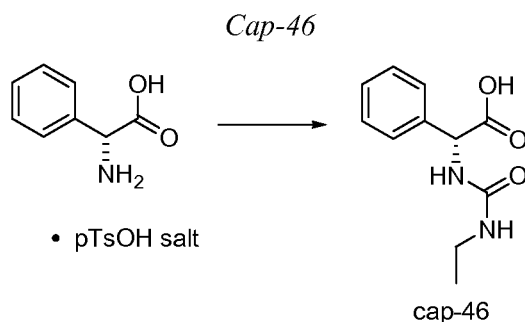


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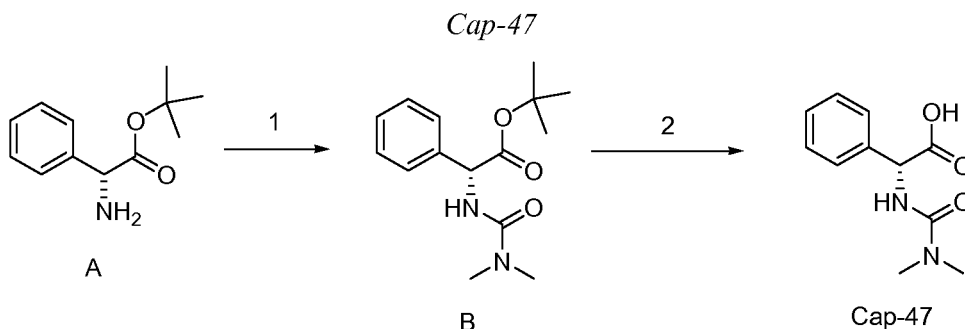
HMDS (1.85 mL, 8.77 mmol) was added to a suspension of (R)-2-amino-2-phenylacetic acid p-toluenesulfonate (2.83 g, 8.77 mmol) in CH₂Cl₂ (10 mL) and the mixture was stirred at room temperature for 30 minutes. Methyl isocyanate (0.5 g, 8.77 mmol) was added in one portion stirring continued for 30 minutes. The reaction was quenched by addition of H₂O (5 mL) and the resulting precipitate was filtered, washed with H₂O and n-hexanes, and dried under vacuum. (R)-2-(3-methylureido)-2-phenylacetic acid (1.5 g; 82 %) was recovered as a white solid and it was used

10

without further purification. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.54 (d, $J=4.88$ Hz, 3H) 5.17 (d, $J=7.93$ Hz, 1H) 5.95 (q, $J=4.48$ Hz, 1H) 6.66 (d, $J=7.93$ Hz, 1H) 7.26-7.38 (m, 5H) 12.67 (s, 1H). LCMS: Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_3$ 208.08 found 209.121 ($\text{M}+\text{H}$) $^+$; HPLC Phenomenex C-18 3.0×46 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=1.38 min, 90% homogeneity index.



The desired product was prepared according to the method described for Cap-45a. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 0.96 (t, $J=7.17$ Hz, 3H) 2.94-3.05 (m, 2H) 5.17 (d, $J=7.93$ Hz, 1H) 6.05 (t, $J=5.19$ Hz, 1H) 6.60 (d, $J=7.63$ Hz, 1H) 7.26-7.38 (m, 5H) 12.68 (s, 1H). LCMS: Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_3$ 222.10 found 223.15 ($\text{M}+\text{H}$) $^+$. HPLC XTERRA C-18 3.0×506 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% H_3PO_4 , B=10% water, 90% methanol, 0.2% H_3PO_4 , RT=0.87 min, 90% homogeneity index.

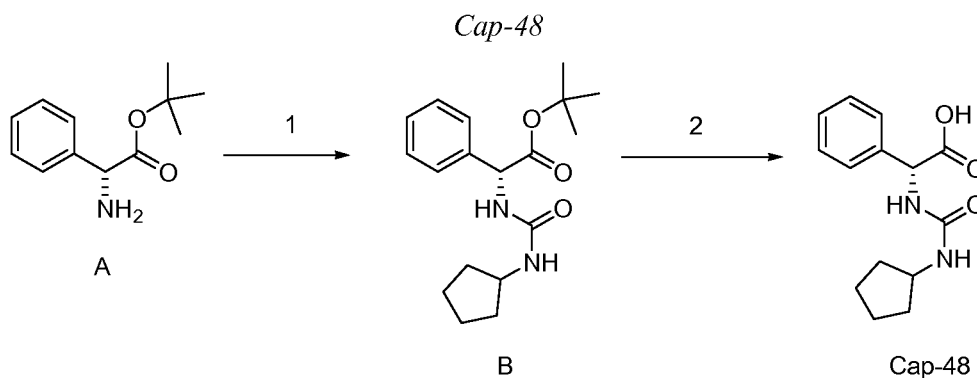


Step 1; (R)-tert-butyl 2-((3,3-dimethylureido)-2-phenylacetate: To a stirred solution of (R)-tert-butyl-2-amino-2-phenylacetate (1.0 g, 4.10 mmol) and Hunig's base (1.79 mL, 10.25 mmol) in DMF (40 mL) was added dimethylcarbonyl chloride (0.38 mL, 4.18 mmol) dropwise over 10 minutes. After stirring at room

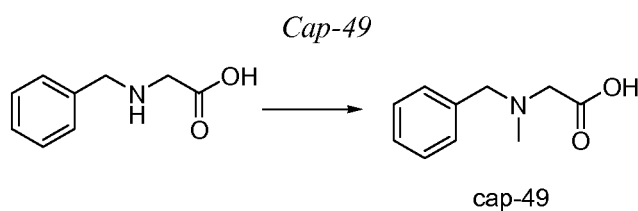
temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was dissolved in ethyl acetate. The organic layer was washed with H₂O, 1N aq. HCl and brine, dried (MgSO₄), filtered and concentrated under reduced pressure. (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate was
5 obtained as a white solid (0.86 g; 75%) and used without further purification. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.33 (s, 9H) 2.82 (s, 6H) 5.17 (d, *J*=7.63 Hz, 1H) 6.55 (d, *J*=7.32 Hz, 1H) 7.24-7.41 (m, 5H). LCMS: Anal. Calcd. for C₁₅H₂₂N₂O₃ 278.16 found 279.23 (M+H)⁺; HPLC Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1%
10 TFA, B=10% water, 90% methanol, 0.1% TFA, RT=2.26 min, 97% homogeneity index.

Step 2; (R)-2-(3,3-dimethylureido)-2-phenylacetic acid: To a stirred solution of ((R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate (0.86 g, 3.10 mmol) in CH₂Cl₂ (250 mL) was added TFA (15 mL) dropwise and the resulting solution was
15 stirred at rt for 3 hours. The desired compound was then precipitated out of solution with a mixture of EtOAc:Hexanes (5:20), filtered off and dried under reduced pressure. (R)-2-(3,3-dimethylureido)-2-phenylacetic acid was isolated as a white solid (0.59g, 86%) and used without further purification. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 2.82 (s, 6H) 5.22 (d, *J*=7.32 Hz, 1H) 6.58 (d, *J*=7.32 Hz, 1H) 7.28
20 (t, *J*=7.17 Hz, 1H) 7.33 (t, *J*=7.32 Hz, 2H) 7.38-7.43 (m, 2H) 12.65 (s, 1H). LCMS: Anal. Calcd. for C₁₁H₁₄N₂O₃: 222.24; found: 223.21 (M+H)⁺. HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% H₃PO₄, B=10% water, 90% methanol, 0.2% H₃PO₄, RT=0.75 min, 93% homogeneity index.

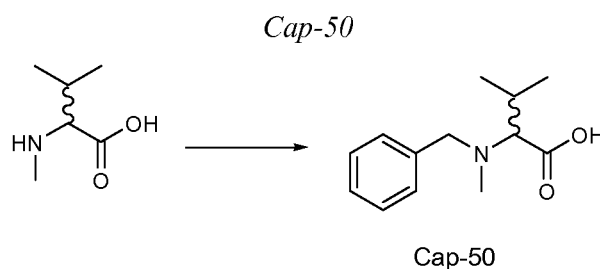
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- Step 1;* (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate: To a stirred solution of (R)-2-amino-2-phenylacetic acid hydrochloride (1.0 g, 4.10 mmol) and Hunig's base (1.0 mL, 6.15 mmol) in DMF (15 mL) was added cyclopentyl isocyanate (0.46 mL, 4.10 mmol) dropwise and over 10 minutes. After stirring at room temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was taken up in ethyl acetate. The organic layer was washed with H₂O and brine, dried (MgSO₄), filtered, and concentrated under reduced pressure. (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate was obtained as an opaque oil (1.32 g; 100 %) and used without further purification. ¹H NMR (500 MHz, CD₃Cl-D) δ ppm 1.50-1.57 (m, 2H) 1.58-1.66 (m, 2H) 1.87-1.97 (m, 2H) 3.89-3.98 (m, 1H) 5.37 (s, 1H) 7.26-7.38 (m, 5H). LCMS: Anal. Calcd. for C₁₈H₂₆N₂O₃ 318.19 found 319.21 (M+H)⁺; HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=2.82 min, 96% homogeneity index.
- Step 2;* (R)-2-(3-cyclopentylureido)-2-phenylacetic acid: To a stirred solution of (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate (1.31 g, 4.10 mmol) in CH₂Cl₂ (25 mL) was added TFA (4 mL) and triethylsilane (1.64 mL; 10.3 mmol) dropwise, and the resulting solution was stirred at room temperature for 6 hours. The volatile components were removed under reduced pressure and the crude product was recrystallized in ethyl acetate/pentanes to yield (R)-2-(3-cyclopentylureido)-2-phenylacetic acid as a white solid (0.69 g, 64%). ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.17-1.35 (m, 2H) 1.42-1.52 (m, 2H) 1.53-1.64 (m, 2H) 1.67-1.80 (m, 2H) 3.75-3.89 (m, 1H) 5.17 (d, *J*=7.93 Hz, 1H) 6.12 (d, *J*=7.32 Hz, 1H) 6.48 (d, *J*=7.93 Hz, 1H) 7.24-7.40 (m, 5H) 12.73 (s, 1H). LCMS: Anal. Calcd. for C₁₄H₁₈N₂O₃; 262.31; found: 263.15 (M+H)⁺. HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% H₃PO₄, B=10% water, 90% methanol, 0.2% H₃PO₄, RT=1.24 min, 100% homogeneity index.



To a stirred solution of 2-(benzylamino)acetic acid (2.0 g, 12.1 mmol) in formic acid (91 mL) was added formaldehyde (6.94 mL, 93.2 mmol). After five hours at 70 °C, the reaction mixture was concentrated under reduced pressure to 20 mL and a white solid precipitated. Following filtration, the mother liquors were collected and further concentrated under reduced pressure providing the crude product. Purification by reverse-phase preparative HPLC (Xterra 30 X 100 mm, detection at 220 nm, flow rate 35 mL/min, 0 to 35% B over 8 min; A= 90% water, 10 % methanol, 0.1% TFA, B=10% water, 90 % methanol, 0.1% TFA) provided the title compound 2-(benzyl(methyl)-amino)acetic acid as its TFA salt (723 mg, 33%) as a colorless wax. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 2.75 (s, 3H) 4.04 (s, 2H) 4.34 (s, 2H) 7.29-7.68 (m, 5H). LCMS: Anal. Calcd. for: C₁₀H₁₃NO₂ 179.09; Found: 180.20 (M+H)⁺.

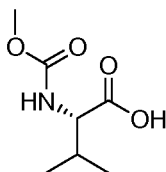


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To a stirred solution of 3-methyl-2-(methylamino)butanoic acid (0.50 g, 3.81 mmol) in water (30 mL) was added K₂CO₃ (2.63 g, 19.1 mmol) and benzyl chloride (1.32 g, 11.4 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was extracted with ethyl acetate (30 mL x 2) and the aqueous layer was concentrated under reduced pressure providing the crude product which was purified by reverse-phase preparative HPLC (Xterra 30 x 100mm, detection at 220 nm, flow rate 40 mL/min, 20 to 80% B over 6 min; A= 90% water, 10 % methanol, 0.1% TFA, B=10% water, 90 % methanol, 0.1% TFA) to provide 2-(benzyl(methyl)amino)-3-methylbutanoic acid, TFA salt (126 mg, 19%) as a colorless wax. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 0.98 (d, 3H) 1.07 (d, 3H) 2.33-2.48 (m, 1H) 2.54-2.78 (m, 3H) 3.69 (s, 1H) 4.24 (s, 2H) 7.29-7.65 (m, 5H). LCMS: Anal. Calcd. for: C₁₃H₁₉NO₂ 221.14; Found: 222.28 (M+H)⁺.

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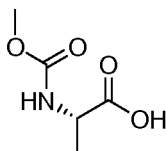
Cap-51



Na₂CO₃ (1.83g, 17.2 mmol) was added to NaOH (33 mL of 1M/H₂O, 33 mmol) solution of L-valine (3.9 g, 33.29 mmol) and the resulting solution was cooled
5 with ice-water bath. Methyl chloroformate (2.8 mL, 36.1 mmol) was added dropwise over 15 min, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 3.25 hr. The reaction mixture was washed with ether (50 mL, 3x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2, and extracted with CH₂Cl₂ (50 mL, 3x). The
10 organic phase was dried (MgSO₄) and evaporated *in vacuo* to afford Cap-51 as a white solid (6 g). ¹H NMR for the dominant rotamer (DMSO-d₆, δ=2.5 ppm, 500 MHz): 12.54 (s, 1H), 7.33 (d, *J*=8.6, 1H), 3.84 (dd, *J*=8.4, 6.0, 1H), 3.54 (s, 3H), 2.03 (m, 1H), 0.87 (m, 6H). HRMS: Anal. Calcd. for [M+H]⁺ C₇H₁₄NO₄: 176.0923; found 176.0922.

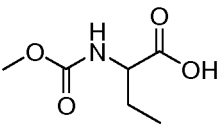
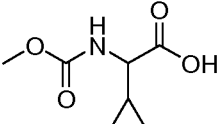
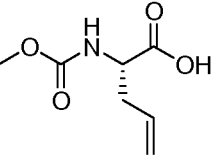
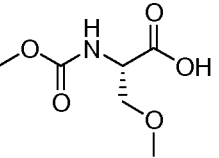
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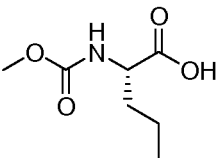
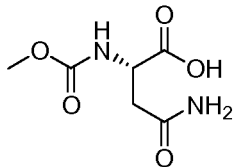
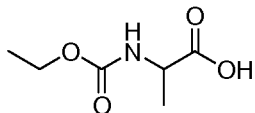
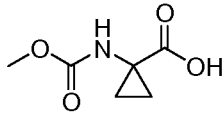
Cap-52 (Same as Cap-12)

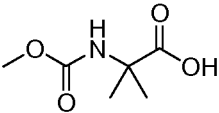
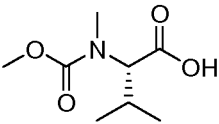
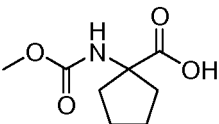
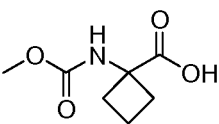


Cap-52 was synthesized from L-alanine according to the procedure described for the synthesis of Cap-51. For characterization purposes, a portion of the crude
20 material was purified by a reverse phase HPLC (H₂O/methanol/TFA) to afford Cap-52 as a colorless viscous oil. ¹H NMR (DMSO-d₆, δ=2.5 ppm, 500 MHz): 12.49 (br s, 1H), 7.43 (d, *J*=7.3, 0.88H), 7.09 (app br s, 0.12H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, *J*=7.3, 3H).

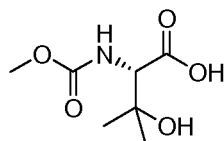
25 Cap-53 to -64 were prepared from appropriate starting materials according to the procedure described for the synthesis of Cap-51, with noted modifications if any.

Cap	Structure	Data
<i>Cap-53a:</i> (R) <i>Cap-53b:</i> (S)		¹H NMR (DMSO-d₆, δ = 2.5 ppm, 500 MHz): δ 12.51 (br s, 1H), 7.4 (d, <i>J</i> = 7.9, 0.9H), 7.06 (app s, 0.1H), 3.86-3.82 (m, 1H), 3.53 (s, 3H), 1.75-1.67 (m, 1H), 1.62-1.54 (m, 1H), 0.88 (d, <i>J</i> = 7.3, 3H). RT = 0.77 minutes (Cond. 2); LC/MS: Anal. Calcd. for [M+Na]⁺ C₆H₁₁NNaO₄: 184.06; found 184.07. HRMS Calcd. for [M+Na]⁺ C₆H₁₁NNaO₄: 184.0586; found 184.0592.
<i>Cap-54a:</i> (R) <i>Cap-54b:</i> (S)		¹H NMR (DMSO-d₆, δ = 2.5 ppm, 500 MHz): δ 12.48 (s, 1H), 7.58 (d, <i>J</i> = 7.6, 0.9H), 7.25 (app s, 0.1H), 3.52 (s, 3H), 3.36-3.33 (m, 1H), 1.10-1.01 (m, 1H), 0.54-0.49 (m, 1H), 0.46-0.40 (m, 1H), 0.39-0.35 (m, 1H), 0.31-0.21 (m, 1H). HRMS Calcd. for [M+H]⁺ C₇H₁₂NO₄: 174.0766; found 174.0771
<i>Cap-55</i>		¹H NMR (DMSO-d₆, δ = 2.5 ppm, 500 MHz): δ 12.62 (s, 1H), 7.42 (d, <i>J</i> = 8.2, 0.9H), 7.07 (app s, 0.1H), 5.80-5.72 (m, 1H), 5.10 (d, <i>J</i> = 17.1, 1H), 5.04 (d, <i>J</i> = 10.4, 1H), 4.01-3.96 (m, 1H), 3.53 (s, 3H), 2.47-2.42 (m, 1H), 2.35-2.29 (m, 1H).
<i>Cap-56</i>		¹H NMR (DMSO-d₆, δ = 2.5 ppm, 500 MHz): δ 12.75 (s, 1H), 7.38 (d, <i>J</i> = 8.3, 0.9H), 6.96 (app s, 0.1H), 4.20-4.16 (m, 1H), 3.60-3.55 (m, 2H), 3.54 (s, 3H), 3.24 (s, 3H).

Cap-57		¹ H NMR (DMSO-d ₆ , δ = 2.5 ppm, 500 MHz): δ 12.50 (s, 1H), 8.02 (d, <i>J</i> = 7.7, 0.08H), 7.40 (d, <i>J</i> = 7.9, 0.76H), 7.19 (d, <i>J</i> = 8.2, 0.07H), 7.07 (d, <i>J</i> = 6.7, 0.09H), 4.21-4.12 (m, 0.08H), 4.06-3.97 (m, 0.07H), 3.96-3.80 (m, 0.85H), 3.53 (s, 3H), 1.69-1.51 (m, 2H), 1.39-1.26 (m, 2H), 0.85 (t, <i>J</i> = 7.4, 3H). LC (Cond. 2): RT = 1.39 LC/MS: Anal. Calcd. for [M+H] ⁺ C ₇ H ₁₄ NO ₄ : 176.09; found 176.06.
Cap-58		¹ H NMR (DMSO-d ₆ , δ = 2.5 ppm, 500 MHz): δ 12.63 (br s, 1H), 7.35 (s, 1H), 7.31 (d, <i>J</i> = 8.2, 1H), 6.92 (s, 1H), 4.33-4.29 (m, 1H), 3.54 (s, 3H), 2.54 (dd, <i>J</i> = 15.5, 5.4, 1H), 2.43 (dd, <i>J</i> = 15.6, 8.0, 1H). RT = 0.16 min (Cond. 2); LC/MS: Anal. Calcd. for [M+H] ⁺ C ₆ H ₁₁ N ₂ O ₅ : 191.07; found 191.14.
Cap-59a: (R) Cap-59b: (S)		¹ H NMR (DMSO-d ₆ , δ = 2.5 ppm, 400 MHz): δ 12.49 (br s, 1H), 7.40 (d, <i>J</i> = 7.3, 0.89H), 7.04 (br s, 0.11H), 4.00-3.95 (m, 3H), 1.24 (d, <i>J</i> = 7.3, 3H), 1.15 (t, <i>J</i> = 7.2, 3H). HRMS: Anal. Calcd. for [M+H] ⁺ C ₆ H ₁₂ NO ₄ : 162.0766; found 162.0771.
Cap-60		The crude material was purified with a reverse phase HPLC (H ₂ O/MeOH/TFA) to afford a colorless viscous oil that crystallized to a white solid upon exposure to high vacuum. ¹ H NMR (DMSO-d ₆ , δ = 2.5 ppm, 400 MHz): δ 12.38 (br s, 1H), 7.74 (s, 0.82H), 7.48 (s, 0.18H), 3.54/3.51 (two s, 3H), 1.30 (m, 2H), 0.98 (m, 2H).

		HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{10}NO_4$: 160.0610; found 160.0604.
Cap-61		1H NMR (DMSO- d_6 , δ = 2.5 ppm, 400 MHz): δ 12.27 (br s, 1H), 7.40 (br s, 1H), 3.50 (s, 3H), 1.32 (s, 6H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; found 162.0765.
Cap-62		1H NMR (DMSO- d_6 , δ = 2.5 ppm, 400 MHz): δ 12.74 (br s, 1H), 4.21 (d, J = 10.3, 0.6H), 4.05 (d, J = 10.0, 0.4H), 3.62/3.60 (two singlets, 3H), 3.0 (s, 3H), 2.14-2.05 (m, 1H), 0.95 (d, J = 6.3, 3H), 0.81 (d, J = 6.6, 3H). LC/MS: Anal. Calcd. for $[M-H]^-$ $C_8H_{14}NO_4$: 188.09; found 188.05.
Cap-63		[Note: the reaction was allowed to run for longer than what was noted for the general procedure.] 1H NMR (DMSO- d_6 , δ = 2.5 ppm, 400 MHz): 12.21 (br s, 1H), 7.42 (br s, 1H), 3.50 (s, 3H), 2.02-1.85 (m, 4H), 1.66-1.58 (m, 4H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{14}NO_4$: 188.09; found 188.19.
Cap-64		[Note: the reaction was allowed to run for longer than what was noted for the general procedure.] 1H NMR (DMSO- d_6 , δ = 2.5 ppm, 400 MHz): 12.35 (br s, 1H), 7.77 (s, 0.82H), 7.56/7.52 (overlapping br s, 0.18H), 3.50 (s, 3H), 2.47-2.40 (m, 2H), 2.14-2.07 (m, 2H), 1.93-1.82 (m, 2H).

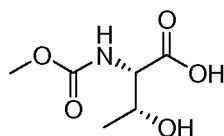
Cap-65



Methyl chloroformate (0.65 mL, 8.39 mmol) was added dropwise over 5 min to a cooled (ice-water) mixture of Na_2CO_3 (0.449 g, 4.23 mmol), NaOH (8.2 mL of 1M/ H_2O , 8.2 mmol) and (S)-2-amino-3-hydroxy-3-methylbutanoic acid (1.04 g, 7.81 mmol). The reaction mixture was stirred for 45 min, and then the cooling bath was removed and stirring was continued for an additional 3.75 hr. The reaction mixture was washed with CH_2Cl_2 , and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2. The volatile component was removed *in vacuo* and the residue was taken up in a 2:1 mixture of MeOH/ CH_2Cl_2 (15 mL) and filtered, and the filtrate was rotovaped to afford Cap-65 as a white semi-viscous foam (1.236 g). ^1H NMR (DMSO-d_6 , $\delta = 2.5$ ppm, 400 MHz): δ 6.94 (d, $J = 8.5$, 0.9 H), 6.53 (br s, 0.1H), 3.89 (d, $J = 8.8$, 1H), 2.94 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H).

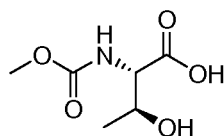
Cap-66 and -67 were prepared from appropriate commercially available starting materials by employing the procedure described for the synthesis of Cap-65.

Cap-66



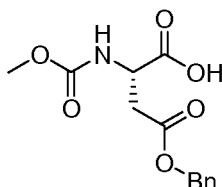
^1H NMR (DMSO-d_6 , $\delta = 2.5$ ppm, 400 MHz): δ 12.58 (br s, 1H), 7.07 (d, $J = 8.3$, 0.13H), 6.81 (d, $J = 8.8$, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, $J = 9.1$, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, $J = 6.2$, 3H). [Note: only the dominant signals of NH were noted].

Cap-67



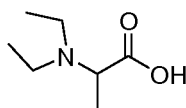
¹H NMR (DMSO-d₆, δ = 2.5 ppm, 400 MHz): 12.51 (br s, 1H), 7.25 (d, *J* = 8.4, 0.75H), 7.12 (br d, *J* = 0.4, 0.05H), 6.86 (br s, 0.08H), 3.95-3.85 (m, 2H), 3.54 (s, 3H), 1.08 (d, *J* = 6.3, 3H). [Note: only the dominant signals of NH were noted].

5

Cap-68

Methyl chloroformate (0.38 ml, 4.9 mmol) was added drop-wise to a mixture of 1N NaOH (aq) (9.0 ml, 9.0 mmol), 1M NaHCO₃ (aq) (9.0 ml, 9.0 mol), L-aspartic acid β-benzyl ester (1.0 g, 4.5 mmol) and Dioxane (9 ml). The reaction mixture was stirred at ambient conditions for 3 hr, and then washed with Ethyl acetate (50 ml, 3x). The aqueous layer was acidified with 12N HCl to a pH ~ 1-2, and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to afford *Cap-68* as a light yellow oil (1.37g; mass is above theoretical yield, and the product was used without further purification). ¹H NMR (DMSO-d₆, δ = 2.5 ppm, 500 MHz): δ 12.88 (br s, 1H), 7.55 (d, *J* = 8.5, 1H), 7.40-7.32 (m, 5H), 5.13 (d, *J* = 12.8, 1H), 5.10 (d, *J* = 12.9, 1H), 4.42-4.38 (m, 1H), 3.55 (s, 3H), 2.87 (dd, *J* = 16.2, 5.5, 1H), 2.71 (dd, *J* = 16.2, 8.3, 1H). LC (Cond. 2): RT = 1.90 min; LC/MS: Anal. Calcd. For [M+H]⁺ C₁₃H₁₆NO₆: 282.10; found 282.12.

20

Cap-69a and -69b

Cap-69a: (R)-enantiomer
Cap-69b: (S)-enantiomer

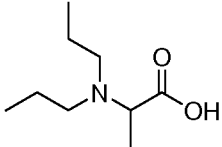
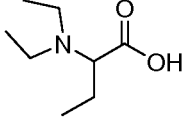
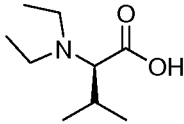
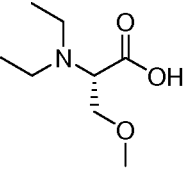
NaCNBH₃ (2.416 g, 36.5 mmol) was added in batches to a chilled (~15 °C) water (17 mL)/MeOH (10 mL) solution of alanine (1.338 g, 15.0 mmol). A few minutes later acetaldehyde (4.0 mL, 71.3 mmol) was added drop-wise over 4 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 6 hr. An additional acetaldehyde (4.0 mL) was added and the reaction was stirred for 2 hr. Concentrated HCl was added slowly to the reaction mixture until the pH

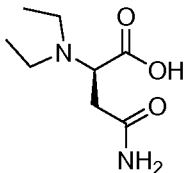
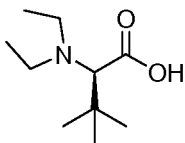
25

reached ~ 1.5, and the resulting mixture was heated for 1 hr at 40 °C. Most of the volatile component was removed *in vacuo* and the residue was purified with a Dowex® 50WX8-100 ion-exchange resin (column was washed with water, and the compound was eluted with dilute NH₄OH, prepared by mixing 18 ml of NH₄OH and 282 ml of water) to afford *Cap-69* (2.0 g) as an off-white soft hygroscopic solid. ¹H NMR (DMSO-d₆, δ = 2.5 ppm, 400 MHz): δ 3.44 (q, *J* = 7.1, 1H), 2.99-2.90 (m, 2H), 2.89-2.80 (m, 2H), 1.23 (d, *J* = 7.1, 3H), 1.13 (t, *J* = 7.3, 6H).

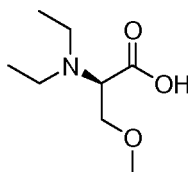
Cap-70 to *-74x* were prepared according to the procedure described for the synthesis of *Cap-69* by employing appropriate starting materials.

10

<i>Cap-70a:</i> (R) <i>Cap-70b:</i> (S)		¹ H NMR (DMSO-d ₆ , δ = 2.5 ppm, 400 MHz): δ 3.42 (q, <i>J</i> = 7.1, 1H), 2.68-2.60 (m, 4H), 1.53-1.44 (m, 4H), 1.19 (d, <i>J</i> = 7.3, 3H), 0.85 (t, <i>J</i> = 7.5, 6H). LC/MS: Anal. Calcd. for [M+H] ⁺ C ₉ H ₂₀ NO ₂ : 174.15; found 174.13.
<i>Cap-71a:</i> (R) <i>Cap-71b:</i> (S)		¹ H NMR (DMSO-d ₆ , δ = 2.5 ppm, 500 MHz): δ 3.18-3.14 (m, 1H), 2.84-2.77 (m, 2H), 2.76-2.68 (m, 2H), 1.69-1.54 (m, 2H), 1.05 (t, <i>J</i> = 7.2, 6H), 0.91 (t, <i>J</i> = 7.3, 3H). LC/MS: Anal. Calcd. for [M+H] ⁺ C ₈ H ₁₈ NO ₂ : 160.13; found 160.06.
<i>Cap-72</i>		¹ H NMR (DMSO-d ₆ , δ = 2.5 ppm, 400 MHz): δ 2.77-2.66 (m, 3H), 2.39-2.31 (m, 2H), 1.94-1.85 (m, 1H), 0.98 (t, <i>J</i> = 7.1, 6H), 0.91 (d, <i>J</i> = 6.5, 3H), 0.85 (d, <i>J</i> = 6.5, 3H). LC/MS: Anal. Calcd. for [M+H] ⁺ C ₉ H ₂₀ NO ₂ : 174.15; found 174.15.
<i>Cap-73</i>		¹ H NMR (DMSO-d ₆ , δ = 2.5 ppm, 500 MHz): δ 9.5 (br s, 1H), 3.77 (dd, <i>J</i> = 10.8, 4.1, 1H), 3.69-3.61 (m, 2H), 3.26 (s, 3H), 2.99-2.88 (m, 4H), 1.13 (t, <i>J</i> = 7.2, 6H).

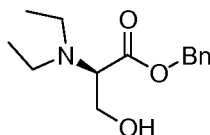
Cap-74		^1H NMR (DMSO- d_6 , δ = 2.5 ppm, 500 MHz): δ 7.54 (s, 1H), 6.89 (s, 1H), 3.81 (t, J = 6.6, k, 1H), 2.82-2.71 (m, 4H), 2.63 (dd, J = 15.6, 7.0, 1H), 2.36 (dd, J = 15.4, 6.3, 1H), 1.09 (t, J = 7.2, 6H). RT = 0.125 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_8\text{H}_{17}\text{N}_2\text{O}_3$: 189.12; found 189.13.
Cap-74x		LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{10}\text{H}_{22}\text{NO}_2$: 188.17; found 188.21

Cap-75



5

Cap-75, step a



NaBH₃CN (1.6 g, 25.5 mmol) was added to a cooled (ice/water bath) water (25 ml)/methanol (15 ml) solution of H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). Acetaldehyde (1.5 ml, 12.5 mmol) was added drop-wise over 5 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 2 hr. The reaction was carefully quenched with 12N HCl and concentrated *in vacuo*. The residue was dissolved in water and purified with a reverse phase HPLC (MeOH/H₂O/TFA) to afford the TFA salt of (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate as a colorless viscous oil (1.9g). ^1H NMR (DMSO- d_6 , δ = 2.5 ppm, 500 MHz): δ 9.73 (br s, 1H), 7.52-7.36 (m, 5H), 5.32 (d, J = 12.2, 1H), 5.27 (d, J = 12.5, 1H), 4.54-4.32 (m, 1H), 4.05-3.97 (m, 2H), 3.43-3.21 (m, 4H), 1.23 (t, J =

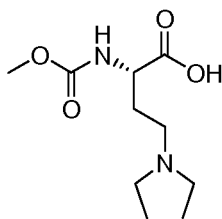
7.2, 6H). LC/MS (Cond. 2): RT = 1.38 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{22}NO_3$: 252.16; found 252.19.

Cap-75

5 NaH (0.0727 g, 1.82 mmol, 60%) was added to a cooled (ice-water) THF (3.0 mL) solution of the TFA salt (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate (0.3019 g, 0.8264 mmol) prepared above, and the mixture was stirred for 15 min. Methyl iodide (56 μ L, 0.90 mmol) was added and stirring was continued for 18 hr while allowing the bath to thaw to ambient condition. The reaction was quenched
10 with water and loaded onto a MeOH pre-conditioned MCX (6 g) cartridge, and washed with methanol followed by compound elution with 2N NH_3 /Methanol. Removal of the volatile component *in vacuo* afforded *Cap-75*, contaminated with (R)-2-(diethylamino)-3-hydroxypropanoic acid, as a yellow semi-solid (100 mg). The product was used as is without further purification.

15

Cap-76

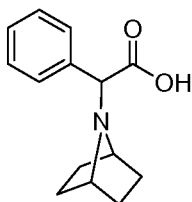


NaCNBH₃ (1.60 g, 24.2 mmol) was added in batches to a chilled (~15 °C) water/MeOH (12 mL each) solution of (S)-4-amino-2-(tert-butoxycarbonylamino)
20 butanoic acid (2.17 g, 9.94 mmol). A few minutes later acetaldehyde (2.7 mL, 48.1 mmol) was added drop-wise over 2 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 3.5 hr. An additional acetaldehyde (2.7 mL, 48.1 mmol) was added and the reaction was stirred for 20.5 hr. Most of the MeOH component was removed *in vacuo*, and the remaining mixture
25 was treated with concentrated HCl until its pH reached ~ 1.0 and then heated for 2 hr at 40 °C. The volatile component was removed *in vacuo*, and the residue was treated with 4 M HCl/dioxane (20 mL) and stirred at ambient condition for 7.5 hr. The volatile component was removed *in vacuo* and the residue was purified with Dowex® 50WX8-100 ion-exchange resin (column was washed with water and the

compound was eluted with dilute NH_4OH , prepared from 18 ml of NH_4OH and 282 ml of water) to afford intermediate (S)-2-amino-4-(diethylamino)butanoic acid as an off-white solid (1.73 g).

Methyl chloroformate (0.36 mL, 4.65 mmol) was added drop-wise over 11 min to a cooled (ice-water) mixture of Na_2CO_3 (0.243 g, 2.29 mmol), NaOH (4.6 mL of 1M/ H_2O , 4.6 mmol) and the above product (802.4 mg). The reaction mixture was stirred for 55 min, and then the cooling bath was removed and stirring was continued for an additional 5.25 hr. The reaction mixture was diluted with equal volume of water and washed with CH_2Cl_2 (30 mL, 2x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 2. The volatile component was then removed *in vacuo* and the crude material was free-based with MCX resin (6.0g; column was washed with water, and sample was eluted with 2.0 M NH_3/MeOH) to afford impure *Cap-76* as an off-white solid (704 mg). ^1H NMR (MeOH- d_4 , δ = 3.29 ppm, 400 MHz): δ 3.99 (dd, J = 7.5, 4.7, 1H), 3.62 (s, 3H), 3.25-3.06 (m, 6H), 2.18-2.09 (m, 1H), 2.04-1.96 (m, 1H), 1.28 (t, J = 7.3, 6H). LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{10}\text{H}_{21}\text{N}_2\text{O}_4$: 233.15; found 233.24.

Cap-77a and -77b

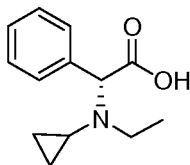


Cap-77a: enantiomer-1
Cap-77b: enantiomer-2

The synthesis of *Cap-77* was conducted according to the procedure described for *Cap-7* by using 7-azabicyclo[2.2.1]heptane for the $\text{S}_\text{N}2$ displacement step, and by effecting the enantiomeric separation of the intermediate benzyl 2-(7-azabicyclo[2.2.1]heptan-7-yl)-2-phenylacetate using the following condition: the intermediate (303.7 mg) was dissolved in ethanol, and the resulting solution was injected on a chiral HPLC column (Chiracel AD-H column, 30 x 250 mm, 5 μm) eluting with 90% CO_2 -10% EtOH at 70 mL/min, and a temperature of 35 $^\circ\text{C}$ to provide 124.5 mg of enantiomer-1 and 133.8 mg of enantiomer-2. These benzyl esters were hydrogenolysed according to the preparation of *Cap-7* to provide *Cap-77*: ^1H NMR (DMSO- d_6 , δ = 2.5 ppm, 400 MHz): δ 7.55 (m, 2H), 7.38-7.30 (m, 3H),

4.16 (s, 1H), 3.54 (app br s, 2H), 2.08-1.88 (m, 4 H), 1.57-1.46 (m, 4H). LC (Cond. 1): RT = 0.67 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}NO_2$: 232.13; found 232.18. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}NO_2$: 232.1338; found 232.1340.

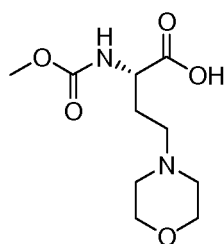
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Cap-78

NaCNBH₃ (0.5828 g, 9.27 mmol) was added to a mixture of the HCl salt of (*R*)-2-(ethylamino)-2-phenylacetic acid (an intermediate in the synthesis of *Cap-3*; 0.9923 mg, 4.60 mmol) and (1-ethoxycyclopropoxy)trimethylsilane (1.640 g, 9.40 mmol) in MeOH (10 mL), and the semi-heterogeneous mixture was heated at 50 °C with an oil bath for 20 hr. More (1-ethoxycyclopropoxy)trimethylsilane (150 mg, 0.86 mmol) and NaCNBH₃ (52 mg, 0.827 mmol) were added and the reaction mixture was heated for an additional 3.5 hr. It was then allowed to cool to ambient temperature and acidified to a ~ pH region of 2 with concentrated HCl, and the mixture was filtered and the filtrate was rotovaped. The resulting crude material was taken up in *i*-PrOH (6 mL) and heated to effect dissolution, and the non-dissolved part was filtered off and the filtrate concentrated *in vacuo*. About 1/3 of the resultant crude material was purified with a reverse phase HPLC (H₂O/MeOH/TFA) to afford the TFA salt of *Cap-78* as a colorless viscous oil (353 mg). ¹H NMR (DMSO-*d*₆, δ = 2.5 ppm, 400 MHz; after D₂O exchange): δ 7.56-7.49 (m, 5H), 5.35 (s, 1H), 3.35 (m, 1H), 3.06 (app br s, 1H), 2.66 (m, 1H), 1.26 (t, *J* = 7.3, 3H), 0.92 (m, 1H), 0.83-0.44 (m, 3H). LC (Cond. 1): RT = 0.64 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.13; found 220.21. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.1338; found 220.1343.

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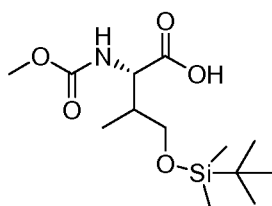
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Cap-79

Ozone was bubbled through a cooled (-78 °C) CH₂Cl₂ (5.0 mL) solution *Cap*-55 (369 mg, 2.13 mmol) for about 50 min until the reaction mixture attained a tint of
5 blue color. Me₂S (10 pipet drops) was added, and the reaction mixture was stirred for 35 min. The -78 °C bath was replaced with a -10 °C bath and stirring continued for an additional 30 min, and then the volatile component was removed *in vacuo* to afford a colorless viscous oil.

NaBH₃CN (149 mg, 2.25 mmol) was added to a MeOH (5.0 mL) solution of
10 the above crude material and morpholine (500 µL, 5.72 mmol) and the mixture was stirred at ambient condition for 4 hr. It was cooled to ice-water temperature and treated with concentrated HCl to bring its pH to ~2.0, and then stirred for 2.5 hr. The volatile component was removed *in vacuo*, and the residue was purified with a combination of MCX resin (MeOH wash; 2.0 N NH₃/MeOH elution) and a reverse
15 phase HPLC (H₂O/MeOH/TFA) to afford *Cap-79* containing unknown amount of morpholine.

In order to consume the morpholine contaminant, the above material was dissolved in CH₂Cl₂ (1.5 mL) and treated with Et₃N (0.27 mL, 1.94 mmol) followed by acetic anhydride (0.10 mL, 1.06 mmol) and stirred at ambient condition for 18 hr.
20 THF (1.0 mL) and H₂O (0.5 mL) were added and stirring continued for 1.5 hr. The volatile component was removed *in vacuo*, and the resultant residue was passed through MCX resin (MeOH wash; 2.0 N NH₃/MeOH elution) to afford impure *Cap-79* as a brown viscous oil, which was used for the next step without further purification.

Cap-80a and -80b

Cap-80a: S/S-diastereomer
Cap-80b: S/R-diastereomer

SOCl₂ (6.60 mL, 90.5 mmol) was added drop-wise over 15 min to a cooled (ice-water) mixture of (S)-3-amino-4-(benzyloxy)-4-oxobutanoic acid (10.04g, 44.98 mmol) and MeOH (300 mL), the cooling bath was removed and the reaction mixture was stirred at ambient condition for 29 hr. Most of the volatile component was removed *in vacuo* and the residue was carefully partitioned between EtOAc (150 mL) and saturated NaHCO₃ solution. The aqueous phase was extracted with EtOAc (150 mL, 2x), and the combined organic phase was dried (MgSO₄), filtered, and concentrated *in vacuo* to afford (S)-1-benzyl 4-methyl 2-aminosuccinate as a colorless oil (9.706g). ¹H NMR (DMSO-d₆, δ = 2.5 ppm, 400 MHz): δ 7.40-7.32 (m, 5H), 5.11 (s, 2H), 3.72 (app t, *J* = 6.6, 1H), 3.55 (s, 3H), 2.68 (dd, *J* = 15.9, 6.3, 1H), 2.58 (dd, *J* = 15.9, 6.8, 1H), 1.96 (s, 2H). LC (Cond. 1): RT = 0.90 min; LC/MS: Anal. Calcd. for [M+H]⁺ C₁₂H₁₆NO₄: 238.11; found 238.22.

Pb(NO₃)₂ (6.06 g, 18.3 mmol) was added over 1 min to a CH₂Cl₂ (80 mL) solution of (S)-1-benzyl 4-methyl 2-aminosuccinate (4.50 g, 19.0 mmol), 9-bromo-9-phenyl-9H-fluorene (6.44 g, 20.0 mmol) and Et₃N (3.0 mL, 21.5 mmol), and the heterogeneous mixture was stirred at ambient condition for 48 hr. The mixture was filtered and the filtrate was treated with MgSO₄ and filtered again, and the final filtrate was concentrated. The resulting crude material was submitted to a Biotage purification (350 g silica gel, CH₂Cl₂ elution) to afford (S)-1-benzyl 4-methyl 2-(9-phenyl-9H-fluoren-9-ylamino)succinate as highly viscous colorless oil (7.93 g). ¹H NMR (DMSO-d₆, δ = 2.5 ppm, 400 MHz): δ 7.82 (m, 2H), 7.39-7.13 (m, 16H), 4.71 (d, *J* = 12.4, 1H), 4.51 (d, *J* = 12.6, 1H), 3.78 (d, *J* = 9.1, NH), 3.50 (s, 3H), 2.99 (m, 1H), 2.50-2.41 (m, 2H, partially overlapped with solvent). LC (Cond. 1): RT = 2.16 min; LC/MS: Anal. Calcd. for [M+H]⁺ C₃₁H₂₈NO₄: 478.20; found 478.19.

LiHMDS (9.2 mL of 1.0 M/THF, 9.2 mmol) was added drop-wise over 10 min to a cooled (-78 °C) THF (50 mL) solution of (S)-1-benzyl 4-methyl 2-(9-phenyl-9H-fluoren-9-ylamino)succinate (3.907 g, 8.18 mmol) and stirred for ~1 hr.

MeI (0.57 mL, 9.2 mmol) was added drop-wise over 8 min to the mixture, and stirring was continued for 16.5 hr while allowing the cooling bath to thaw to room temperature. After quenching with saturated NH₄Cl solution (5 mL), most of the organic component was removed *in vacuo* and the residue was partitioned between
5 CH₂Cl₂ (100 mL) and water (40 mL). The organic layer was dried (MgSO₄), filtered, and concentrated *in vacuo*, and the resulting crude material was purified with a Biotage (350 g silica gel; 25% EtOAc/hexanes) to afford 3.65 g of a 2S/3S and 2S/3R diastereomeric mixtures of 1-benzyl 4-methyl 3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)succinate in ~1.0:0.65 ratio (¹H NMR). The stereochemistry of the
10 dominant isomer was not determined at this juncture, and the mixture was submitted to the next step without separation. Partial ¹H NMR data (DMSO-d₆, δ = 2.5 ppm, 400 MHz): major diastereomer, δ 4.39 (d, *J* = 12.3, 1H of CH₂), 3.33 (s, 3H, overlapped with H₂O signal), 3.50 (d, *J* = 10.9, NH), 1.13 (d, *J* = 7.1, 3H); minor diastereomer, δ 4.27 (d, *J* = 12.3, 1H of CH₂), 3.76 (d, *J* = 10.9, NH), 3.64 (s, 3H),
15 0.77 (d, *J* = 7.0, 3H). LC (Cond. 1): RT = 2.19 min; LC/MS: Anal. Calcd. for [M+H]⁺ C₃₂H₃₀NO₄: 492.22; found 492.15.

Diisobutylaluminum hydride (20.57 ml of 1.0 M in hexanes, 20.57 mmol) was added drop-wise over 10 min to a cooled (-78 °C) THF (120 mL) solution of (2S)-1-benzyl 4-methyl 3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)succinate (3.37
20 g, 6.86 mmol) prepared above, and stirred at -78 °C for 20 hr. The reaction mixture was removed from the cooling bath and rapidly poured into ~1M H₃PO₄/H₂O (250 mL) with stirring, and the mixture was extracted with ether (100 mL, 2x). The combined organic phase was washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. A silica gel mesh of the crude material was prepared and
25 submitted to chromatography (25% EtOAc/hexanes; gravity elution) to afford 1.1g of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate, contaminated with benzyl alcohol, as a colorless viscous oil and (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate containing the
(2S,3R) stereoisomer as an impurity. The later sample was resubmitted to the same
30 column chromatography purification conditions to afford 750 mg of purified material as a white foam. [Note: the (2S, 3S) isomer elutes before the (2S,3R) isomer under the above condition]. (2S, 3S) isomer: ¹H NMR (DMSO-d₆, δ = 2.5 ppm, 400 MHz):

7.81 (m, 2H), 7.39-7.08 (m, 16H), 4.67 (d, $J = 12.3$, 1H), 4.43 (d, $J = 12.4$, 1H), 4.21 (app t, $J = 5.2$, OH), 3.22 (d, $J = 10.1$, NH), 3.17 (m, 1H), 3.08 (m, 1H), ~2.5 (m, 1H, overlapped with the solvent signal), 1.58 (m, 1H), 0.88 (d, $J = 6.8$, 3H). LC (Cond. 1): RT = 2.00 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; found 464.22. (2S, 3R) isomer: 1H NMR (DMSO- d_6 , $\delta = 2.5$ ppm, 400 MHz): 7.81 (d, $J = 7.5$, 2H), 7.39-7.10 (m, 16H), 4.63 (d, $J = 12.1$, 1H), 4.50 (app t, $J = 4.9$, 1H), 4.32 (d, $J = 12.1$, 1H), 3.59-3.53 (m, 2H), 3.23 (m, 1H), 2.44 (dd, $J = 9.0$, 8.3, 1H), 1.70 (m, 1H), 0.57 (d, $J = 6.8$, 3H). LC (Cond. 1): RT = 1.92 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; found 464.52.

10 The relative stereochemical assignments of the DIBAL-reduction products were made based on NOE studies conducted on lactone derivatives prepared from each isomer by employing the following protocol: LiHMDS (50 μ L of 1.0 M/THF, 0.05 mmol) was added to a cooled (ice-water) THF (2.0 mL) solution of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate (62.7 mg, 15 0.135 mmol), and the reaction mixture was stirred at similar temperature for ~2 hr. The volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (30 mL), water (20 mL) and saturated aqueous NH_4Cl solution (1 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and the resulting crude material was submitted to a Biotage purification (40 g silica gel; 20 10-15% EtOAc/hexanes) to afford (3S,4S)-4-methyl-3-(9-phenyl-9H-fluoren-9-ylamino)dihydrofuran-2(3H)-one as a colorless film of solid (28.1 mg). (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate was elaborated similarly to (3S,4R)-4-methyl-3-(9-phenyl-9H-fluoren-9-ylamino)dihydrofuran-2(3H)-one. (3S,4S)-lactone isomer: 1H NMR (DMSO- d_6 , $\delta =$ 25 2.5 ppm, 400 MHz), 7.83 (d, $J = 7.5$, 2H), 7.46-7.17 (m, 11H), 4.14 (app t, $J = 8.3$, 1H), 3.60 (d, $J = 5.8$, NH), 3.45 (app t, $J = 9.2$, 1H), ~2.47 (m, 1H, partially overlapped with solvent signal), 2.16 (m, 1H), 0.27 (d, $J = 6.6$, 3H). LC (Cond. 1): RT = 1.98 min; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; found 378.42. (3S,4R)-lactone isomer: 1H NMR (DMSO- d_6 , $\delta = 2.5$ ppm, 400 MHz), 7.89 (d, $J = 7.6$, 1H), 7.85 (d, $J = 7.3$, 1H), 7.46-7.20 (m, 11H), 3.95 (dd, $J = 9.1$, 4.8, 1H), 3.76 (d, $J = 8.8$, 1H), 2.96 (d, $J = 3.0$, NH), 2.92 (dd, $J = 6.8$, 3, NCH), 1.55 (m,

1H), 0.97 (d, $J = 7.0$, 3H). LC (Cond. 1): RT = 2.03 min; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; found 378.49.

TBDMS-Cl (48 mg, 0.312 mmol) followed by imidazole (28.8 mg, 0.423 mmol) were added to a CH_2Cl_2 (3 ml) solution of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate (119.5 mg, 0.258 mmol), and the mixture was stirred at ambient condition for 14.25 hr. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with water (15 mL), and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant crude material was purified with a Biotage (40 g silica gel; 5% EtOAc/hexanes) to afford (2S,3S)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate, contaminated with TBDMS based impurities, as a colorless viscous oil (124.4 mg). (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate was elaborated similarly to (2S,3R)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate.

(2S,3S)-silyl ether isomer: 1H NMR ($DMSO-d_6$, $\delta = 2.5$ ppm, 400 MHz), 7.82 (d, $J = 4.1$, 1H), 7.80 (d, $J = 4.0$, 1H), 7.38-7.07 (m, 16 H), 4.70 (d, $J = 12.4$, 1H), 4.42 (d, $J = 12.3$, 1H), 3.28-3.19 (m, 3H), 2.56 (dd, $J = 10.1$, 5.5, 1H), 1.61 (m, 1H), 0.90 (d, $J = 6.8$, 3H), 0.70 (s, 9H), -0.13 (s, 3H), -0.16 (s, 3H). LC (Cond. 1, where the run time was extended to 4 min): RT = 3.26 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{44}NO_3Si$: 578.31; found 578.40. (2S,3R)-silyl ether isomer: 1H NMR ($DMSO-d_6$, $\delta = 2.5$ ppm, 400 MHz), 7.82 (d, $J = 3.0$, 1H), 7.80 (d, $J = 3.1$, 1H), 7.39-7.10 (m, 16H), 4.66 (d, $J = 12.4$, 1H), 4.39 (d, $J = 12.4$, 1H), 3.61 (dd, $J = 9.9$, 5.6, 1H), 3.45 (d, $J = 9.5$, 1H), 3.41 (dd, $J = 10$, 6.2, 1H), 2.55 (dd, $J = 9.5$, 7.3, 1H), 1.74 (m, 1H), 0.77 (s, 9H), 0.61 (d, $J = 7.1$, 3H), -0.06 (s, 3H), -0.08 (s, 3H).

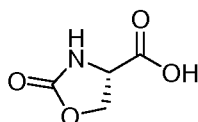
A balloon of hydrogen was attached to a mixture of (2S,3S)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate (836 mg, 1.447 mmol) and 10% Pd/C (213 mg) in EtOAc (16 mL) and the mixture was stirred at room temperature for ~ 21 hr, where the balloon was recharged with H_2 as necessary. The reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of diatomaceous earth (Celite-545[®]), and the pad was washed with EtOAc (200 mL), EtOAc/MeOH (1:1 mixture, 200 mL) and MeOH (750 mL). The combined organic phase was concentrated, and a silica gel mesh was prepared from the resulting crude

material and submitted to a flash chromatography (8:2:1 mixture of EtOAc/i-PrOH/H₂O) to afford (2S,3S)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid as a white fluffy solid (325 mg). (2S,3R)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate was similarly elaborated to (2S,3R)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid. (2S,3S)-amino acid isomer: ¹H NMR (Methanol-d₄, δ = 3.29 ppm, 400 MHz), 3.76 (dd, *J* = 10.5, 5.2, 1H), 3.73 (d, *J* = 3.0, 1H), 3.67 (dd, *J* = 10.5, 7.0, 1H), 2.37 (m, 1H), 0.97 (d, *J* = 7.0, 3H), 0.92 (s, 9H), 0.10 (s, 6H). LC/MS: Anal. Calcd. for [M+H]⁺ C₁₁H₂₆NO₃Si: 248.17; found 248.44. (2S,3R)-amino acid isomer: ¹H NMR (Methanol-d₄, δ = 3.29 ppm, 400 MHz), 3.76-3.75 (m, 2H), 3.60 (d, *J* = 4.1, 1H), 2.16 (m, 1H), 1.06 (d, *J* = 7.3, 3H), 0.91 (s, 9H), 0.09 (s, 6H). Anal. Calcd. for [M+H]⁺ C₁₁H₂₆NO₃Si: 248.17; found 248.44.

Water (1 mL) and NaOH (0.18 mL of 1.0 M/H₂O, 0.18 mmol) were added to a mixture of (2S,3S)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid (41.9 mg, 0.169 mmol) and Na₂CO₃ (11.9 mg, 0.112 mmol), and sonicated for about 1 min to effect dissolution of reactants. The mixture was then cooled with an ice-water bath, methyl chloroformate (0.02 mL, 0.259 mmol) was added over 30 s, and vigorous stirring was continued at similar temperature for 40 min and then at ambient temperature for 2.7 hr. The reaction mixture was diluted with water (5 mL), cooled with ice-water bath and treated drop-wise with 1.0 N HCl aqueous solution (~0.23 mL). The mixture was further diluted with water (10 mL) and extracted with CH₂Cl₂ (15 mL, 2x). The combined organic phase was dried (MgSO₄), filtered, and concentrated *in vacuo* to afford *Cap*-80a as an off-white solid. (2S,3R)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid was similarly elaborated to *Cap*-80b. *Cap*-80a: ¹H NMR (DMSO-d₆, δ = 2.5 ppm, 400 MHz), 12.57 (br s, 1H), 7.64 (d, *J* = 8.3, 0.3H), 7.19 (d, *J* = 8.8, 0.7H), 4.44 (dd, *J* = 8.1, 4.6, 0.3H), 4.23 (dd, *J* = 8.7, 4.4, 0.7H), 3.56/3.53 (two singlets, 3H), 3.48-3.40 (m, 2H), 2.22-2.10 (m, 1H), 0.85 (s, 9H), ~0.84 (d, 0.9H, overlapped with t-Bu signal), 0.79 (d, *J* = 7, 2.1H), 0.02/0.01/0.00 (three overlapping singlets, 6H). LC/MS: Anal. Calcd. for [M+Na]⁺ C₁₃H₂₇NNaO₅Si: 328.16; found 328.46. *Cap*-80b: ¹H NMR (CDCl₃, δ = 7.24 ppm, 400 MHz), 6.00 (br d, *J* = 6.8, 1H), 4.36 (dd, *J* = 7.1, 3.1, 1H), 3.87 (dd, *J* = 10.5, 3.0, 1H), 3.67 (s, 3H), 3.58 (dd, *J* = 10.6, 4.8, 1H), 2.35 (m, 1H), 1.03 (d, *J* = 7.1,

3H), 0.90 (s, 9H), 0.08 (s, 6H). LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; found 328.53. The crude products were utilized without further purification.

Cap-81

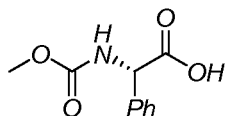


5

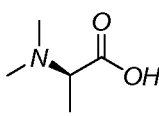
Prepared according to the protocol described by Falb et al. *Synthetic Communications* 1993, 23, 2839.

Cap-82 to Cap-85

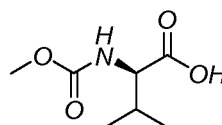
10 *Cap-82 to Cap-85* were synthesized from appropriate starting materials according to the procedure described for *Cap-51* or *Cap-13*. The samples exhibited similar spectral profiles as that of their enantiomers (i.e., *Cap-4*, *Cap-13*, *Cap-51* and *Cap-52*, respectively).



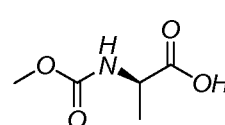
Cap-82



Cap-83



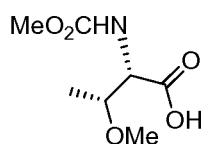
Cap-84



Cap-85

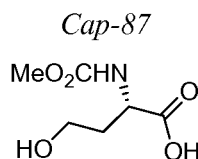
15

Cap-86



To a mixture of O-methyl-L-threonine (3.0 g, 22.55 mmol), NaOH (0.902 g, 22.55 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (1.74 mL, 22.55 mmol) dropwise at $0^\circ C$. The mixture was allowed to stir for 12 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2x250 mL) and 10% MeOH in CH_2Cl_2 (250 mL) and the combined organic phases were concentrated under *in vacuo* to afford a colorless oil (4.18 g, 97%) which was of sufficient purity for use in subsequent steps. 1H NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 1H), 3.92-3.97 (m, 1H), 3.66 (s, 3H), 1.17 (d, $J = 7.7$ Hz, 3H). LCMS: Anal. Calcd. for $C_7H_{13}NO_5$: 191; found: 190 (M-H) $^-$.

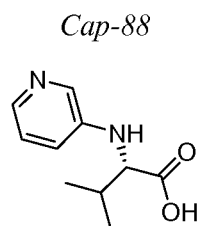
25



To a mixture of L-homoserine (2.0 g, 9.79 mmol), Na₂CO₃ (2.08 g, 19.59 mmol) in H₂O (15 mL) was added ClCO₂Me (0.76 mL, 9.79 mmol) dropwise at 0°C.

5 The mixture was allowed to stir for 48 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2X250 mL) and the combined organic phases were concentrated *in vacuo* to afford a colorless solid (0.719 g, 28%) which was of sufficient purity for use in subsequent steps. ¹HNMR (400 MHz, CDCl₃) δ 4.23 (dd, *J* = 4.5, 9.1 Hz, 1H), 3.66 (s, 3H), 3.43-3.49 (m, 2H), 2.08 – 2.14 (m, 1H),

10 1.82 – 1.89 (m, 1H). LCMS: Anal. Calcd. for C₇H₁₃NO₅: 191; found: 192 (M+H)⁺.

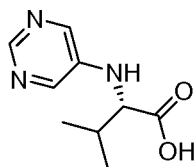


A mixture of L-valine (1.0 g, 8.54 mmol), 3-bromopyridine (1.8 mL, 18.7 mmol), K₂CO₃ (2.45 g, 17.7 mmol) and CuI (169 mg, 0.887 mmol) in DMSO (10 mL) was heated at 100°C for 12h. The reaction mixture was cooled to rt, poured into H₂O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of H₂O and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 20g of cation

20 exchange resin (Strata) was added. The slurry was allowed to stand for 20 min and loaded onto a pad of cation exchange resin (Strata) (ca. 25g). The pad was washed with H₂O (200 mL), MeOH (200 mL), and then NH₃ (3M in MeOH, 2X200 mL). The appropriate fractions was concentrated *in vacuo* and the residue (ca. 1.1 g) was dissolved in H₂O, frozen and lyophilized. The title compound was obtained as a

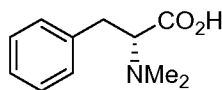
25 foam (1.02 g, 62%). ¹HNMR (400 MHz, DMSO-d₆) δ 8.00 (s, br, 1H), 7.68 – 7.71 (m, 1H), 7.01 (s, br, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 5.75 (s, br, 1H), 3.54 (s, 1H), 2.04 – 2.06 (m, 1H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H). LCMS: Anal. Calcd. for C₁₀H₁₄N₂O₂: 194; found: 195 (M+H)⁺.

Cap-89



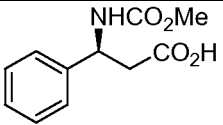
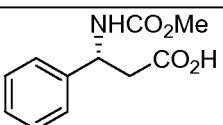
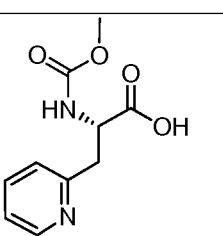
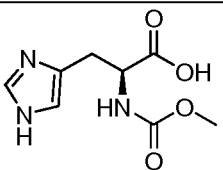
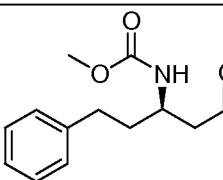
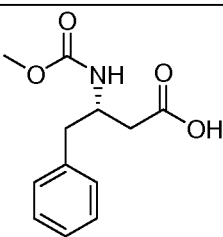
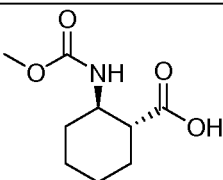
A mixture of L-valine (1.0 g, 8.54 mmol), 5-bromopyrimidine (4.03 g, 17.0 mmol), K_2CO_3 (2.40 g, 17.4 mmol) and CuI (179 mg, 0.94 mmol) in DMSO (10 mL) was heated at 100°C for 12h. The reaction mixture was cooled to RT, poured into H_2O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of H_2O and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 20g of cation exchange resin (Strata) was added. The slurry was allowed to stand for 20 min and loaded onto a pad of cation exchange resin (Strata) (ca. 25g). The pad was washed with H_2O (200 mL), MeOH (200 mL), and then NH_3 (3M in MeOH, 2x200 mL). The appropriate fractions was concentrated *in vacuo* and the residue (ca. 1.1 g) was dissolved in H_2O , frozen and lyophilized. The title compound was obtained as a foam (1.02 g, 62%). 1H NMR (400 MHz, CD_3OD) showed the mixture to contain valine and the purity could not be estimated. The material was used as is in subsequent reactions. LCMS: Anal. Calcd. for $C_9H_{13}N_3O_2$: 195; found: 196 (M+H)⁺.

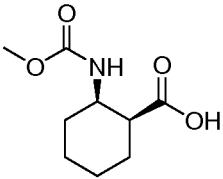
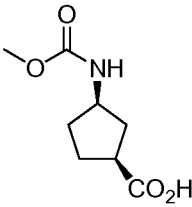
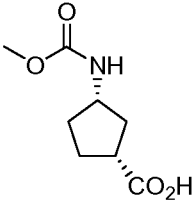
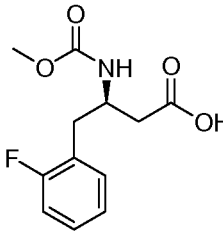
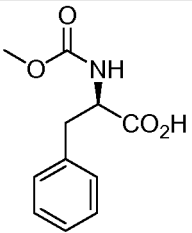
Cap-90

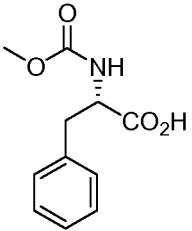
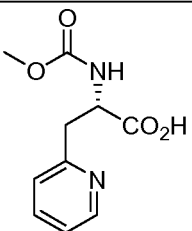
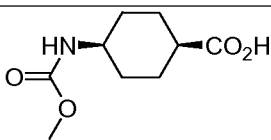
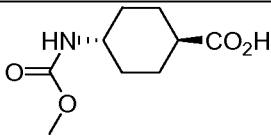
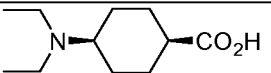


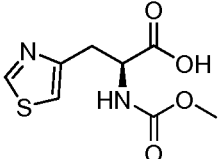
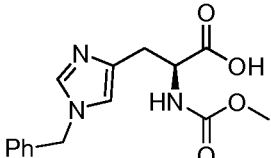
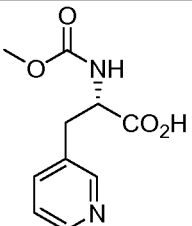
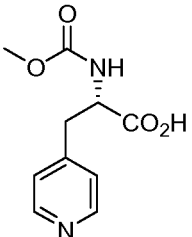
Cap-90 was prepared according to the method described for the preparation of Cap-1. The crude material was used as is in subsequent steps. LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 192 (M-H)⁻.

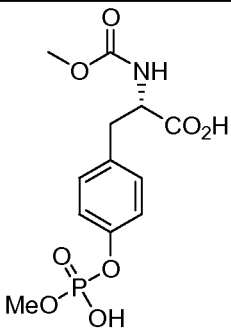
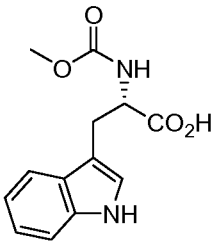
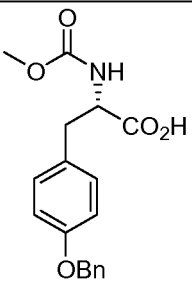
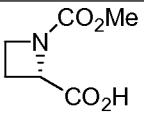
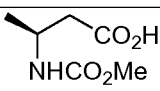
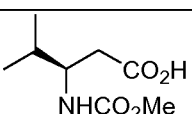
The following caps were prepared according to the method used for preparation of cap 51 unless noted otherwise:

Cap	Structure	LCMS
Cap-91		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 (M-H) ⁻ .
Cap-92		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 (M-H) ⁻ .
Cap-93		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 (M+H) ⁺ .
Cap-94		LCMS: Anal. Calcd. for $C_8H_{11}N_3O_4$: 213; found: 214 (M+H) ⁺ .
Cap-95		LCMS: Anal. Calcd. for $C_{13}H_{17}NO_4$: 251; found: 250 (M-H) ⁻ .
Cap-96		LCMS: Anal. Calcd. for $C_{12}H_{15}NO_4$: 237; found: 236 (M-H) ⁻ .
Cap-97		LCMS: Anal. Calcd. for $C_9H_{15}NO_4$: 201; found: 200 (M-H) ⁻ .

<i>Cap-98</i>		LCMS: Anal. Calcd. for $C_9H_{15}NO_4$: 201; found: 202 (M+H) ⁺ .
<i>Cap-99</i>		¹ HNMR (400 MHz, CD ₃ OD) δ 3.88 – 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 – 1.94 (m, 3H), 1.45 – 1.71 (m, 2H).
<i>Cap-99a</i>		¹ HNMR (400 MHz, CD ₃ OD) δ 3.88 – 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 – 1.94 (m, 3H), 1.45 – 1.71 (m, 2H).
<i>Cap-100</i>		LCMS: Anal. Calcd. for $C_{12}H_{14}NO_4F$: 255; found: 256 (M+H) ⁺ .
<i>Cap-101</i>		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 (M-H) ⁻ .

Cap-102		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 ($M-H$) ⁻
Cap-103		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 ($M+H$) ⁺ .
Cap-104		¹ HNMR (400 MHz, CD ₃ OD) δ 3.60 (s, 3H), 3.50 – 3.53 (m, 1H), 2.66 – 2.69 and 2.44 – 2.49 (m, 1H), 1.91 – 2.01 (m, 2H), 1.62 – 1.74 (m, 4H), 1.51 – 1.62 (m, 2H).
Cap-105		¹ HNMR (400 MHz, CD ₃ OD) δ 3.60 (s, 3H), 3.33 – 3.35 (m, 1H, partially obscured by solvent), 2.37 – 2.41 and 2.16 – 2.23 (m, 1H), 1.94 – 2.01 (m, 4H), 1.43 – 1.53 (m, 2H), 1.17 – 1.29 (m, 2H).
Cap-106	 Prepared from cis-4-aminocyclohexane carboxylic acid and	¹ HNMR (400 MHz, CD ₃ OD) δ 3.16 (q, J = 7.3 Hz, 4H), 2.38 – 2.41 (m, 1H), 2.28 – 2.31 (m, 2H), 1.79 – 1.89 (m, 2H), 1.74 (app, ddd J = 3.5,

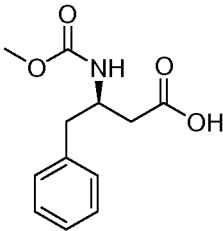
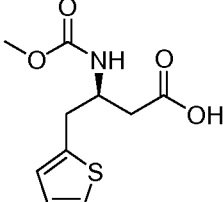
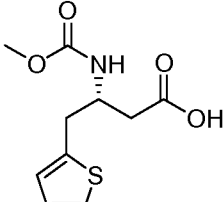
	acetaldehyde by employing a similar procedure described for the synthesis of Cap-2. The crude HCl salt was passed through MCX (MeOH/H₂O/CH₂Cl₂ wash; 2 N NH₃/MeOH elution) to afford an oil, which was dissolved in CH₃CN/H₂O and lyophilized to afford a tan solid.	12.5, 15.9 Hz, 2H), 1.46 (app dt $J = 4.0, 12.9$ Hz, 2H), 1.26 (t, $J = 7.3$ Hz, 6H)
Cap-107		LCMS: Anal. Calcd. for C₈H₁₀N₂O₄S: 230; found: 231 (M+H)⁺.
Cap-108		LCMS: Anal. Calcd. for C₁₅H₁₇N₃O₄: 303; found: 304 (M+H)⁺.
Cap-109		LCMS: Anal. Calcd. for C₁₀H₁₂N₂O₄: 224; found: 225 (M+H)⁺.
Cap-110		LCMS: Anal. Calcd. for C₁₀H₁₂N₂O₄: 224; found: 225 (M+H)⁺.

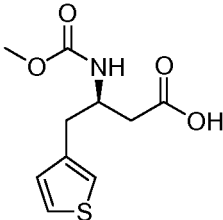
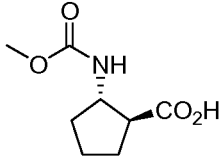
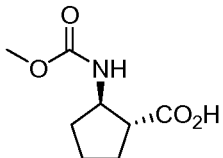
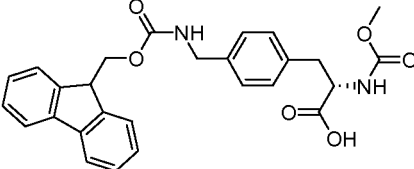
Cap-111		LCMS: Anal. Calcd. for $C_{12}H_{16}NO_8P$: 333; found: 334 (M+H) ⁺ .
Cap-112		LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_4$: 262; found: 263 (M+H) ⁺ .
Cap-113		LCMS: Anal. Calcd. for $C_{18}H_{19}NO_5$: 329; found: 330 (M+H) ⁺ .
Cap-114		¹ HNMR (400 MHz, CDCl ₃) δ 4.82 – 4.84 (m, 1H), 4.00 – 4.05 (m, 2H), 3.77 (s, 3H), 2.56 (s, br, 2H)
Cap-115		¹ HNMR (400 MHz, CDCl ₃) δ 5.13 (s, br, 1H), 4.13 (s, br, 1H), 3.69 (s, 3H), 2.61 (d, <i>J</i> = 5.0 Hz, 2H), 1.28 (d, <i>J</i> = 9.1 Hz, 3H).
Cap-116		¹ HNMR (400 MHz, CDCl ₃) δ 5.10 (d, <i>J</i> = 8.6 Hz, 1H), 3.74 – 3.83 (m,

		1H), 3.69 (s, 3H), 2.54 – 2.61 (m, 2H), 1.88 (sept, J = 7.0 Hz, 1H), 0.95 (d, J = 7.0 Hz, 6H).
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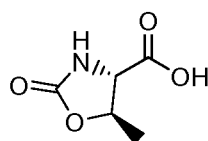
Cap-117 to Cap-123

For the preparation of *Cap-117* to *Cap-123* the Boc amino acids were obtained from commercially sources and were deprotected by treatment with 25% TFA in CH₂Cl₂. After complete reaction as judged by LCMS the solvents were removed *in vacuo* and the corresponding TFA salt of the amino acid was carbamoylated with methyl chloroformate according to the procedure described for *Cap-51*.

Cap	Structure	LCMS
<i>Cap-117</i>		LCMS: Anal. Calcd. for C ₁₂ H ₁₅ NO ₄ : 237; found: 238 (M+H) ⁺ .
<i>Cap-118</i>		LCMS: Anal. Calcd. for C ₁₀ H ₁₃ NO ₄ S: 243; found: 244 (M+H) ⁺ .
<i>Cap-119</i>		LCMS: Anal. Calcd. for C ₁₀ H ₁₃ NO ₄ S: 243; found: 244 (M+H) ⁺ .

Cap-120		LCMS: Anal. Calcd. for C ₁₀ H ₁₃ NO ₄ S: 243; found: 244 (M+H) ⁺ .
Cap-121		¹ HNMR (400 MHz, CDCl ₃) δ 4.06 – 4.16 (m, 1H), 3.63 (s, 3H), 3.43 (s, 1H), 2.82 and 2.66 (s, br, 1H), 1.86 – 2.10 (m, 3H), 1.64 – 1.76 (m, 2H), 1.44 – 1.53 (m, 1H).
Cap-122		¹ HNMR profile is similar to that of its enantiomer, Cap-121.
Cap-123		LCMS: Anal. Calcd. for C ₂₇ H ₂₆ N ₂ O ₆ : 474; found: 475 (M+H) ⁺ .

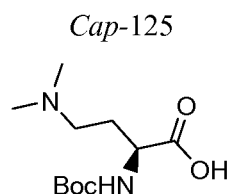
Cap-124



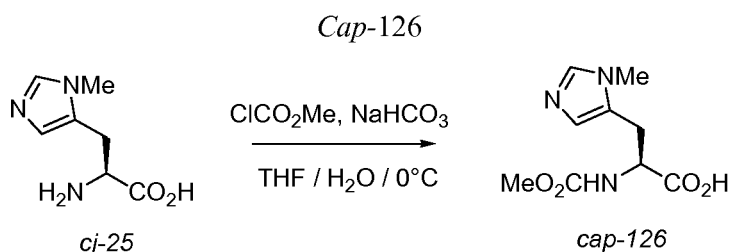
The hydrochloride salt of L-threonine tert-butyl ester was carbamoylated according to the procedure for Cap-51. The crude reaction mixture was acidified with 1N HCl to pH~1 and the mixture was extracted with EtOAc (2X50 mL). The combined organic phases were concentrated *in vacuo* to give a colorless oil which solidified on standing. The aqueous layer was concentrated *in vacuo* and the resulting mixture of product and inorganic salts was triturated with EtOAc-CH₂Cl₂-MeOH (1:1:0.1) and then the organic phase concentrated *in vacuo* to give a colorless

oil which was shown by LCMS to be the desired product. Both crops were combined to give 0.52 g of a solid. ^1H NMR (400 MHz, CD_3OD) δ 4.60 (m, 1H), 4.04 (d, J = 5.0 Hz, 1H), 1.49 (d, J = 6.3 Hz, 3H). LCMS: Anal. Calcd. for $\text{C}_5\text{H}_7\text{NO}_4$: 145; found: 146 ($\text{M}+\text{H}$) $^+$.

5



To a suspension of $\text{Pd}(\text{OH})_2$ (20%, 100 mg), aqueous formaldehyde (37% wt, 4 ml), acetic acid, (0.5 mL) in methanol (15 mL) was added (S)-4-amino-2-(tert-butoxycarbonylamino)butanoic acid (1 g, 4.48 mmol). The reaction was purged
 10 several times with hydrogen and was stirred overnight with an hydrogen balloon room temp. The reaction mixture was filtered through a pad of diatomaceous earth (Celite[®]), and the volatile component was removed in vacuo. The resulting crude material was used as is for the next step. LC/MS: Anal. Calcd. for $\text{C}_{11}\text{H}_{22}\text{N}_2\text{O}_4$:
 15 246; found: 247 ($\text{M}+\text{H}$) $^+$.



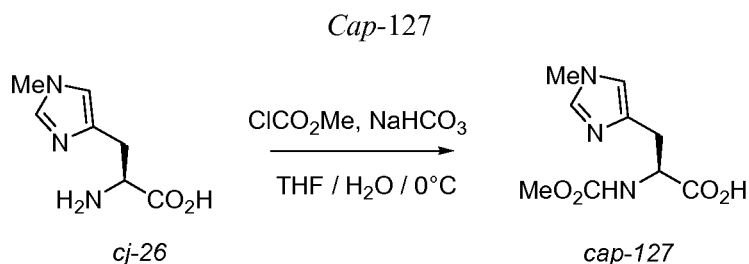
This procedure is a modification of that used to prepare *Cap-51*. To a
 20 suspension of 3-methyl-L-histidine (0.80 g, 4.70 mmol) in THF (10mL) and H_2O (10 mL) at 0°C was added NaHCO_3 (0.88 g, 10.5 mmol). The resulting mixture was treated with ClCO_2Me (0.40 mL, 5.20 mmol) and the mixture allowed to stir at 0°C . After stirring for ca. 2h LCMS showed no starting material remaining. The reaction was acidified to pH 2 with 6 N HCl.

25 The solvents were removed *in vacuo* and the residue was suspended in 20 mL of 20% MeOH in CH_2Cl_2 . The mixture was filtered and concentrated to give a light yellow foam (1.21 g,). LCMS and ^1H NMR showed the material to be a 9:1 mixture

of the methyl ester and the desired product. This material was taken up in THF (10mL) and H₂O (10mL), cooled to 0°C and LiOH (249.1 mg, 10.4 mmol) was added. After stirring ca. 1h LCMS showed no ester remaining. Therefore the mixture was acidified with 6N HCl and the solvents removed *in vacuo*. LCMS and

5 ¹H NMR confirm the absence of the ester. The title compound was obtained as its HCl salt contaminated with inorganic salts (1.91 g, >100%). The compound was used as is in subsequent steps without further purification. ¹HNMR (400 MHz, CD₃OD) δ 8.84, (s, 1H), 7.35 (s, 1H), 4.52 (dd, *J* = 5.0, 9.1 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (dd, *J* = 4.5, 15.6 Hz, 1H, partially obscured by solvent), 3.12 (dd,

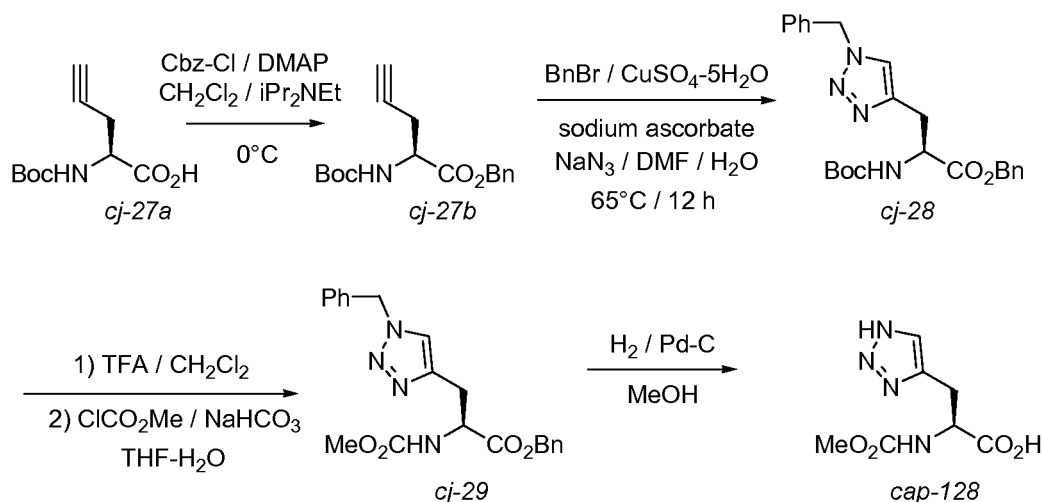
10 *J* = 9.0, 15.6 Hz, 1H).LCMS: Anal. Calcd. for C₉H₁₃N₃O₄: 227.09; found: 228.09 (M+H)⁺.



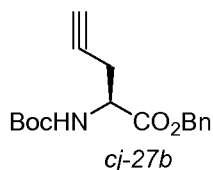
15 *Cap-127* was prepared according to the method for *Cap-126* above starting from (S)-2-amino-3-(1-methyl-1H-imidazol-4-yl)propanoic acid (1.11 g, 6.56 mmol), NaHCO₃ (1.21 g, 14.4 mmol) and ClCO₂Me (0.56 mL, 7.28 mmol). The title compound was obtained as its HCl salt (1.79 g, >100%) contaminated with inorganic salts. LCMS and ¹H NMR showed the presence of ca. 5% of the methyl ester. The

20 crude mixture was used as is without further purification. ¹HNMR (400 MHz, CD₃OD) δ 8.90 (s, 1H), 7.35 (s, 1H), 4.48 (dd, *J* = 5.0, 8.6 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (m, 1H), 3.08 (m, 1H); LCMS: Anal. Calcd. for C₉H₁₃N₃O₄: 227.09; found: 228 (M+H)⁺.

Preparation of Cap-128

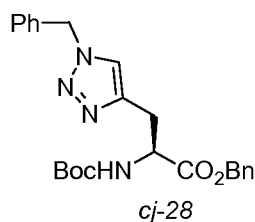


Step 1. Preparation of (S)-benzyl 2-(tert-butoxycarbonylamino)pent-4-ynoate (*cj-27b*).



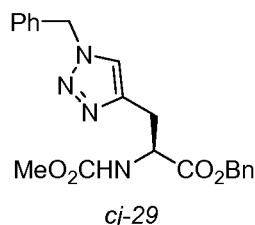
To a solution of *cj-27a* (1.01 g, 4.74 mmol), DMAP (58 mg, 0.475 mmol) and iPr₂NEt (1.7 mL, 9.8 mmol) in CH₂Cl₂ (100 mL) at 0°C was added Cbz-Cl (0.68 mL, 4.83 mmol). The solution was allowed to stir for 4 h at 0°C, washed (1N KHSO₄, brine), dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (TLC 6:1 hex:EtOAc) to give the title compound (1.30 g, 91%) as a colorless oil. ¹HNMR (400 MHz, CDCl₃) δ 7.35 (s, 5H), 5.35 (d, br, *J* = 8.1 Hz, 1H), 5.23 (d, *J* = 12.2 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 4.48 – 4.53 (m, 1H), 2.68 – 2.81 (m, 2H), 2.00 (t, *J* = 2.5 Hz, 1H), 1.44 (s, 9H). LCMS: Anal. Calcd. for C₁₇H₂₁NO₄: 303; found: 304 (M+H)⁺.

Step 2. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(tert-butoxycarbonylamino)propanoate (*cj-28*).



To a mixture of (S)-benzyl 2-(tert-butoxycarbonylamino)pent-4-ynoate (0.50 g, 1.65 mmol), sodium ascorbate (0.036 g, 0.18 mmol), CuSO₄·5H₂O (0.022 g, 0.09 mmol) and NaN₃ (0.13 g, 2.1 mmol) in DMF-H₂O (5 mL, 4:1) at rt was added BnBr (0.24 mL, 2.02 mmol) and the mixture was warmed to 65°C. After 5h LCMS indicated low conversion. A further portion of NaN₃ (100 mg) was added and heating was continued for 12h. The reaction was poured into EtOAc and H₂O and shaken. The layers were separated and the aqueous layer extracted 3x with EtOAc and the combined organic phases washed (H₂O x3, brine), dried (Na₂SO₄), filtered, and concentrated. The residue was purified by flash (Biotage, 40+M 0-5% MeOH in CH₂Cl₂; TLC 3% MeOH in CH₂Cl₂) to afford a light yellow oil which solidified on standing (748.3 mg, 104%). The NMR was consistent with the desired product but suggests the presence of DMF. The material was used as is without further purification. ¹HNMR (400 MHz, DMSO-d₆) δ 7.84 (s, 1H), 7.27 – 7.32 (m, 10H), 5.54 (s, 2H), 5.07 (s, 2H), 4.25 (m, 1H), 3.16 (dd, *J* = 1.0, 5.3 Hz, 1H), 3.06 (dd, *J* = 5.3, 14.7 Hz), 2.96 (dd, *J* = 9.1, 14.7 Hz, 1H), 1.31 (s, 9H). LCMS: Anal. Calcd. for C₂₄H₂₈N₄O₄: 436; found: 437 (M+H)⁺.

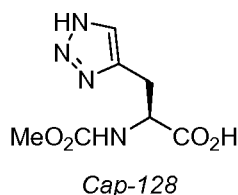
Step 3. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (cj-29).



A solution of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(tert-butoxycarbonylamino)propanoate (0.52 g, 1.15 mmol) in CH₂Cl₂ was added TFA (4 mL). The mixture was allowed to stir at room temperature for 2h. The mixture was concentrated *in vacuo* to give a colorless oil which solidified on standing. This

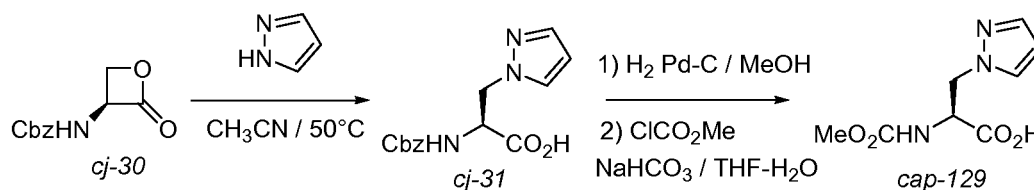
material was dissolved in THF-H₂O and cooled to 0°C. Solid NaHCO₃ (0.25 g, 3.00 mmol) was added followed by ClCO₂Me (0.25 mL, 3.25 mmol). After stirring for 1.5h the mixture was acidified to pH~2 with 6N HCl and then poured into H₂O-EtOAc. The layers were separated and the aq phase extracted 2x with EtOAc. The
5 combined org layers were washed (H₂O, brine), dried (Na₂SO₄), filtered, and concentrated *in vacuo* to give a colorless oil (505.8 mg, 111%, NMR suggested the presence of an unidentified impurity) which solidified while standing on the pump. The material was used as is without further purification. ¹HNMR (400 MHz, DMSO-d₆) δ 7.87 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.27 – 7.32 (m, 10H), 5.54 (s, 2H), 5.10
10 (d, *J* = 12.7 Hz, 1H), 5.06 (d, *J* = 12.7 Hz, 1H), 4.32 – 4.37 (m, 1H), 3.49 (s, 3H), 3.09 (dd, *J* = 5.6, 14.7 Hz, 1H), 2.98 (dd, *J* = 9.6, 14.7 Hz, 1H). LCMS: Anal. Calcd. for C₂₁H₂₂N₄O₄: 394; found: 395 (M+H)⁺.

Step 4. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid (*Cap-128*).
15

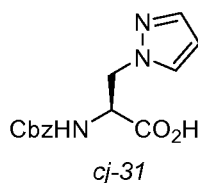


(S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (502 mg, 1.11 mmol) was hydrogenated in the presence of Pd-C (82 mg) in MeOH (5 mL) at atmospheric pressure for 12h. The
20 mixture was filtered through diatomaceous earth (Celite[®]) and concentrated *in vacuo*. (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid was obtained as a colorless gum (266 mg, 111%) which was contaminated with ca. 10% of the methyl ester. The material was used as is without further purification. ¹HNMR (400 MHz, DMSO-d₆) δ 12.78 (s, br, 1H), 7.59 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 4.19 –
25 4.24 (m, 1H), 3.49 (s, 3H), 3.12 (dd, *J* = 4.8 Hz, 14.9 Hz, 1H), 2.96 (dd, *J* = 9.9, 15.0 Hz, 1H). LCMS: Anal. Calcd. for C₇H₁₀N₄O₄: 214; found: 215 (M+H)⁺.

Preparation of Cap-129

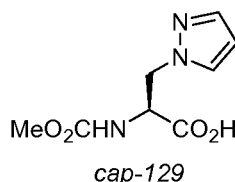


Step 1. Preparation of (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (*cj-31*).



A suspension of (S)-benzyl 2-oxooxetan-3-ylcarbamate (0.67 g, 3.03 mmol), and pyrazole (0.22 g, 3.29 mmol) in CH₃CN (12 mL) was heated at 50 °C for 24h. The mixture was cooled to rt overnight and the solid filtered to afford (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (330.1 mg). The filtrate was concentrated *in vacuo* and then triturated with a small amount of CH₃CN (ca. 4 mL) to afford a second crop (43.5 mg). Total yield 370.4 mg (44%). m.p. 165.5 – 168°C. lit m.p. 168.5 – 169.5 [Vederas et al. *J. Am. Chem. Soc.* 1985, 107, 7105]. ¹HNMR (400 MHz, CD₃OD) δ 7.51 (d, *J* = 2.0, 1H), 7.48 (s, *J* = 1.5 Hz, 1H), 7.24 – 7.34 (m, 5H), 6.23 m, 1H), 5.05 (d, 12.7 H, 1H), 5.03 (d, *J* = 12.7 Hz, 1H), 4.59 – 4.66 (m, 2H), 4.42 – 4.49 (m, 1H). LCMS: Anal. Calcd. for C₁₄H₁₅N₃O₄: 289; found: 290 (M+H)⁺.

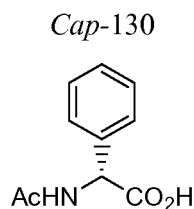
Step 2. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (*Cap-129*).



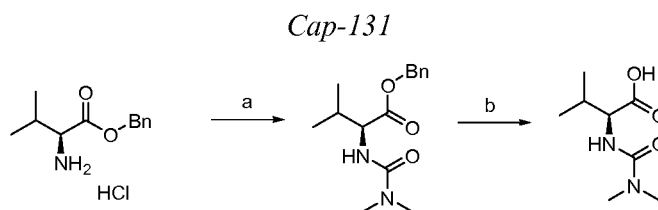
(S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (0.20 g, 0.70 mmol) was hydrogenated in the presence of Pd-C (45 mg) in MeOH (5 mL) at atmospheric pressure for 2h. The product appeared to be insoluble in MeOH,

therefore the reaction mixture was diluted with 5 mL H₂O and a few drops of 6N HCl. The homogeneous solution was filtered through diatomaceous earth (Celite[®]), and the MeOH removed *in vacuo*. The remaining solution was frozen and lyophilized to give a yellow foam (188.9 mg). This material was suspended in THF-H₂O (1:1, 10 mL) and then cooled to 0°C. To the cold mixture was added NaHCO₃ (146.0 mg, 1.74 mmol) carefully (evolution of CO₂). After gas evolution had ceased (ca. 15 min) ClCO₂Me (0.06 mL, 0.78 mmol) was added dropwise. The mixture was allowed to stir for 2h and was acidified to pH~2 with 6N HCl and poured into EtOAc. The layers were separated and the aqueous phase extracted with EtOAc (x5). The combined organic layers were washed (brine), dried (Na₂SO₄), filtered, and concentrated to give the title compound as a colorless solid (117.8 mg, 79%).

¹HNMR (400 MHz, DMSO-d₆) δ 13.04 (s, 1H), 7.63 (d, *J* = 2.6 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 1.5 Hz, 1H), 6.19 (app t, *J* = 2.0 Hz, 1H), 4.47 (dd, *J* = 3.0, 12.9 Hz, 1H), 4.29 – 4.41 (m, 2H), 3.48 (s, 3H). LCMS: Anal. Calcd. for C₈H₁₁N₃O₄: 213; found: 214 (M+H)⁺.



Cap-130 was prepared by acylation of commercially available (R)-phenylglycine analogous to the procedure given in: Calmes, M.; Daunis, J.; Jacquier, R.; Verducci, J. *Tetrahedron*, 1987, 43(10), 2285.



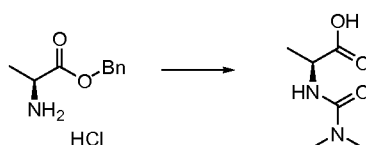
Step a: Dimethylcarbamoyl chloride (0.92 mL, 10 mmol) was added slowly to a solution of (S)-benzyl 2-amino-3-methylbutanoate hydrochloride (2.44 g; 10 mmol) and Hunig's base (3.67 mL, 21 mmol) in THF (50 mL). The resulting white suspension was stirred at room temperature overnight (16 hours) and concentrated

under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (MgSO₄), filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography, eluting with ethyl acetate:hexanes (1:1). Collected fractions were concentrated under vacuum providing 2.35 g (85%) of clear oil. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.84 (d, *J*=6.95 Hz, 3H), 0.89 (d, *J*=6.59 Hz, 3H), 1.98-2.15 (m, 1H), 2.80 (s, 6H), 5.01-5.09 (m, *J*=12.44 Hz, 1H), 5.13 (d, *J*=12.44 Hz, 1H), 6.22 (d, *J*=8.05 Hz, 1H), 7.26-7.42 (m, 5H). LC (Cond. 1): RT = 1.76 min; MS: Anal. Calcd. for [M+H]⁺ C₁₆H₂₂N₂O₃: 279.17; found 279.03.

10

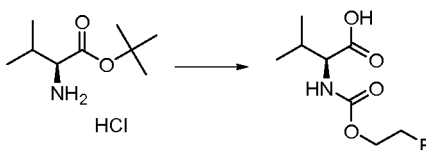
Step b: To a MeOH (50 mL) solution of the intermediate prepared above (2.35 g; 8.45 mmol) was added Pd/C (10%; 200 mg) and the resulting black suspension was flushed with N₂ (3x) and placed under 1 atm of H₂. The mixture was stirred at room temperature overnight and filtered through a microfiber filter to remove the catalyst. The resulting clear solution was then concentrated under reduced pressure to obtain 1.43 g (89%) of *Cap-131* as a white foam, which was used without further purification. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 0.87 (d, *J*=4.27 Hz, 3H), 0.88 (d, *J*=3.97 Hz, 3H), 1.93-2.11 (m, 1H), 2.80 (s, 6H), 3.90 (dd, *J*=8.39, 6.87 Hz, 1H), 5.93 (d, *J*=8.54 Hz, 1H), 12.36 (s, 1H). LC (Cond. 1): RT = 0.33 min; MS: Anal. Calcd. for [M+H]⁺ C₈H₁₇N₂O₃: 189.12; found 189.04.

20

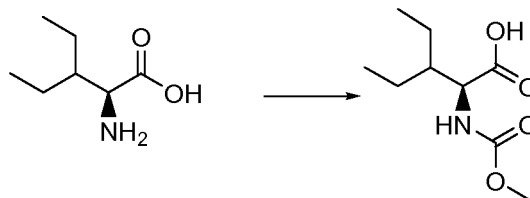
Cap-132

Cap-132 was prepared from (S)-benzyl 2-aminopropanoate hydrochloride according to the method described for *Cap-131*. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.27 (d, *J*=7.32 Hz, 3H), 2.80 (s, 6H), 4.06 (qt, 1H), 6.36 (d, *J*=7.32 Hz, 1H), 12.27 (s, 1H). LC (Cond. 1): RT = 0.15 min; MS: Anal. Calcd. for [M+H]⁺ C₆H₁₃N₂O₃: 161.09; found 161.00.

30

Cap-133

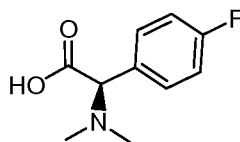
Cap-133 was prepared from (S)-tert-butyl 2-amino-3-methylbutanoate hydrochloride and 2-fluoroethyl chloroformate according to the method described for *Cap-47*. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 0.87 (t, *J* = 6.71 Hz, 6H), 1.97-2.10 (m, 1H), 3.83 (dd, *J*=8.39, 5.95 Hz, 1H), 4.14-4.18 (m, 1H), 4.20-4.25 (m, 1H), 4.50-4.54 (m, 1H), 4.59-4.65 (m, 1H), 7.51 (d, *J* = 8.54 Hz, 1H), 12.54 (s, 1H).

Cap-134

10

Cap-134 was prepared from (S)-diethyl alanine and methyl chloroformate according to the method described for *Cap-51*. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 0.72-0.89 (m, 6H), 1.15-1.38 (m, 4H), 1.54-1.66 (m, 1H), 3.46-3.63 (m, 3H), 4.09 (dd, *J* = 8.85, 5.19 Hz, 1H), 7.24 (d, *J* = 8.85 Hz, 1H), 12.55 (s, 1H). LC (Cond. 2): RT = 0.66 min; LC/MS: Anal. Calcd. for [M+H]⁺ C₉H₁₈NO₄: 204.12; found 204.02.

15

Cap-135

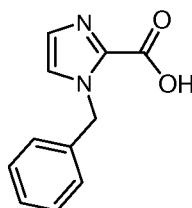
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A solution of D-2-amino-(4-fluorophenyl)acetic acid (338 mg, 2.00 mmol), 1N HCl in diethylether (2.0 mL, 2.0 mmol) and formalin (37%, 1 mL) in methanol (5 mL) was subjected to balloon hydrogenation over 10% palladium on carbon (60 mg) for 16 h at 25 °C. The mixture was then filtered through Celite to afford the HCl salt of *Cap-135* as a white foam (316 mg, 80%). ¹H NMR (300 MHz, MeOH-d₄) δ 7.59

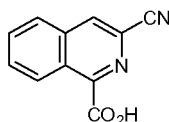
25

(dd, $J = 8.80, 5.10$ Hz, 2H), 7.29 (t, $J = 8.6$ Hz, 2H), 5.17 (s, 1H), 3.05 (v br s, 3H), 2.63 (v br s, 3H); $R_t = 0.19$ min (Cond.-MS-W5); 95% homogeneity index; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{13}FNO_2$: 198.09; found: 198.10.

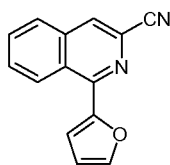
5

Cap-136

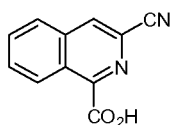
To a cooled (-50 °C) suspension of 1-benzyl-1*H*-imidazole (1.58 g, 10.0 mmol) in anhydrous diethyl ether (50 mL) under nitrogen was added *n*-butyl lithium (2.5 M in hexanes, 4.0 mL, 10.0 mmol) dropwise. After being stirred for 20 min at -
10 50 °C, dry carbon dioxide (passed through Drierite) was bubbled into the reaction mixture for 10 min before it was allowed to warm up to 25 °C. The heavy precipitate which formed on addition of carbon dioxide to the reaction mixture was filtered to yield a hygroscopic, white solid which was taken up in water (7 mL), acidified to pH = 3, cooled, and induced to crystallize with scratching. Filtration of this precipitate
15 gave a white solid which was suspended in methanol, treated with 1*N* HCl/diethyl ether (4 mL) and concentrated *in vacuo*. Lyophilization of the residue from water (5 mL) afforded the HCl salt of *Cap-136* as a white solid (817 mg, 40%). 1H NMR (300 MHz, DMSO- d_6) δ 7.94 (d, $J = 1.5$ Hz, 1H), 7.71 (d, $J = 1.5$ Hz, 1H), 7.50-7.31 (m, 5H), 5.77 (s, 2H); $R_t = 0.51$ min (Cond.-MS-W5); 95% homogeneity index; LRMS:
20 Anal. Calc. for $[M+H]^+$ $C_{11}H_{12}N_2O_2$: 203.08; found: 203.11.

Cap-137

25

Cap-137, step a

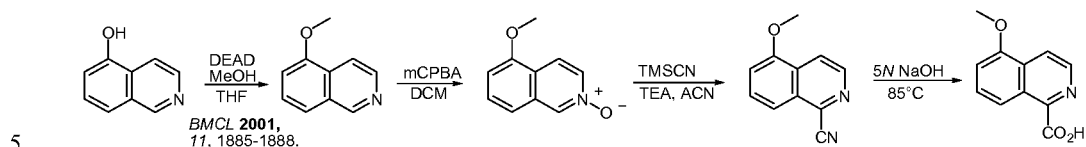
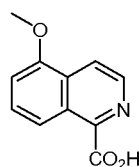
A suspension of 1-chloro-3-cyanoisoquinoline (188 mg, 1.00 mmol; prepared
5 according to the procedure in WO 2003/ 099274) (188 mg, 1.00 mmol), cesium
fluoride (303.8 mg, 2.00 mmol), bis(tri-*tert*-butylphosphine)palladium dichloride (10
mg, 0.02 mmol) and 2-(tributylstannyl)furan (378 μ L, 1.20 mmol) in anhydrous
dioxane (10 mL) under nitrogen was heated at 80 °C for 16 h before it was cooled to
25 °C and treated with saturated, aqueous potassium fluoride solution with vigorous
10 stirring for 1 h. The mixture was partitioned between ethyl acetate and water and the
organic phase was separated, washed with brine, dried over Na₂SO₄, filtered and
concentrated. Purification of the residue on silica gel (elution with 0% to 30% ethyl
acetate/hexanes) afforded *Cap-137, step a* as a white solid which was used as is (230
mg, 105%). R_t = 1.95 min (Cond.-MS-W2); 90% homogeneity index; LRMS: Anal.
15 Calc. for [M+H]⁺ C₁₄H₈N₂O: 221.07; found: 221.12.

Cap-137

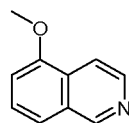
To a suspension of *Cap 137, step a*, (110 mg, 0.50 mmol) and sodium
20 periodate (438 mg, 2.05 mmol) in carbon tetrachloride (1 mL), acetonitrile (1 mL)
and water (1.5 mL) was added ruthenium trichloride hydrate (2 mg, 0.011 mmol).
The mixture was stirred at 25 °C for 2 h and then partitioned between
dichloromethane and water. The aqueous layer was separated, extracted twice more
with dichloromethane and the combined dichloromethane extracts were dried over
25 Na₂SO₄, filtered and concentrated. Trituration of the residue with hexanes afforded
Cap-137 (55 mg, 55%) as a grayish-colored solid. R_t = 1.10 min (Cond.-MS-W2);
90% homogeneity index; LCMS: Anal. Calc. for [M+H]⁺ C₁₁H₈N₂O₂: 200.08;
found: 200.08.

Caps 138 to 158

Synthetic Strategy. Method A.

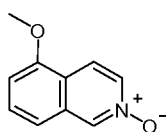
*Cap-138*

10

Cap-138, step a

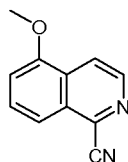
To a stirred suspension of 5-hydroxyisoquinoline (prepared according to the procedure in WO 2003/ 099274) (2.0 g, 13.8 mmol) and triphenylphosphine (4.3 g, 16.5 mmol) in dry tetrahydrofuran (20 mL) was added dry methanol (0.8 mL) and diethyl azodicarboxylate (3.0 mL, 16.5 mmol) portionwise. The mixture was stirred at room temperature for 20 h before it was diluted with ethyl acetate and washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was preabsorbed onto silica gel and purified (elution with 40% ethyl acetate/hexanes) to afford *Cap-138, step a* as a light yellow solid (1.00 g, 45%). ¹H NMR (CDCl₃, 500 MHz) δ 9.19 (s, 1H), 8.51 (d, *J* = 6.0 Hz, 1H), 7.99 (d, *J* = 6.0 Hz, 1H), 7.52-7.50 (m, 2H), 7.00-6.99 (m, 1H), 4.01 (s, 3H); R_t = 0.66 min (Cond. D2); 95% homogeneity index; LCMS: Anal. Calc. for [M+H]⁺ C₁₀H₁₀NO: 160.08; found 160.10.

25

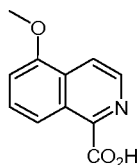
Cap-138, step b

To a stirred solution of *Cap 138, step a* (2.34 g, 14.7 mmol) in anhydrous dichloromethane (50 mL) at room temperature was added *meta*-chloroperbenzoic acid (77%, 3.42 g, 19.8 mmol) in one portion. After being stirred for 20 h, powdered potassium carbonate (2.0 g) was added and the mixture was stirred for 1 h at room temperature before it was filtered and concentrated to afford *Cap-138, step b* as a pale, yellow solid which was sufficiently pure to carry forward (2.15 g, 83.3%). ¹H NMR (CDCl₃, 400 MHz) δ 8.73 (d, *J* = 1.5 Hz, 1H), 8.11 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.04 (d, *J* = 7.1 Hz, 1H), 7.52 (t, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 4.00 (s, 3H); *R*_t = 0.92 min, (Cond.-D1); 90% homogeneity index; LCMS: Anal. Calc. for [M+H]⁺ C₁₀H₁₀NO₂: 176.07; found: 176.0.

Cap-138, step c

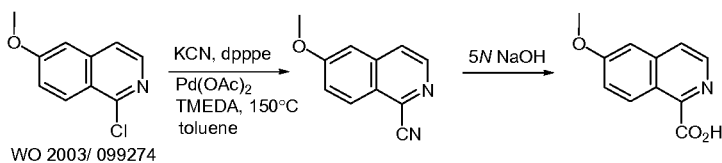


To a stirred solution of *Cap 138, step b* (0.70 g, 4.00 mmol) and triethylamine (1.1 mL, 8.00 mmol) in dry acetonitrile (20 mL) at room temperature under nitrogen was added trimethylsilylcyanoide (1.60 mL, 12.00 mmol). The mixture was heated at 75 °C for 20 h before it was cooled to room temperature, diluted with ethyl acetate and washed with saturated sodium bicarbonate solution and brine prior to drying over Na₂SO₄ and solvent concentration. The residue was flash chromatographed on silica gel (elution with 5% ethyl acetate/hexanes) to 25% ethyl acetate/hexanes to afford *Cap-138, step c* (498.7 mg) as a white, crystalline solid along with 223 mg of additional *Cap-138, step c* recovered from the filtrate. ¹H NMR (CDCl₃, 500 MHz) δ 8.63 (d, *J* = 5.5 Hz, 1H), 8.26 (d, *J* = 5.5 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 4.04 (s, 3H); *R*_t = 1.75 min, (Cond.-D1); 90% homogeneity index; LCMS: Anal. Calc. for [M+H]⁺ C₁₁H₉N₂O: 185.07; found: 185.10.

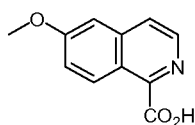
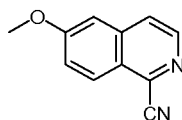
Cap-138

Cap-138, step c (0.45 g, 2.44 mmol) was treated with 5*N* sodium hydroxide solution (10 mL) and the resulting suspension was heated at 85 °C for 4 h, cooled to 25 °C, diluted with dichloromethane and acidified with 1*N* hydrochloric acid. The organic phase was separated, washed with brine, dried over Na₂SO₄, concentrated to ¼ volume and filtered to afford *Cap-138* as a yellow solid (0.44g, 88.9%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 13.6 (br s, 1H), 8.56 (d, *J* = 6.0 Hz, 1H), 8.16 (d, *J* = 6.0 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.71-7.67 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 4.02 (s, 3H); *R*_t = 0.70 min (Cond.-D1); 95% homogeneity index; LCMS: Anal. Calc. for [M+H]⁺ C₁₁H₁₀NO₃: 204.07; found: 204.05.

Synthetic Strategy. Method B (derived from *Tetrahedron Letters*, **2001**, 42, 6707).



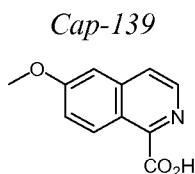
15

Cap-139*Cap-139, step a*

20

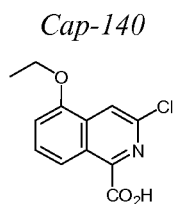
To a thick-walled, screw-top vial containing an argon-degassed suspension of 1-chloro-6-methoxyisoquinoline (1.2 g, 6.2 mmol; prepared according to the procedure in WO 2003/ 099274), potassium cyanide (0.40 g, 6.2 mmol), 1,5-bis(diphenylphosphino)pentane (0.27 g, 0.62 mmol) and palladium (II) acetate (70

mg, 0.31 mmol) in anhydrous toluene (6 mL) was added *N,N,N',N'*-tetramethylethylenediamine (0.29 mL, 2.48 mmol). The vial was sealed, heated at 150 °C for 22 h and then allowed to cool to 25 °C. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified on silica gel eluting with 5% ethyl acetate/hexanes to 25% ethyl acetate/hexanes to afford *Cap-139, step a* as a white solid (669.7 mg). ¹H NMR (CDCl₃, 500 MHz) δ 8.54 (d, *J* = 6.0 Hz, 1H), 8.22 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 5.5 Hz, 1H), 7.41-7.39 (m, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 3.98 (s, 3H); R_t = 1.66 min (Cond.-D1); 90% homogeneity index; LCMS: Anal. Calc. for [M+H]⁺ C₁₁H₉N₂O: 185.07; found: 185.20.

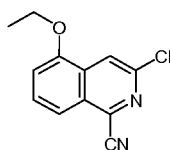


Cap-139 was prepared from the basic hydrolysis of *Cap-139, step a* with 5*N* NaOH according to the procedure described for *Cap 138*. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.63 (v br s, 1H), 8.60 (d, *J* = 9.3 Hz, 1H), 8.45 (d, *J* = 5.6 Hz, 1H), 7.95 (d, *J* = 5.9 Hz, 1H), 7.49 (d, *J* = 2.2 Hz, 1H), 7.44 (dd, *J* = 9.3, 2.5 Hz, 1H), 3.95 (s, 3H); R_t = 0.64 min (Cond.-D1); 90% homogeneity index; LCMS: Anal. Calc. for [M+H]⁺ C₁₁H₁₀NO₃: 204.07; found: 204.05.

20



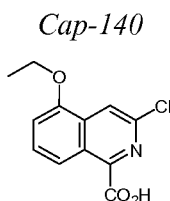
Cap-140, step a



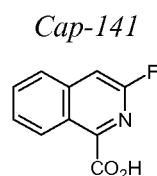
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To a vigorously-stirred mixture of 1,3-dichloro-5-ethoxyisoquinoline (482 mg, 2.00 mmol; prepared according to the procedure in WO 2005/ 051410), palladium (II) acetate (9 mg, 0.04 mmol), sodium carbonate (223 mg, 2.10 mmol) and 1,5-bis(diphenylphosphino)pentane (35 mg, 0.08 mmol) in dry
5 dimethylacetamide (2 mL) at 25 °C under nitrogen was added N,N,N',N'-tetramethylethylenediamine (60 mL, 0.40 mmol). After 10 min, the mixture was heated to 150 °C, and then a stock solution of acetone cyanohydrin (prepared from 457 µL of acetone cyanohydrin in 4.34 mL DMA) was added in 1 mL portions over 18 h using a syringe pump. The mixture was then partitioned between ethyl acetate
10 and water and the organic layer was separated, washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified on silica gel eluting with 10% ethyl acetate/hexanes to 40% ethyl acetate/hexanes to afford *Cap-140*, *step a* as a yellow solid (160 mg, 34%). R_t = 2.46 min (Cond.-MS-W2); 90% homogeneity index; LCMS: Anal. Calc. for [M+H]⁺ C₁₂H₉ClN₂O: 233.05; found: 233.08.

15

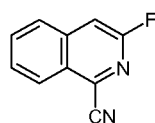


Cap-140 was prepared by the acid hydrolysis of *Cap-140*, *step a* with 12N HCl as described in the procedure for the preparation of *Cap 141*, described below.
20 R_t = 2.24 min (Cond.-MS-W2); 90% homogeneity index; LCMS: Anal. Calc. for [M+H]⁺ C₁₂H₁₁ClNO₃: 252.04; found: 252.02.

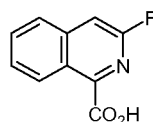


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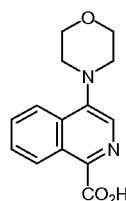
Cap-141, step a

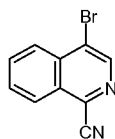


Cap-141, step a was prepared from 1-bromo-3-fluoroisoquinoline (prepared from 3-amino-1-bromoisoquinoline using the procedure outlined in *J. Med. Chem.* **1970**, *13*, 613) as described in the procedure for the preparation of *Cap-140, step a* (*vide supra*). ¹H NMR (500 MHz, CDCl₃) δ 8.35 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.83 (t, *J* = 7.63 Hz, 1H), 7.77-7.73 (m, 1H), 7.55 (s, 1H); R_t = 1.60 min (Cond.-D1); 90% homogeneity index; LCMS: Anal. Calc. for [M+H]⁺ C₁₀H₆FN₂: 173.05; found: 172.99.

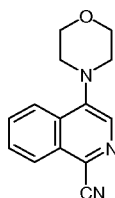
Cap-141

Cap-141, step a (83 mg, 0.48 mmol) was treated with 12*N* HCl (3 mL) and the resulting slurry was heated at 80 °C for 16 h before it was cooled to room temperature and diluted with water (3 mL). The mixture was stirred for 10 min and then filtered to afford *Cap-141* as an off-white solid (44.1 mg, 47.8%). The filtrate was diluted with dichloromethane and washed with brine, dried over Na₂SO₄, and concentrated to afford additional *Cap-141* which was sufficiently pure to be carried forward directly (29.30 mg, 31.8%). ¹H NMR (DMSO-d₆, 500 MHz) δ 14.0 (br s, 1H), 8.59-8.57 (m, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.88-7.85 (m, 2H), 7.74-7.71 (m, 1H); R_t = 1.33 min (Cond.-D1); 90% homogeneity index; LCMS: Anal. Calc. for [M+H]⁺ C₁₀H₇FNO₂: 192.05; found: 191.97.

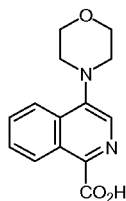
Cap-142

Cap-142, step a

Cap-142, step a was prepared from 4-bromoisoquinoline N-oxide as described in the two-step procedure for the preparation of *Cap-138, steps b and c*. R_t = 1.45 min (Cond.-MS-W1); 90% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_6BrN_2$: 232.97; found: 233.00.

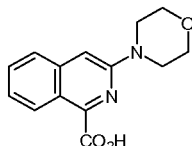
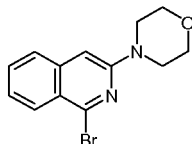
Cap-142, step b

To an argon-degassed suspension of *Cap-142, step a* (116 mg, 0.50 mmol), potassium phosphate tribasic (170 mg, 0.80 mmol), palladium (II) acetate (3.4 mg, 0.015 mmol) and 2-(dicyclohexylphosphino)biphenyl (11 mg, 0.03 mmol) in anhydrous toluene (1 mL) was added morpholine (61 μ L, 0.70 mmol). The mixture was heated at 100 °C for 16 h, cooled to 25 °C and filtered through diatomaceous earth (Celite[®]). Purification of the residue on silica gel, eluting with 10% to 70% ethyl acetate/hexanes afforded *Cap-142, step b* (38 mg, 32%) as a yellow solid, which was carried forward directly. R_t = 1.26 min (Cond.-MS-W1); 90% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{14}N_3O$: 240.11; found: 240.13.

Cap-142

Cap-142 was prepared from *Cap-142*, *step b* with 5*N* sodium hydroxide as described in the procedure for *Cap 138*. $R_t = 0.72$ min (Cond.-MS-W1); 90% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; found: 259.08.

5

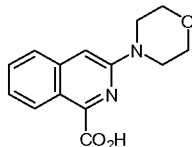
Cap-143*Cap-143, step a*

10

To a stirred solution of 3-amino-1-bromoisoquinoline (444 mg, 2.00 mmol) in anhydrous dimethylformamide (10 mL) was added sodium hydride (60%, unwashed, 96 mg, 2.4 mmol) in one portion. The mixture was stirred at 25 °C for 5 min before 2-bromoethyl ether (90%, 250 μ L, 2.00 mmol) was added. The mixture was stirred further at 25 °C for 5 h and at 75 °C for 72 h before it was cooled to 25 °C, quenched with saturated ammonium chloride solution and diluted with ethyl acetate. The organic layer was separated, washed with water and brine, dried over Na_2SO_4 , filtered and concentrated. Purification of the residue on silica gel eluting with 0% to 70% ethyl acetate/hexanes afforded *Cap-143, step a* as a yellow solid (180 mg, 31%).

$R_t = 1.75$ min (Cond.-MS-W1); 90% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{13}H_{14}BrN_2O$: 293.03; found: 293.04.

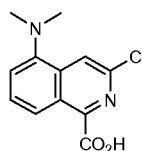
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Cap-143

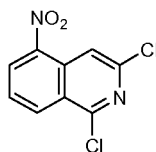
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To a cold (-60 °C) solution of *Cap-143, step a* (154 mg, 0.527 mmol) in anhydrous tetrahydrofuran (5 mL) was added a solution of *n*-butyllithium in hexanes

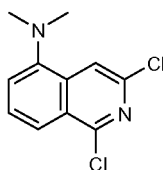
(2.5 M, 0.25 mL, 0.633 mmol). After 10 min, dry carbon dioxide was bubbled into the reaction mixture for 10 min before it was quenched with 1N HCl and allowed to warm to 25 °C. The mixture was then extracted with dichloromethane (3 x 30 mL) and the combined organic extracts were concentrated *in vacuo*. Purification of the
5 residue by a reverse phase HPLC (MeOH/water/TFA) afforded *Cap-143* (16 mg, 12%). $R_t = 1.10$ min (Cond.-MS-W1); 90% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; found: 259.08.

Cap-144

10

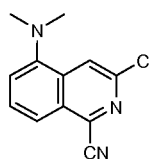
Cap-144, step a

1,3-Dichloroisoquinoline (2.75 g, 13.89 mmol) was added in small portions to
15 a cold (0 °C) solution of fuming nitric acid (10 mL) and concentrated sulfuric acid (10 mL). The mixture was stirred at 0 °C for 0.5 h before it was gradually warmed to 25 °C where it stirred for 16 h. The mixture was then poured into a beaker containing chopped ice and water and the resulting suspension was stirred for 1 h at 0 °C before it was filtered to afford *Cap-144, step a* (2.73 g, 81%) as a yellow solid which was
20 used directly. $R_t = 2.01$ min. (Cond.-D1); 95% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_9H_5Cl_2N_2O_2$: 242.97; found: 242.92.

Cap-144, step b

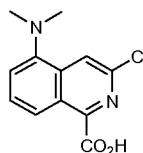
Cap-144, step a (0.30 g, 1.23 mmol) was taken up in methanol (60 mL) and treated with platinum oxide (30 mg), and the suspension was subjected to Parr hydrogenation at 7 psi H₂ for 1.5 h. Then formalin (5 mL) and additional platinum oxide (30 mg) were added, and the suspension was resubjected to Parr hydrogenation at 45 psi H₂ for 13 h. It was then suction-filtered through diatomaceous earth (Celite[®]) and concentrated down to ¼ volume. Suction-filtration of the ensuing precipitate afforded the title compound as a yellow solid which was flash chromatographed on silica gel eluting with 5% ethyl acetate in hexanes to 25% ethyl acetate in hexanes to afford *Cap-144, step b* (231 mg, 78%) as a pale yellow solid. R_t = 2.36 min (Cond.-D1); 95% homogeneity index; ¹H NMR (400 MHz, CDCl₃) δ 8.02 (s, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.57-7.53 (m, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 2.88 (s, 6H); LCMS: Anal. Calc. for [M+H]⁺ C₁₁H₁₁Cl₂N₂: 241.03; found: 241.02. HRMS: Anal. Calc. for [M+H]⁺ C₁₁H₁₁Cl₂N₂: 241.0299; found: 241.0296.

15

Cap-144, step c

Cap-144, step c was prepared from *Cap-144, step b* according to the procedure described for the preparation of *Cap-139, step a*. R_t = 2.19 min (Cond.-D1); 95% homogeneity index; LCMS: Anal. Calc. for [M+H]⁺ C₁₂H₁₁ClN₃: 232.06; found: 232.03. HRMS: Anal. Calc. for [M+H]⁺ C₁₂H₁₁ClN₃: 232.0642; found: 232.0631.

20

Cap-144

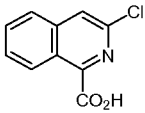
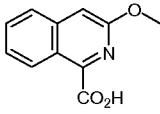
Cap-144 was prepared according to the procedure described for *Cap-141*. R_t = 2.36 min (Cond.-D1); 90%; LCMS: Anal. Calc. for [M+H]⁺ C₁₂H₁₂ClN₂O₂: 238.01; found: 238.09.

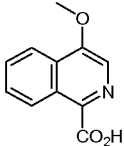
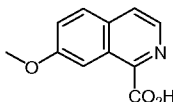
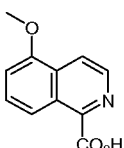
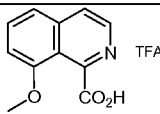
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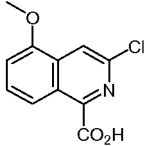
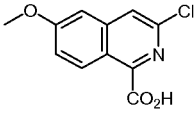
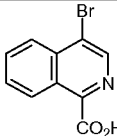
Caps-145 to 162

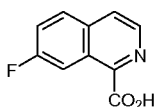
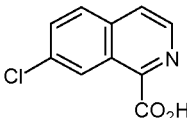
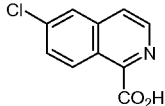
Caps-145 to 162 were prepared from the appropriate 1-chloroisoquinolines according to the procedure described for the preparation of *Cap-138* (Method A) or *Cap-139* (Method B) unless noted otherwise as outlined below.

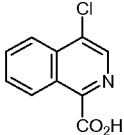
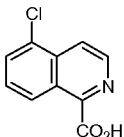
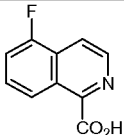
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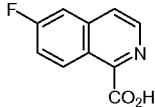
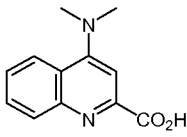
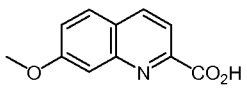
<i>Cap #</i>	Cap	Method	Hydrolysis	R _t (LC-Cond.); % homogeneity index; MS data
<i>Cap-145</i>	 Prepared from commercially available 1,3-dichloroisoquinoline	B	12N HCl	1.14 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for [M+H] ⁺ C ₁₀ H ₇ ClNO ₂ : 208.02; found: 208.00.
<i>Cap-146</i>	 Prepared from commercially available 3-hydroxyisoquinoline	A	5N NaOH	1.40 min (Cond.-D1); 95%; LCMS: Anal. Calc. for [M+H] ⁺ C ₁₁ H ₁₀ NO ₃ : 204.07; found: 204.06.

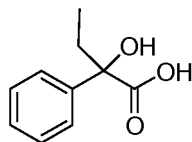
Cap-147	 Prepared from commercially available 1-chloro-4-hydroxyisoquinoline	B	5N NaOH	0.87 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.
Cap-148	 Prepared from commercially available 7-hydroxyisoquinoline	A	5N NaOH	0.70 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.
Cap-149	 Prepared from commercially available 5-hydroxyisoquinoline	A	5N NaOH	0.70 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.
Cap-150		A	12N HCl	0.26 min (Cond.-D1);

	Prepared from 8-methoxy-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274			95%; LCMS: Anal. Calc. for [M+H] ⁺ C ₁₁ H ₁₀ NO ₃ : 204.07; found: 204.04.
Cap-151	 Prepared from 5-methoxy-1,3-dichloroisoquinoline, which can be synthesized following the procedure in WO 2005 / 051410.	B	12N HCl	1.78 min (Cond.-D1); 90%; LCMS: Anal. Calc. for [M+H] ⁺ C ₁₁ H ₉ ClNO ₃ : 238.03; found: 238.09.
Cap-152	 Prepared from commercially available 6-methoxy-1,3-dichloroisoquinoline	B	12N HCl	1.65 min (Cond.-D1); 95%; LCMS: Anal. Calc. for [M+H] ⁺ C ₁₁ H ₉ ClNO ₃ : 238.00; found: 238.09.
Cap-153	 Prepared from 4-	A	6N HCl	1.18 min (Cond.-MS-W1); 95%; LCMS: Anal.

	bromoisquinoline, which can be synthesized following the procedure in WO 2003/062241			Calc. for $[M+H]^+$ $C_{10}H_7BrNO_2$: 251.97; found: 251.95.
Cap-154	 Prepared from 7-fluoro-1-chloroisquinoline, which can be synthesized following the procedure in WO 2003/099274	B	5N NaOH	0.28 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 192.03.
Cap-155	 Prepared from 1,7-dichloroisquinoline, which can be synthesized following the procedure in WO 2003/099274	B	5N NaOH	0.59 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.00.
Cap-156	 Prepared from 1,6-dichloroisquinoline, which can be synthesized following the procedure in WO 2003/	B	5N NaOH	0.60 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$

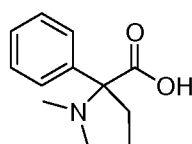
	099274			C ₁₀ H ₇ ClNO ₂ : 208.02; found: 208.03.
Cap-157	 Prepared from 1,4-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 062241	B	12N HCl	1.49 min (Cond.-D1); 95%; LCMS: Anal. Calc. for [M+H] ⁺ C ₁₀ H ₇ ClNO ₂ : 208.02; found: 208.00.
Cap-158	 Prepared from 1,5-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274	B	5N NaOH	0.69 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for [M+H] ⁺ C ₁₀ H ₇ ClNO ₂ : 208.02; found: 208.01.
Cap-159	 Prepared from 5-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274	B	5N NaOH	0.41 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for [M+H] ⁺ C ₁₀ H ₇ FNO ₂ : 192.05;

				found: 192.03.
Cap- 160	 Prepared from 6-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274	B	5N NaOH	0.30 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for [M+H] ⁺ C ₁₀ H ₇ FNO ₂ : 192.05; found: 192.03.
Cap- 161	 Prepared from 4-bromoquinoline-2-carboxylic acid and dimethylamine (DMSO, 100 °C)	--	--	0.70 min (Cond. D1); 95%; LCMS: Anal. Calc. for [M+H] ⁺ C ₁₂ H ₁₃ N ₂ O ₂ : 217.10; found: 217.06.
Cap- 162	 Prepared from <i>m</i>-anisidine following the procedure described in <i>J. Hetero. Chem.</i> 1993, 17 and <i>Heterocycles</i>, 2003, 60, 953.	--	--	0.65 min (Cond.-M3); 95%; LCMS: Anal. Calc. for [M+H] ⁺ C ₁₁ H ₁₀ NO ₃ : 204.07; found: 203.94.

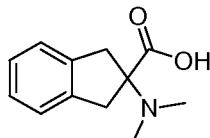
Cap-163

5 To a solution of 2-ketobutyric acid (1.0 g, 9.8 mmol) in diethylether (25 ml) was added phenylmagnesium bromide (22 ml, 1M in THF) dropwise. The reaction was stirred at ~25 °C under nitrogen for 17.5h. The reaction was acidified with 1N HCl and the product was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was washed with water followed by brine and dried over MgSO₄. After
10 concentration *in vacuo*, a white solid was obtained. The solid was recrystallized from hexanes/ethyl acetate to afford *Cap-163* as white needles (883.5 mg). ¹H NMR (DMSO-d₆, δ = 2.5 ppm, 500 MHz): 12.71 (br s, 1 H), 7.54-7.52 (m, 2H), 7.34-7.31 (m, 2H), 7.26-7.23 (m, 1H), 5.52-5.39 (br s, 1H), 2.11 (m, 1H), 1.88 (m, 1H), 0.79 (app t, J = 7.4 Hz, 3H).

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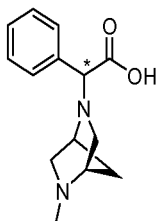
Cap-164

20 A mixture of 2-amino-2-phenylbutyric acid (1.5 g, 8.4 mmol), formaldehyde (14 mL, 37% in water), 1N HCl (10 mL) and 10% Pd/C (0.5 mg) in MeOH (40 mL) was exposed to H₂ at 50 psi in a Parr bottle for 42 h. The reaction was filtered over Celite and concentrated *in vacuo*, the residue was taken up in MeOH (36 mL) and the product was purified with a reverse phase HPLC (MeOH/H₂O/TFA) to afford the
25 TFA salt of *Cap-164* as a white solid (1.7 g). ¹H NMR (DMSO-d₆, δ = 2.5 ppm, 500 MHz) 7.54-7.47 (m, 5H), 2.63 (m, 1H), 2.55 (s, 6H), 2.31 (m, 1H), 0.95 (app t, J = 7.3 Hz, 3H).

Cap-165

5 To a mixture of 2-amino-2-indanecarboxylic acid (258.6 mg, 1.46 mmol) and formic acid (0.6 ml, 15.9 mmol) in 1,2-dichloroethane (7 ml) was added formaldehyde (0.6 ml, 37% in water). The mixture was stirred at ~25 °C for 15 min then heated at 70 °C for 8h. The volatile component was removed *in vacuo*, and the residue was dissolved in DMF (14 mL) and purified by a reverse phase HPLC
10 (MeOH/H₂O/TFA) to afford the TFA salt of *Cap-165* as a viscous oil (120.2 mg). ¹H NMR (DMSO-d₆, δ = 2.5 ppm, 500 MHz): 7.29-7.21 (m, 4 H), 3.61 (d, J = 17.4 Hz, 2H), 3.50 (d, J = 17.4 Hz, 2H), 2.75 (s, 6H). LC/MS: Anal. Calcd. for [M+H]⁺ C₁₂H₁₆NO₂: 206.12; found: 206.07.

15

Cap-166a and -166b

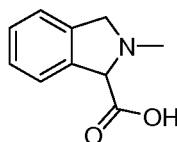
Cap-166a: Diastereomer-1
Cap-166b: Diastereomer-2

Caps-166a and *-166b* were prepared from (1S, 4S)-(+)-2-methyl-2,5-diazabicyclo[2.2.1]heptane (2HBr) according to the method described for the
20 synthesis of *Cap-7a* and *Cap-7b*, with the exception that the benzyl ester intermediate was separated using a semi-prep Chrialcel OJ column, 20 x 250 mm, 10 μm eluting with 85:15 heptane/ethanol mixture at 10 mL/min elution rate for 25 min.
Cap-166b: ¹H NMR (DMSO-d₆, δ = 2.5 ppm, 500 MHz): 7.45 (d, J = 7.3 Hz, 2H),
25 7.27-7.19 (m, 3H), 4.09 (s, 1H), 3.34 (app br s, 1H), 3.16 (app br s, 1H), 2.83 (d, J=10.1 Hz, 1H), 2.71 (m, 2H), 2.46 (m, 1H), 2.27 (s, 3H), 1.77 (d, J = 9.8 Hz, 1H),

1.63 (d, $J = 9.8$ Hz, 1H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{19}N_2O_2$: 247.14; found: 247.11.

Cap-167

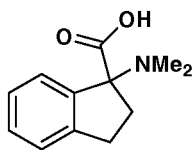
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A solution of racemic Boc-1,3-dihydro-2H-isoindole carboxylic acid (1.0g, 3.8 mmol) in 20% TFA/ CH_2Cl_2 was stirred at ~ 25 °C for 4h. All the volatile component was removed *in vacuo*. A mixture of the resultant crude material, formaldehyde (15 mL, 37% in water), 1N HCl (10 mL) and 10% Pd/C (10 mg) in MeOH was exposed to H_2 (40 PSI) in a Parr bottle for 23 h. The reaction mixture was filtered over Celite and concentrated *in vacuo* to afford *Cap-167* as a yellow foam (873.5 mg). 1H NMR (DMSO- d_6 , $\delta = 2.5$ ppm, 500 MHz) 7.59-7.38 (m, 4H), 5.59 (s, 1H), 4.84 (d, $J = 14$ Hz, 1H), 4.50 (d, $J = 14.1$ Hz, 1H), 3.07 (s, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_2$: 178.09; found: 178.65.

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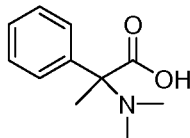
Cap-168



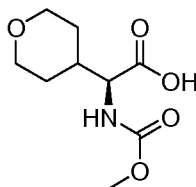
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Racemic *Cap-168* was prepared from racemic Boc-aminoindane-1-carboxylic acid according to the procedure described for the preparation of *Cap-167*. The crude material was employed as such.

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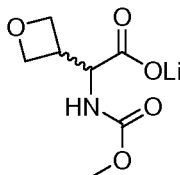
Cap-169

A mixture of 2-amino-2-phenylpropanoic acid hydrochloride (5.0 g, 2.5
5 mmol), formaldehyde (15 ml, 37% in water), 1N HCl (15 ml), and 10% Pd/C (1.32 g)
in MeOH (60 mL) was placed in a Parr bottle and shaken under hydrogen (55 PSI)
for 4 days. The reaction mixture was filtered over Celite and concentrated *in vacuo*.
The residue was taken up in MeOH and purified by reverse phase prep-HPLC
(MeOH/water/TFA) to afford the TFA salt of *Cap-169* as a viscous semi-solid (2.1
10 g). ¹H NMR (CDCl₃, δ = 7.26 ppm, 500 MHz): 7.58-7.52 (m, 2 H), 7.39-7.33 (m,
3H), 2.86 (br s, 3H), 2.47 (br s, 3H), 1.93 (s, 3H). LC/MS: Anal. Calcd. for [M+H]⁺
C₁₁H₁₆NO₂: 194.12; found: 194.12.

Cap-170

15 To (*S*)-2-amino-2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (505mg; 3.18mmol;
obtained from Astatech) in water (15ml) was added sodium carbonate (673mg;
6.35mmol), and the resultant mixture was cooled to 0 °C and then methyl
chloroformate (0.26ml; 3.33mmol) was added dropwise over 5 minutes. The reaction
20 was allowed to stir for 18 hours while allowing the bath to thaw to ambient
temperature. The reaction mixture was then partitioned between 1N HCl and ethyl
acetate. The organic layer was removed and the aqueous layer was further extracted
with 2 additional portions of ethyl acetate. The combined organic layers were
washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*
25 to afford *Cap-170* a colorless residue. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.65
(1 H, br s), 7.44 (1 H, d, *J*=8.24 Hz), 3.77 - 3.95 (3 H, m), 3.54 (3 H, s), 3.11 - 3.26 (2

H, m), 1.82 - 1.95 (1 H, m), 1.41 - 1.55 (2 H, m), 1.21 - 1.39 (2 H, m); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{16}NO_5$: 218.1; found 218.1.

Cap-171

5

A solution of methyl 2-(benzyloxycarbonylamino)-2-(oxetan-3-ylidene)acetate (200 mg, 0.721 mmol; Il Farmaco (2001), 56, 609–613) in ethyl acetate (7 ml) and CH_2Cl_2 (4.00 ml) was degassed by bubbling nitrogen for 10min. Dimethyl dicarbonate (0.116 ml, 1.082 mmol) and Pd/C (20 mg, 0.019 mmol) were then added, the reaction mixture was fitted with a hydrogen balloon and allowed to stir at ambient temperature overnight at which time TLC (95:5 CH_2Cl_2 / MeOH: visulalized with stain made from 1g $Ce(NH_4)_2SO_4$, 6g ammonium molybdate, 6ml sulfuric acid, and 100ml water) indicated complete conversion. The reaction was filtered through celite and concentrated. The residue was purified via Biotage[®] (load with dichloromethane on 25 samplet; elute on 25S column with dichloromethane for 3CV then 0 to 5% MeOH / dichloromethane over 250ml then hold at 5% MeOH / dichloromethane for 250ml; 9ml fractions). Collected fractions containing desired material and concentrated to 120mg (81%) of methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate as a colorless oil. 1H NMR (500 MHz, $CHCl_3$ -D) δ ppm 3.29 - 3.40 (m, $J=6.71$ Hz, 1 H) 3.70 (s, 3 H) 3.74 (s, 3 H) 4.55 (t, $J=6.41$ Hz, 1 H) 4.58 - 4.68 (m, 2 H) 4.67 - 4.78 (m, 2 H) 5.31 (br s, 1 H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{14}NO_5$: 204.2; found 204.0.

To methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate (50 mg, 0.246 mmol) in THF (2 mL) and water (0.5 mL) was added lithium hydroxide monohydrate (10.33 mg, 0.246 mmol). The resultant solution was allowed to stir overnite at ambient temperature. TLC (1:1 EA / Hex; Hanessian stain [1g $Ce(NH_4)_2SO_4$, 6g ammonium molybdate, 6ml sulfuric acid, and 100ml water]) indicated ~10% starting material remaining. Added an additional 3mg LiOH and allowed to stir overnight at which time TLC showed no starting material remaining. Concentrated *in vacuo* and

25

placed on high vac overnight providing 55mg lithium 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate as a colorless solid. ¹H NMR (500 MHz, MeOD) δ ppm 3.39 - 3.47 (m, 1 H) 3.67 (s, 3 H) 4.28 (d, *J*=7.93 Hz, 1 H) 4.64 (t, *J*=6.26 Hz, 1 H) 4.68 (t, *J*=7.02 Hz, 1 H) 4.73 (d, *J*=7.63 Hz, 2 H).

5

EXAMPLES

The present disclosure will now be described in connection with certain embodiments which are not intended to limit its scope. On the contrary, the present disclosure covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include specific
10 embodiments, will illustrate one practice of the present disclosure, it being understood that the examples are for the purposes of illustration of certain embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

15 Solution percentages express a weight to volume relationship, and solution ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker 300, 400, or 500 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. Flash chromatography was carried out on silica gel (SiO₂) according to Still's flash
20 chromatography technique (*J. Org. Chem.* **1978**, 43, 2923).

Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters Micromass ZQ MS system. It should be noted that retention times may vary slightly between machines. The LC conditions employed in determining the retention time (RT) were:

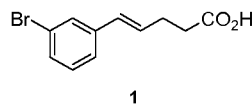
25 Retention times were determined according to the following LC/MS conditions:

Condition 1

Column = Phenomenex-Luna 3.0X 50 mm S10
Start %B = 0
Final %B = 100
30 Gradient time = 2 min
Stop time = 3 min
Flow Rate = 4 mL/min
Wavelength = 220 nm

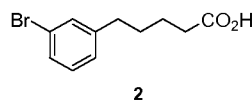
- Solvent A = 0.1% TFA in 10% methanol/90% H₂O
Solvent B = 0.1% TFA in 90% methanol/10% H₂O
Condition 2
Column = Phenomenex-Luna 4.6X50 mm S10
5 Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 3 min
Flow Rate = 4 mL/min
10 Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90% H₂O
Solvent B = 0.1% TFA in 90% methanol/10% H₂O
Condition 3
Column = LCMS. GEMINI C-18 4.6 □ 50 mm
15 Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
20 Wavelength = 220 nm
Solvent A = 0.1% NH₄OAc in 10% acetonitrile /90% H₂O
Solvent B = 0.1% NH₄OAc in 90% acetonitrile /10% H₂O
Condition 4
Column = Phenomenex-Luna 3.0X 50 mm S10
25 Start %B = 0
Final %B = 100
Gradient time = 4 min
Stop time = 5 min
Flow Rate = 4 mL/min
30 Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90% H₂O
Solvent B = 0.1% TFA in 90% methanol/10% H₂O

Reference: (Wittig/reduction/cyclization) *J.Med.Chem.* (2005) 48, 7351-7362.



A 1M solution of potassium tert-butoxide in THF (80 mL) was added dropwise to (3-carboxypropyl)triphenylphosphonium bromide (17 g, 40 mmol) in anhydrous DMSO (20 mL) under nitrogen at 24 °C, and the solution was stirred 30 min before addition of 3-bromobenzaldehyde (4.7 mL, 40 mmol). After several minutes a precipitate was observed and an additional 20 mL of DMSO was added to aid solvation, and the reaction was stirred 18 hours. The solution was poured onto water (120 mL) and washed with chloroform. The aqueous layer was acidified with conc. HCl and extracted with chloroform (3 x 250 mL). The organic phase was concentrated and applied to a 65 (M) Biotage[®] silica gel column; Gradient elution from 15-65% B (A = Hexanes; B = EtOAc) over 2L to give Example 1, (E)-5-(3-bromophenyl)pent-4-enoic acid 8.2 g (82%). ¹H NMR (300 MHz, CDCl₃) δ 7.45 (t, *J* = 1.5 Hz, 1H), 7.30 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.2-7.16 (m, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.40-6.32 (m, 1H), 6.23-6.14 (m, 1H), 2.52 (s, 4H). RT = 2.0 minutes (condition 1); LRMS: Anal. Calcd. for C₁₁H₁₁BrO₂: 252.97; found: 252.98 (M-H).

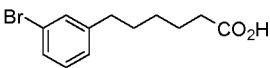
Example 1a		RT = 2.1 minutes (condition 1); LRMS: Anal. Calcd. for C ₁₂ H ₁₃ BrO ₂ : 267.00; found: 267.00 (M-H).
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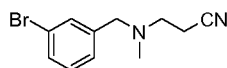
Example 1, (E)-5-(3-Bromophenyl)pent-4-enoic acid (4 g, 15.8 mmol), was dissolved in absolute ethanol (200 mL) and flushed with nitrogen before addition of 5% platinum sulfide on carbon (2.5 g). The solution was flushed with hydrogen at

atmospheric pressure and stirred 5 hours. The catalyst was removed by filtration through diatomaceous earth (Celite[®]) and the solvent immediately removed by rotary evaporation (in order to minimized esterification) to give Example 2, 5-(3-bromophenyl)pentanoic acid 4 g (99%) which was carried forward without further purification. ¹H NMR (500 MHz, CDCl₃) δ 7.31-7.30 (m, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.09-7.07 (d, *J* = 7.6 Hz, 1H), 2.60 (t, *J* = 7.0 Hz, 2H), 2.37 (t, *J* = 7.0 Hz, 2H), 1.68-1.65 (m, 4H). RT = 2.1 minutes (condition 1); LRMS: Anal. Calcd. for C₁₁H₁₃BrO₂: 255.00; found: 254.99 (M-H).

Example 2a (Derived from Example 1a).		RT = 2.2 minutes (condition 1); LRMS: Anal. Calcd. for C₁₂H₁₅BrO₂: 269.02; found: 269.04 (M-H).
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Reference: (Alkylation/hydrolysis) *J.Am.Chem.Soc.* (1946) 68, 1468-1470.

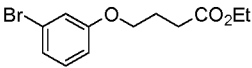


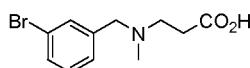
4

Hunig's base (26.5 mL, 0.15 mol) was added to 3-bromobenzyl bromide (38g, 0.15 mol) and N-methyl-β-alanine nitrile (14.2 mL, 0.15 mol) in dry DMF (400 mL). The solution was stirred 16 h, concentrated *in vacuo* to near dryness, triturated with ether/EtOAc, and filtered. [A second reaction was repeated on 12 g]. The combined filtrates were concentrated by rotary evaporation and the residue was charged (CH₂Cl₂) to a 65 (M) Biotage[®] silica gel column; Segment 1: Gradient elution from 5-15% B over 1.3 L; Segment 2: 15%-100% B (A = Hexanes; B = EtOAc) over 6.75 L to give Example 4, 3-((3-bromobenzyl)(methyl)amino)-propanenitrile 44.4 g (88%). ¹H NMR (500 MHz, DMSO-d₆) δ 7.54 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 3.54 (s, 2H), 2.71 (t, *J* = 6.4 Hz, 2H),

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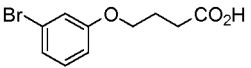
2.63 (t, $J = 6.4$ Hz, 2H), 2.17 (s, 3H). RT = 1.1 minutes (condition 2); LRMS: Anal. Calcd. for $C_{11}H_{13}BrN_2$: 253.03; found: 253.05 (M+H).

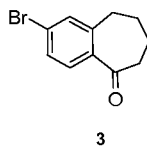
Example 4a Prepared as in J.Med.Chem. 2000 43, 2049		RT = 2.0 minutes (condition 2); LCMS: Anal. Calcd. for $C_{12}H_{15}BrO_3$: 287.14; found: 289.2 (M+2H).
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6N HCl was added to Example 4, 3-((3-bromobenzyl)(methyl)amino)-
propanenitrile (44.4 g, 0.175 mol) in a 1 L screw cap pressure vessel and the sealed
solution was heated at 90 °C for 40 hours. After being cooled, the solution was
concentrated *in vacuo* to ¼ vol. Filtration, concentration of mother liquor, and
10 filtration (2x) gave a quantitative yield of Example 5, 3-((N-(3-bromobenzyl)-N-
methylamino)propanoic acid as a white solid (HCl salt). 1H NMR (500 MHz,
DMSO- d_6) δ 7.90 (t, $J = 1.5$ Hz, 1H), 7.67 (dd, $J = 7.3, 1.5$ Hz, 1H), 7.64 (d, $J = 7.9$
Hz, 1H), 7.43 (t, $J = 7.9$ Hz, 1H), 4.33 (br. s, 2H), 3.34 (br. s, 2H), 2.88 (t, $J = 7.6$ Hz,
2H), 2.63 (s, 3H). RT = 1.3 minutes (condition 2); LRMS: Anal. Calcd. for
15 $C_{11}H_{11}BrNO_2$: 272.03; found: 272.10 (M+H).

Example 5a Derived from 4a as in J.Med.Chem. 2000 43, 2049		RT = 1.05 minutes (condition2); LCMS: Anal. Calcd. for $C_{10}H_{11}BrO_3$: 259.09; found: 259.2. (M+2).
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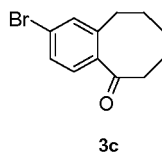


Example 2, 5-(3-bromophenyl)pentanoic acid (4 g, 15.6 mmol) was taken up in polyphosphoric acid (15 g) and heated to 140 °C for 8 hours in a 150 mL pressure vessel, capped to prevent product loss due to sublimation. The reaction mixture was partitioned between 150 mL of water and CH₂Cl₂ (600 mL). [Caution is necessary to avoid boiling of CH₂Cl₂.] The organic phase was washed with water, brine, and concentrated. The crude product was applied to a 40 (S) Biotage[®] silica gel column and gradient eluted from 5 – 60% (EtOAc/Hex) and gave Example 3, 2-bromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one 1.7 g (40%). ¹H NMR (300 MHz, CDCl₃) δ 7.56 (d, *J* = 8.1 Hz, 1H), 7.41 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H), 7.35 (d, *J* = 1.8 Hz, 1H), 2.86 (t, *J* = 5.9 Hz, 2H), 2.69 (t, *J* = 5.8 Hz, 2H), 1.90-1.73 (m, 4H). RT = 2.1 minutes (condition 1); LRMS: Anal. Calcd. for C₁₁H₁₁BrO: 239.00; found: 239.14 (M+H).

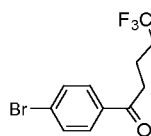
Example 3a (Derived from Example 5)		RT = 1.17 minutes (condition 1); LRMS: Anal. Calcd. for C ₁₁ H ₁₃ BrNO: 254.02; found: 254.16 (M+H).
Example 3b (Derived from Example 5a)		RT = 1.7 minutes (condition 2); LCMS: Anal. Calcd. for C ₁₀ H ₉ BrO ₂ : 241.08; found: 241.2 (M+2).

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Reference: (Cyclization) *JACS* **1962** 27, 70-76.



Thionyl chloride (13.2 mL, 181 mmol) was added (neat) to Example 2a, 6-(3-bromophenyl)hexanoic acid (16 g, 59.2 mmol) in a 1L round-bottomed flask under a nitrogen atmosphere. The mixture was warmed to 60°C for 2 h, excess reagent was removed *in vacuo*, and the residue was subjected to azeotropic conditions (benzene 3x). The acid chloride was dissolved in carbon disulfide (550 mL) and cannulated into a solution of aluminum trichloride (26.3 g, 198 mmol) in carbon disulfide (1315 mL) heated at reflux. The reaction was stirred 20 h, cooled, decanted, concentrated, and the resultant solids were stirred in diethyl ether/THF (1:1, 1L), and 1N HCl (500 mL) for 1.5 hours. The organic layer was filtered, washed with water, and brine to give Example 3c, 2-bromo-7,8,9,10-tetrahydrobenzo[8]annulen-5(6H)-one 10.1 g (66%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.55 (d, *J* = 8.4 Hz, 1H), 7.38 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H), 7.33 (d, *J* = 1.8 Hz, 1H), 2.99 (t, *J* = 6.6 Hz, 2H), 2.89 (t, *J* = 6.6 Hz, 2H), 1.85-1.73 (m, 4H), 1.52-1.44 (m, 2H). RT = 2.8 minutes (condition 2); LRMS: Anal. Calcd. for C₁₂H₁₃BrO: 253.02; found: 253.15 (M+H). Reference: J.Org.Chem. USSR (Engl.Transl.) (1985) p 2201-2205.

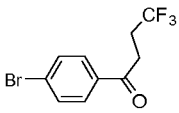


5b

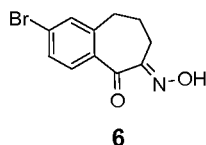
Magnesium (0.636 g, 26.2 mmol) was added to a solution of 4-bromo-1,1,1-trifluorobutane (5 g, 26.2 mmol) in THF (100 mL) and under nitrogen. The solution was stirred for 18 h at 24 °C, and the Grignard reagent was transferred via cannula to a solution of 4-bromobenzaldehyde (4.85 g, 26.2 mmol) in THF (50 mL) at -78 °C under nitrogen. The cold bath was removed and the reaction allowed to warm and stirred 18 h, diluted with Et₂O (1 vol), quenched with sat'd NH₄Cl soln, and washed with brine. Concentrate, take up in CH₂Cl₂ and charged to a 40M Biotage[®] silica gel cartridge. Gradient elution was performed from 15% to 100% B over 1 L (A/B Hexanes/EtOAc) to give 1-(4-bromophenyl)-5,5,5-trifluoropentan-1-ol 6.4 g (82%).

PCC (9.29 g, 43.1 mmol) was admixed with 9 g SiO₂ and ground with mortar & pestle before being added in one portion to a solution of 1-(4-bromophenyl)-5,5,5-trifluoropentan-1-ol (6.4 g, 21.54 mmol) dissolved in dichloromethane (350 mL). The reaction was stirred 4h, filtered through diatomaceous earth (Celite[®]),

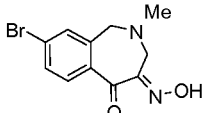
concentrated, and applied to a 160 g Thomson[®] silica gel column. Elution: 10 - 60% B over 1.5 L (A/B Hexanes/EtOAc) gave Example 5b, 1-(4-bromophenyl)-5,5,5-trifluoropentan-1-one 6.1 g (86%). ¹H NMR (500 MHz, CDCl₃) δ 7.81 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H), 3.04 (t, *J* = 7.0 Hz, 2H), 2.25-2.16 (m, 2H), 2.05-1.99 (m, 2H). RT = 2.1 minutes (condition 1). LCMS: Anal. Calcd. For C₁₁H₁₁BrF₃O: 295.00; found: 295.00 (M+H).

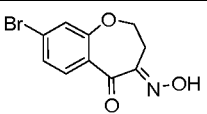
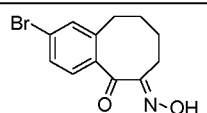
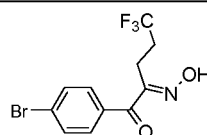
Example 5b.1 (Prepared from 3-bromo-1,1,1-trifluoropropane)		RT = 1.7 minutes (condition 1); LCMS: Anal. Calcd. For C ₁₀ H ₉ BrF ₃ O: 278.97; found: 278.98 (M-H).
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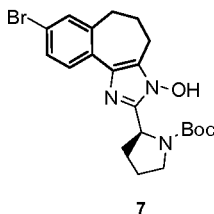
Reference: (Imidazole synthesis) *Bioorg. Med. Chem. Lett.* **2002** 1009-1011.



Example 3, 2-Bromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (1.5 g, 5.9 mmol) was dissolved in 2:1 Et₂O/THF (120 mL) and 1N HCl in Et₂O (9 mL) was added. The solution was cooled to 0°C before addition of *iso*-amyl nitrite (1.2 mL, 9 mmol) and the reaction was stirred 18 hours at 24 °C, concentrated, and applied to 25 (M) Biotage[®] silica gel column. Gradient elution from 15-100% B (A = Hexanes; B = EtOAc) over 1L and gave Example 6, (E)-2-bromo-6-(hydroxyimino)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one 1 g (64%). RT = 1.9 minutes (condition 1). LCMS: Anal. Calcd. For C₁₁H₁₀NBrO₂: 268; found: 268 (M+H).

Example 6a (Derived from Example 3a)		RT = 1.35 minutes (condition 2); LCMS: Anal. Calcd. For C ₁₁ H ₁₁ BrN ₂ O ₂ : 283.00; found: 283.03 (M+H).
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Example 6b (Derived from Example 3b)		RT = 1.55 minutes (condition 2); LCMS: Anal. Calcd. for $C_{10}H_8BrNO_3$: 270.08; found: 270 (M+H).
Example 6c (Derived from Example 3c)		RT = 2.51 minutes (condition 2); LCMS: Anal. Calcd. For $C_{12}H_{12}BrNO_2$: 282.02; found: 282.13 (M+H).
Example 6d (Derived from Example 5b)		RT = 2.1 minutes (condition 1); LCMS: Anal. Calcd. For $C_{11}H_{10}BrF_3NO_2$: 323.98; found: 323.99 (M+H).



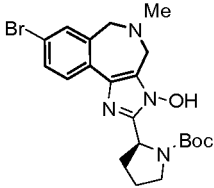
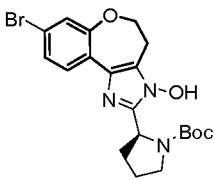
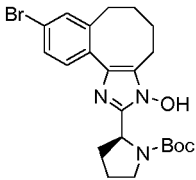
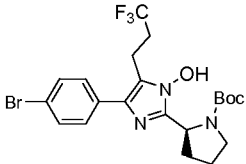
Concentrated 28% ammonium hydroxide solution (12 mL) was added to a solution of Example 6, (E)-2-bromo-6-(hydroxyimino)-6,7,8,9-tetrahydro-5H-benzo[7]-annulen-5-one (1g, 3.7 mmol) and N-Boc-L-prolinal (850 mg, 4.3 mmol) in

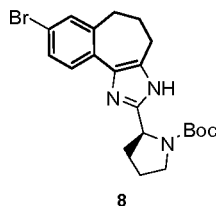
5 methanol (35 mL) and the reaction mixture was stirred 18 hours at 24 °C, partially concentrated to remove methanol, and the aqueous residue extracted with CH_2Cl_2 . The organic phase washed with water and concentrated and the crude product charged (CH_2Cl_2) to a 40 (S) Biotage[®] silica gel column; Gradient elution Segment

10 1. 15%-30% B over 300 mL; Segment 2. 30%-100% B over 700 mL (A = 1:1 hexanes/ CH_2Cl_2 ; B = EtOAc) gave Example 7, 700 mg (44%). ¹H NMR (300 MHz, DMSO- d_6) δ 11.3 (br. s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.35 (dd, J = 8.4, 1.5 Hz, 1H),

7.31 (d, $J = 1.8$ Hz, 1H), 5.0/4.87 (m, 1H), 3.51-3.46 (m, 1H), 3.42-3.36 (m, 1H), 2.90-2.70 (m, 4H), 2.27-1.80 (m, 6H), 1.38/1.11 (s, 9H). RT = 1.9 minutes (condition 1). LRMS: Anal. Calcd. for $C_{21}H_{26}BrN_3O_3$: 488.12; found: 488.14 (M+H). HRMS: Anal. Calcd. for $C_{21}H_{26}BrN_3O_3$: 488.1236; found: 488.1242 (M+H).

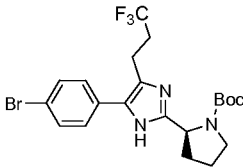
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Example 7a (Derived from Example 6a)		RT = 2.29 minutes (condition 2); LCMS: Anal. Calcd. For $C_{21}H_{28}N_4BrO_3$: 463.13; found: 463.16 (M+H).
Example 7b (Derived from Example 6b)		RT = 1.67 minutes (condition 1); LCMS: Anal. Calcd. For $C_{20}H_{24}N_3BrO_4$: 450.34; found: 450 (M+H).
Example 7c (Derived from Example 6c)		RT = 2.53 minutes (condition 2); LCMS: Anal. Calcd. For $C_{22}H_{29}N_3BrO_3$: 462.13; found: 462.31 (M+H).
Example 7d (Derived from Example 6d)		RT = 1.9 minutes (condition 1); LCMS: Anal. Calcd. For $C_{21}H_{26}N_3BrF_3O_3$: 504.11; found: 504.17 (M+H).

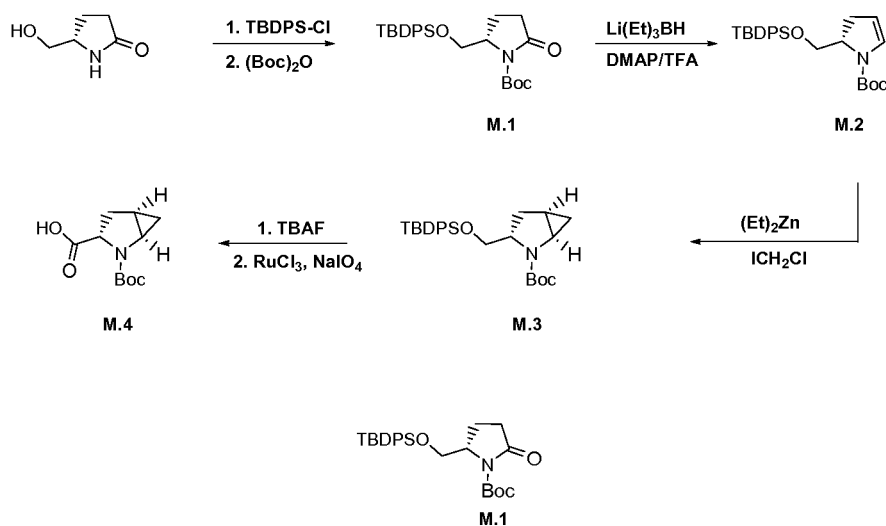


Triethyl phosphite (0.78 mL, 4.7 mmol) was added to a solution Example 7, (700 mg, 1.57 mmol) in DMF (2 mL) and the solution heated at 80°C for 18 hours under a nitrogen atmosphere. The reaction mixture was taken up in ethyl acetate (100 mL) and washed with water and brine. After concentration the crude product was applied to a 40 (S) Biotage[®] silica gel column and subjected to gradient elution; Segment 1. 5%-15% B over 300 mL; Segment 2. 15%-100% B over 600 mL (A = CH₂Cl₂; B = EtOAc) to give Example 8, 675 mg (100%). ¹H NMR (300 MHz, DMSO-d₆) δ 11.7 (br. s, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.29 (s, 1H), 4.78/4.69 (br s, 1H), 3.57-3.48 (m, 1H), 3.38-3.32 (m, 1H), 2.85-2.78 (m, 4H), 2.28-1.77 (m, 6H), 1.39/1.14 (s, 9H). RT = 1.9 minutes (condition 1). LRMS: Anal. Calcd. for C₂₁H₂₆BrN₃O₂: 432.13; found: 432.14 (M+H).

Example 8a (Derived from Example 7a)		RT = 1.83 minutes (condition 2); LCMS: Anal. Calcd. For C ₂₁ H ₂₈ BrN ₄ O ₂ : 447.14; found: 447.06 (M+H).
Example 8b (Derived from Example 7b)		RT = 1.95 minutes (condition 2); LCMS: Anal. Calcd. For C ₂₀ H ₂₄ N ₃ BrO ₃ : 433.24; found: 434 (M+H).

Example 8c (Derived from Example 7d)		RT = 1.80 minutes (condition 1); LCMS: Anal. Calcd. For C₂₁H₂₆BrF₃N₃O₂: 488.11; found: 488.17 (M+H).
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Synthetic route 2.



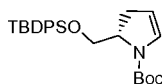
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To a solution of (S)-5-(hydroxymethyl)pyrrolidin-2-one (10 g, 87 mmol) in dichloromethane (50 mL) was added tert-butylchlorodiphenylsilane (25.6 g, 93 mmol), Et₃N (12.1 mL, 87 mmol) and DMAP (1.06 g, 8.7 mmol). The mixture was stirred at room temperature until the starting pyrrolidinone was completely consumed, and then it was diluted with dichloromethane (50 mL) and washed with water (50 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated in vacuo, and the crude material was submitted to flash chromatography (silica gel; 30 to 100% of ethyl acetate/hexanes) to afford the silyl ether as a colorless oil (22.7 g, 74% yield). ¹H-NMR (400 MHz, DMSO-d₆, δ = 2.5 ppm) 7.69 (br s, 1H), 7.64-7.61 (m, 4H), 7.50-7.42 (m, 6H), 3.67-3.62 (m, 1H), 3.58-3.51 (m, 2H), 2.24-2.04 (m, 3H), 1.87-1.81 (m, 1H), 1.00 (s, 9H). LC/MS (M+H) = 354.58.

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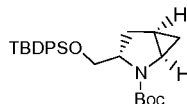
Di-tert-butyl dicarbonate (38.5 g, 177 mmol) was added in portions as a solid over 10 min to a dichloromethane (200 mL) solution of silyl ether (31.2 g, 88.3

mmol), Et₃N (8.93 g, 88 mmol), and DMAP (1.08 g, 8.83 mmol) and stirred for 18 h at 24 °C. Most of the volatile material was removed in vacuo and the crude material taken up in 20% ethyl acetate/hexanes and applied to a 2 L funnel containing 1.3 L of silica gel and then eluted with 3 L of 20% ethyl acetate/hexane and 2 L of 50% ethyl acetate). Upon concentration of the desired fractions in a rotary evaporator, a white slurry of solid formed which was filtered, washed with hexanes and dried in vacuo to afford carbamate M.1 as a white solid (32.65 g, 82% yield). ¹H NMR (400 MHz, DMSO-d₆, δ = 2.5 ppm) 7.61-7.59 (m, 2H), 7.56-7.54 (m, 2H), 7.50-7.38 (m, 6H), 4.18 (m, 1H), 3.90 (dd, J = 10.4, 3.6, 1H), 3.68 (dd, J = 10.4, 2.1, 1H), 2.68-2.58 (m, 1H), 2.40-2.33 (m, 1H), 2.22-2.12 (m, 1H), 2.01-1.96 (m, 1H), 1.35 (s, 9H), 0.97 (s, 9H). LC/MS (M-Boc+H) = 354.58. Calcd. 454.24.

**M.2**

A three-necked flask equipped with a thermometer and a nitrogen inlet was charged with carbamate M.1 (10.05 g, 22.16 mmol) and toluene (36 mL), and lowered into -55 °C cooling bath. When the internal temperature of the mixture reached -50 °C, lithium triethylborohydride (23 mL of 1.0 M/tetrahydrofuran, 23.00 mmol) was added dropwise over 30 min and the mixture stirred for 35 min while maintaining the internal temperature between -50 °C and -45 °C. Hunig's base (16.5 mL, 94 mmol) was added dropwise over 10 min. Then, DMAP (34 mg, 0.278 mmol) was added in one batch, followed by the addition of trifluoroacetic anhydride (3.6 mL, 25.5 mmol) over 15 min, while maintaining the internal temperature between -50 °C and -45 °C. The bath was removed 10 min later, and the reaction mixture was stirred for 14 h while allowing it to rise to ambient temperature. It was diluted with toluene (15 mL), cooled with an ice-water bath, and treated slowly with water (55 mL) over 5 min. The phases were separated and the organic layer washed with water (50 mL, 2x) and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel; 5% ethyl acetate/hexanes) to afford dihydropyrrole M.2 as a colorless viscous oil (7.947 g, 82% yield). Rt = 2.41 min under the following HPLC conditions: Solvent gradient from 100% A : 0% B to 0% A : 100% B (A = 0.1% TFA in 1:9 methanol/water; B = 0.1% TFA in 9:1 methanol/water) over 2 min and hold for 1 min; detection @ 220 nm; Phenomenex-Luna 3.0X50 mm S10

column. $^1\text{H-NMR}$ (400 MHz, DMSO- d_6 , δ = 2.5 ppm) 7.62-7.58 (m, 4H), 7.49-7.40 (m, 6H), 6.47 (br s, 1H), 5.07/5.01 (overlapping br d, 1H), 4.18 (br s, 1H), 3.89 (br s, 0.49H), 3.69 (br s, 1.51H), 2.90-2.58 (br m, 2H), 1.40/1.26 (overlapping br s, 9H), 0.98 (s, 9H). LC/MS: (M+Na) = 460.19.



M.3

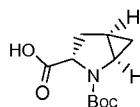
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Diethylzinc (19 mL of ~1.1 M in toluene, 20.9 mmol) was added dropwise over 15 min to a cooled (-30 °C) toluene (27 mL) solution of dihydropyrrole M.2 (3.94 g, 9.0 mmol). Chloriodomethane (stabilized over copper; 3.0 mL, 41.2 mmol) was added dropwise over 10 min, and stirred while maintaining the bath temperature at -25 °C for 1 h and between -25 °C and -21 °C for 18.5 h. The reaction mixture was opened to the air and quenched by the slow addition of 50% saturated NaHCO₃ solution (40 mL), and then removed from the cooling bath and stirred at ambient temperature for 20 min. It was filtered through a filter paper and the white cake was washed with 50 mL of toluene. The organic phase of the filtrate was separated and washed with water (40 mL, 2x), dried (MgSO₄), filtered, and concentrated in vacuo. The crude material was purified using a Biotage[®] system (350 g silica gel; sample was loaded with 7% ethyl acetate/hexanes; eluted with 7-20% ethyl acetate/hexanes) to afford a mixture of methanopyrrolidines (M.3 predominates) as a colorless viscous oil (3.69 g, 90.7%). [Note: the exact cis/trans-isomer ratio was not determined at this stage]. R_t = 2.39 min under the following HPLC conditions: Solvent gradient from 100% A : 0% B to 0% A : 100% B (A = 0.1% TFA in 1:9 methanol/water; B = 0.1% TFA in 9:1 methanol/water) over 2 min, and hold for 1 min; detection @ 220 nm; Phenomenex-Luna 3.0X50 mm S10 column. $^1\text{H-NMR}$ (400 MHz, DMSO- d_6 , δ = 2.5 ppm) 7.62-7.60 (m, 4H), 7.49-7.40 (m, 6H), 3.77/3.67 (overlapping br s, 3H), 3.11-3.07 (m, 1H), 2.23 (app br s, 1H), 2.05-2.00 (m, 1H), 1.56-1.50 (m, 1H), 1.33 (very broad s, 9H), 1.00 (s, 9H), 0.80 (m, 1H), 0.30 (m, 1H). LC/MS: (M+Na) = 474.14.

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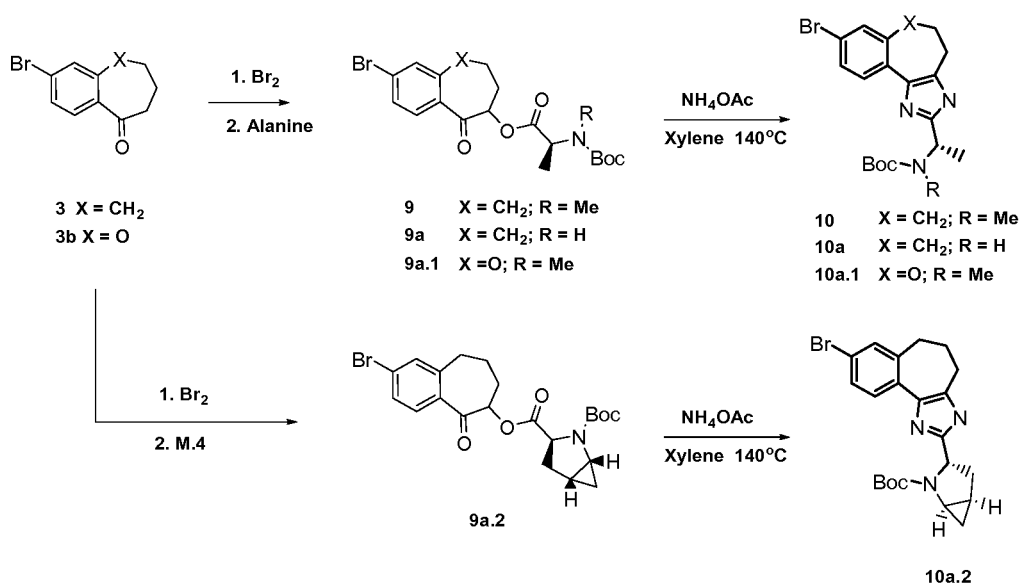
M.4

TBAF (7.27 mL of 1.0 M in tetrahydrofuran, 7.27 mmol) was added dropwise over 5 min to a tetrahydrofuran (30 mL) solution of silyl ethers M.3 (3.13 g, 6.93 mmol) and the mixture stirred at ambient temperature for 4.75 h. After the addition of saturated ammonium chloride solution (5 mL), most of the volatile material was removed in vacuo and the residue partitioned between dichloromethane (70 mL) and 50% saturated ammonium chloride solution (30 mL). The aqueous phase was extracted with dichloromethane (30 mL), and the combined organic phase was dried (MgSO₄), filtered, concentrated in vacuo and then exposed to high vacuum overnight. The crude material was purified using a Biotage[®] (silica gel; 40-50% ethyl acetate/hexanes) to afford a mixture of alcohols, contaminated with traces of a lower R_f spot, as a colorless oil (1.39 g, ~94% yield). [Note: the exact cis/trans isomer ratio was not determined at this stage.] ¹H-NMR (400 MHz, dimethylsulfoxide-d₆, δ= 2.5 ppm) 4.70 (t, J = 5.7, 1H), 3.62-3.56 (m, 1H), 3.49-3.44 (m, 1H), 3.33-3.27 (m, 1H), 3.08-3.04 (m, 1H), 2.07 (br m, 1H), 1.93-1.87 (m, 1H), 1.51-1.44 (m, 1H), 1.40 (s, 9H), 0.76-0.71 (m, 1H), 0.26 (m, 1H). LC/MS (M+Na) = 236.20.

A semi-solution of sodium periodate (6.46 g, 30.2 mmol) in water (31 mL) was added to a solution of alcohols (2.15 g, 10.08 mmol) in acetonitrile (20 mL) and carbon tetrachloride (20 mL). Ruthenium trichloride (0.044 g, 0.212 mmol) was added immediately and the heterogeneous reaction mixture was stirred vigorously for 75 min. The reaction mixture was diluted with water (60 mL) and extracted with dichloromethane (50 mL, 3x). The combined organic phase was treated with 1 mL methanol, allowed to stand for about 5 min, and then filtered through diatomaceous earth (Celite[®]). The pad was washed with dichloromethane (50 mL), and the filtrate was concentrated in vacuo to afford a light charcoal-colored solid. The crude material was dissolved in ethyl acetate (~10 mL) with heating and allowed to stand at ambient temperature with seeding. About 15 min into the cooling phase, a rapid crystal formation was observed. About 1 h later, hexanes (~6 mL) was added and the mixture refrigerated overnight (it did not appear that additional material precipitated out). The mixture was filtered and washed with ice/water-cooled hexanes/ethyl acetate (2:1 ratio; 20 mL) and dried under high vacuum to afford the first crop of acid M.4 (off-white crystals, 1.222 g). The mother liquor was concentrated in vacuo, and the residue dissolved in ~3 mL of ethyl acetate with heating, allowed to stand at

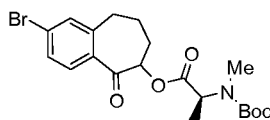
ambient temperature for 1 h, and then 3 mL hexanes was added and stored in a refrigerator for ~15 h. A second crop of acid M.4 was retrieved similarly (grey crystals, 0.133 g), for a combined yield of 59%. $R_t = 1.48$ min under the following HPLC conditions: Solvent gradient from 100% A : 0% B to 0% A : 100% B (A = 0.1% TFA in 1:9 methanol/water; B = 0.1% TFA in 9:1 methanol/water) over 3 min; detection @ 220 nm; Phenomenex-Luna 3.0X50 mm S10 column. MP (dec.) for the first crop = 147.5-149.5 °C. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6 , $\delta = 2.5$ ppm) 12.46 (s, 1H), 3.88 (app br s, 1H), 3.27 (app br s, 1H; overlapped with water signal), 2.28 (br m, 1H), 2.07 (app br s, 1H), 1.56 (app s, 1H), 1.40/1.34 (two overlapped s, 9H), 0.71 (m, 1H), 0.45 (m, 1H). $^{13}\text{C-NMR}$ (100.6 MHz, DMSO-d_6 , $\delta = 39.21$ ppm) 172.96, 172.60, 154.45, 153.68, 78.74, 59.88, 59.58, 36.91, 31.97, 31.17, 27.77, 27.52, 14.86, 14.53, 13.69. LC/MS ($\text{M}+\text{Na}$) = 250.22. Anal. Calcd. For $\text{C}_{11}\text{H}_{17}\text{NO}_4$: C, 58.13; H, 7.54; N, 6.16. Found (for first crop): C, 58.24; H, 7.84; N, 6.07. Optical rotation (10 mg/mL in CHCl_3): $[\alpha]_D = -216$ and -212 for the first and second crop, respectively.

15 *Synthetic route 3.*



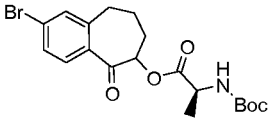
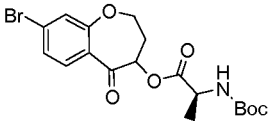
Reference: (Bromination) *JACS* (1952) 74, 6263.

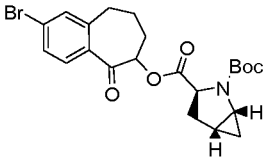
Reference: (Displacement/Cyclization) *J.Med.Chem.* (2001) 44, 2990.

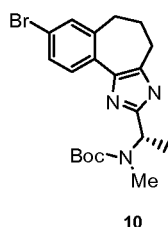


Example 3, 2-Bromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (1.5 g, 5.9 mmol) was dissolved Et₂O (25 mL), cooled to 0°C and bromine (0.35 mL, 6.6 mmol) was added dropwise. The solution was stirred at 24°C until TLC indicated reaction complete (2-18 h; scale dependent). The solvent was removed by rotary
 5 evaporation and the crude product applied to a 25 (M) Biotage[®] silica gel column. Gradient elution from 50-100% B (A = Hexanes; B = 10% EtOAc/hex) over 500 mL and gave 2,6-dibromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one 700 mg, and 1.5 g of a second fraction containing dibromide (1:1). RT = 2.2 minutes (condition 1).

The 2,6-dibromo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (700 mg,
 10 2.22 mmol), and N-methyl-L-alanine (493 mg, 2.4 mmol) were dissolved in acetonitrile (8 mL) and 1.1 mL of Hunig's base was added dropwise, and the reaction was stirred 18 hours at 55°C. The solvent was removed by rotary evaporation, and the residue taken up in EtOAc and washed with 0.1N HCl soln, sat'd NaHCO₃ soln, and brine and concentration gave Example 9, (2S)-2-bromo-5-oxo-6,7,8,9-tetrahydro-
 15 5H-benzo[7]annulen-6-yl 2-(tert-butoxycarbonyl(methyl)amino)propan-oate 960 mg (98%) which was carried forward without further purification. ¹H NMR (300 MHz, CDCl₃) δ 7.55 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.40 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.38 (s, 1H), 5.51-5.45/5.36-5.31 (m, 1H), 4.96-4.79/4.72-4.53 (m, 1H), 3.8 (br s., 3H), 2.94 (t, *J* = 4.8 Hz, 2H), 2.82 (t, *J* = 5.1 Hz, 2H), 2.10-1.95 (m, 2H), 1.43 (s, 9H). RT = 2.3
 20 minutes (condition 1). LRMS: Anal. Calcd. for C₂₀H₂₆BrNO₅: 440.11; found: 440.10 (M+H).

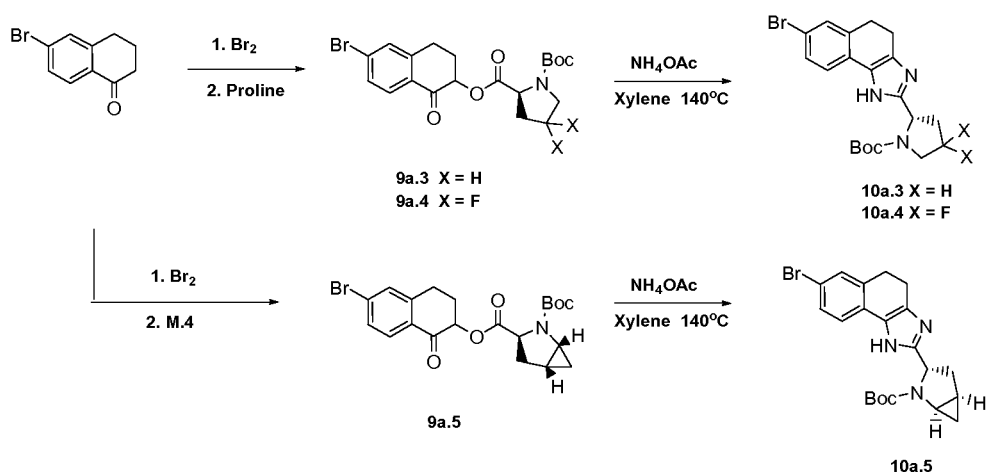
Example 9a (Derived from Example 3)		RT = 2.2 minutes (condition 1); LCMS: Anal. Calcd. For C ₁₉ H ₂₄ BrNO ₅ : 425; found: 425 (M+H).
Example 9a.1 (Derived from Example 3b)		RT = 2.05 minutes (condition 2); LCMS: Anal. Calcd. for C ₁₉ H ₂₄ BrNO ₆ : 442.30;

		found: 344.2 (M-100), (M+2H).
Example 9a.2 (Derived from Example 3)		RT = 2.18 minutes (condition 1); LCMS: Anal. Calcd. For C ₂₂ H ₂₇ BrNO ₅ : 464.10; found: 463.99 (M+H).

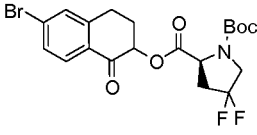
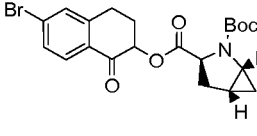
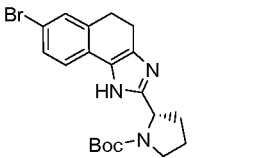
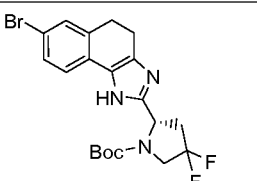


Example 9, (2S)-2-bromo-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl
2-(tert-butoxycarbonyl(methyl)amino)propanoate (960 mg, 2.2 mmol) was taken up
5 in xylene (20 mL) and placed in a 100 mL screw cap pressure vessel. Ammonium
acetate (1.7 g, 10 equiv) was added and the mixture was heated at 120°C (oil bath
temperature) for 4 hours. The cooled mixture was diluted with ethyl acetate (150
mL) and sat'd NaHCO₃ soln and the organic phase concentrated. The crude product
was applied (CH₂Cl₂) to a 25 (M) Biotage[®] silica gel cartridge. Segment 1. Hold
10 15% B for 300 mL; Segment 2. Gradient elution from 10 - 100% B over 600 mL (A
= hexanes; B = EtOAc) to give Example 10, 150 mg (16%) NOTE: Compound loss
occurred during chromatography (yield should be higher). ¹H NMR (500 MHz,
CDCl₃) δ 7.43-.42 (m, 2H), 7.35 (s, 1H), 5.25 (q, *J* = 7.0 Hz, 1H), 3.02 (t, *J* = 6.4 Hz,
2H), 2.96 (s, 3H), 2.83-2.81 (m, 2H), 2.0-1.98 (m, 2H), 1.74 (d, *J* = 7.0 Hz, 3H), 1.47
15 (s, 9H). RT = 1.8 minutes (condition 1). LRMS: Anal. Calcd. for C₂₀H₂₆BrN₃O₂:
420.13; found: 420.10 (M+H).

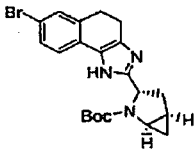
Example 10a (Derived from Example 9a)		RT = 1.9 minutes (condition 1); LRMS: Anal. Calcd. For C ₁₉ H ₂₄ BrN ₃ O ₂ : 406.11; found: 406.23 (M+H).
Example 10a.1 (Derived from Example 9a.1)		RT=1.59 minutes (condition 1); LCMS: Anal. Calcd. for C ₁₉ H ₂₄ BrN ₃ O ₃ : 422.33; found: 424.2 (M+2H).
Example 10a.2 (Derived from Example 9a.2)		RT = 1.74 minutes (condition 1); LRMS: Anal. Calcd. For C ₂₂ H ₂₇ BrN ₃ O ₂ : 443.11; found: 443.07 (M+H).

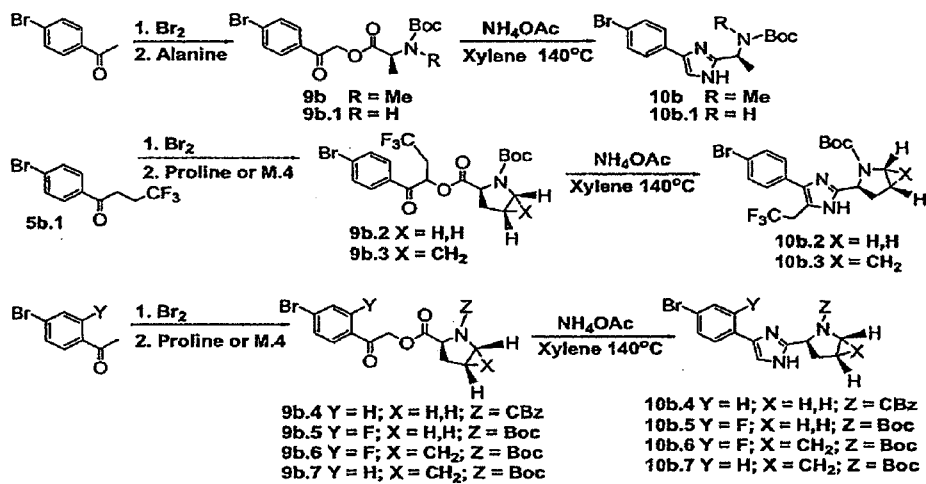
Synthetic route 4.

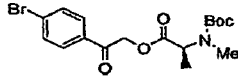
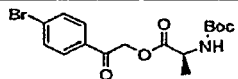
Example 9a.3 (Derived 6-bromo tetra- l-one purchased from J & W PharmLab, LLC.		RT = 3.1 minutes (condition 2); LCMS: Anal. Calcd. For C ₂₀ H ₂₄ BrNO ₅ : 438;
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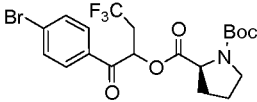
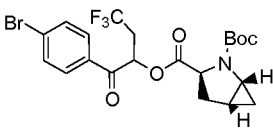
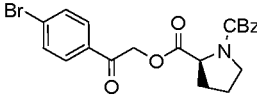
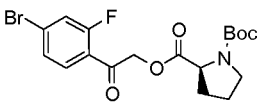
Example 9a.3 was prepared as described for Example 9.)		found: 438 (M+H).
Example 9a.4 (Derived 6-bromo tetral-1-one purchased from J & W PharmLab, LLC)		RT = 3.0 minutes (condition 2); LCMS: Anal. Calcd. For C ₂₀ H ₂₂ BrF ₂ NO ₅ : 474; found: 474 (M+H).
Example 9a.5 (Derived 6-bromo tetral-1-one purchased from J & W PharmLab, LLC)		RT = 2.95 minutes (condition 2); LCMS: Anal. Calcd. For C ₂₁ H ₂₅ BrNO ₅ : 472.07, 474.07; found: 472.02, 474.02 (M+Na).
Example 10a.3 (Derived from Example 9a.3 and prepared as described for Example 10.)		RT = 2.37 minutes (condition 2); LRMS: Anal. Calcd. for C ₂₀ H ₂₅ BrN ₃ O ₂ : 418.11 and 420.10; found: 418.21 and 420.17 (M+H).
Example 10a.4 (Derived from Example 9a.4)		RT = 2.3 minutes (condition 2); HRMS: Anal. Calcd. for C ₂₀ H ₂₂ BrF ₂ N ₃ O ₂ 454.09573; found: 454.09362 (M+H).

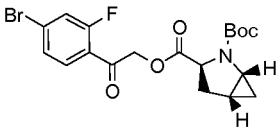
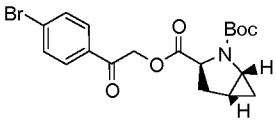
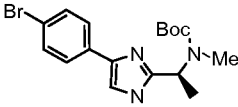
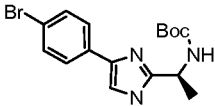
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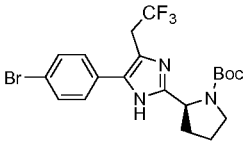
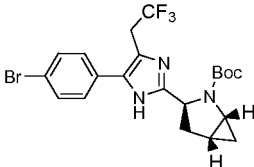
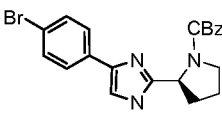
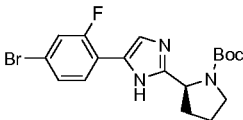
Example 10a.5 (Derived from Example 9a.5)		RT = 2.25 minutes (condition 2); LCMS: Anal. Calcd. For $C_{21}H_{25}BrN_3O_2$: 430.12, 432.12; found: 430.02, 432.02 (M+H).
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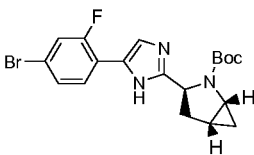
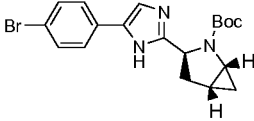
Synthetic route 5.

Example 9b (Prepared described in Example 9.)		RT = 2.2 minutes (condition 1); LCMS: Anal. Calcd. For $C_{15}H_{18}BrNO_5$: 371; found: 371 (M+H).
Example 9b.1		RT = 2.7 minutes (condition 1); LCMS: Anal. Calcd. For

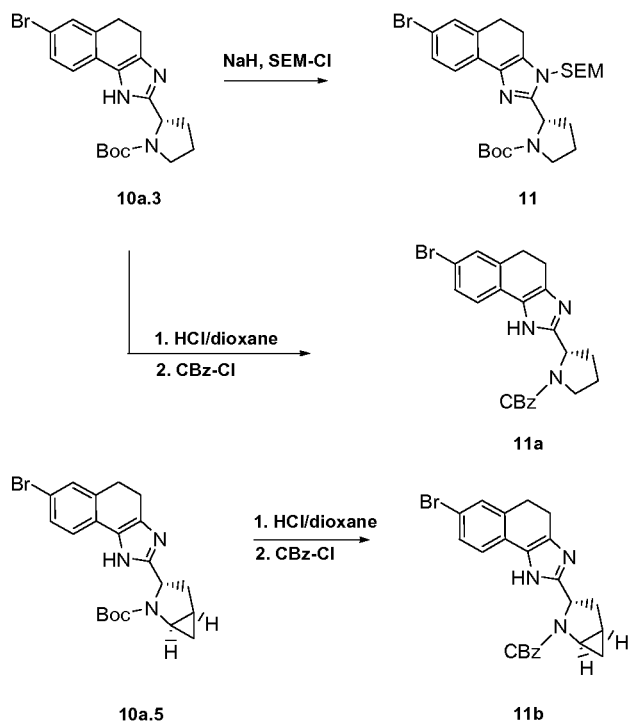
		$C_{16}H_{20}BrNO_5$; 385; found: 385 (M+H).
Example 9b.2 (Derived from Example Example 5b.1)		RT = 1.9 minutes (condition 1); LCMS: Anal. Calcd. For $C_{20}H_{24}BrF_3NO_5$ 494.08; found: 494.03 (M+H).
Example 9b.3 (Derived from Example Example 5b.1 and M.4)		RT = 2.1 minutes (condition 1); LCMS: Anal. Calcd. For $C_{21}H_{24}BrF_3NO_5$ 526.07; found: 525.91 (M+H).
Example 9b.4		RT = 2.2 minutes (condition 1); LCMS: Anal. Calcd. For $C_{21}H_{20}BrNO_5$; 445; found: 445 (M+H).
Example 9b.5		RT = 2.94 minutes (condition 2); LCMS: Anal. Calcd. For $C_{18}H_{22}BrFNO_5$; 452.05, 454.05, 466.05; found: 452.06, 454.06

		(M+Na) .
Example 9b.6 (Derived from Example M.4)		RT = 2.78 minutes (condition 2); LCMS: Anal. Calcd. For C ₁₉ H ₂₁ BrFNO ₅ : 464.05, 466.05; found: 463.92, 465.92 (M+Na) .
Example 9b.7 (Derived from Example M.4)		RT = 2.05 minutes (condition 1); LRMS: Anal. Calcd. For C ₁₉ H ₂₃ BrNO ₅ Na: 446.07; found: 446.08 (M+Na), (M+2).
Example 10b (Derived from Example 9b as described for Example 10)		RT = 1.6 minutes (condition 1); LRMS: Anal. Calcd. For C ₁₇ H ₂₂ BrN ₃ O ₂ : 380.10; found: 379.98 (M+H).
Example 10b.1 (Derived from Example 9b.1)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. For C ₁₆ H ₂₀ BrN ₃ O ₂ : 365; found: 365

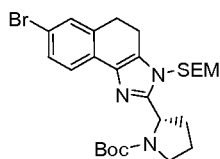
		(M+H).
Example 10b.2 (Derived from Example 9b.2)		RT = 1.66 minutes (condition 1); LCMS: Anal. Calcd. for C ₂₀ H ₂₄ BrF ₃ N ₃ O ₂ 474.10; found: 473.99 (M+H).
Example 10b.3 (Derived from Example 9b.3)		RT = 1.7 minutes (condition 1); LCMS: Anal. Calcd. For C ₂₁ H ₂₄ BrF ₃ N ₃ O ₂ : 486.10; found: 486.10 (M+H).
Example 10b.4 (Derived from Example 9b.4)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. For C ₂₁ H ₂₀ BrN ₃ O ₂ : 426.08; found: 426.09 (M+H).
Example 10b.5 (Derived from Example 9b.5)		RT = 2.27 minutes (condition 2); LCMS: Anal. Calcd. for C ₁₈ H ₂₂ BrFN ₃ O ₂ 410.09; found: 410.08 (M+H).

Example 10b.6 (Derived from Example 9b.6)		RT = 2.15 minutes (condition 2); LCMS: Anal. Calcd. For $C_{19}H_{22}BrFN_3O_2$: 422.09; found: 421.96 (M+H).
Example 10b.7 (Derived from Example 9b.7)		RT = 1.58 minutes (condition 1); LCMS: Anal. Calcd. For $C_{19}H_{23}BrN_3O_2$: 404.10; found: 404.09 (M+H).

Synthetic route 6.

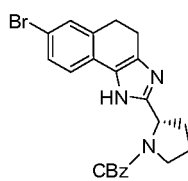


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11

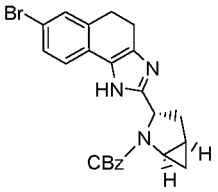
Unwashed 60% sodium hydride (54 mg, 1.35 mmol) was added in one portion to a stirred solution of Example 10a.3 (565 mg, 1.35 mmol) in dry DMF (10 mL) under nitrogen. The mixture was stirred 5 min before addition of SEM-Cl (0.24 mL, 1.35 mmol), stirred for 3 h, quenched with sat'd ammonium chloride (1 mL), diluted with EtOAc (50 mL), and the organic phase was washed with sat'd NaHCO₃ solution and brine. The aqueous phase was extracted twice more with EtOAc and combined with the initial organic extract prior to drying. Concentration gave a residue applied which was applied (CH₂Cl₂) to a 40 (S) Biotage[®] silica gel cartridge. Segment 1. Hold 15% B for 75 mL; Segment 2. Gradient elution from 15% to 50% B over 750 mL; Segment 3: 50-100%B over 750 mL (A = hex; B = EtOAc) B to give regioisomeric products Example 11, 497 mg (67 %). RT = 3.0 minutes (condition 2). ¹H NMR (500 MHz, DMSO-d₆) δ 7.42-7.35 (m, 3H), 5.65/5.39 (d, *J* = 11.6 Hz, 1H), 5.29-5.27 (m, 1H), 5.00/4.93 (s, 1H), 3.54-3.51 (m, 3H), 3.43-3.41 (m, 1H), 3.02-2.99 (m, 2H), 2.89-2.81 (m, 1H), 2.29-2.08 (m, 2H), 1.95 -1.84 (m, 2H), 1.37/1.13 (s, 9H), 0.89-0.86 (m, 2H), -0.02 (s, 9H). LRMS: Anal. Calcd. for C₂₆H₃₉BrN₃O₃Si: 548.19; found: 548.23 (M+H).



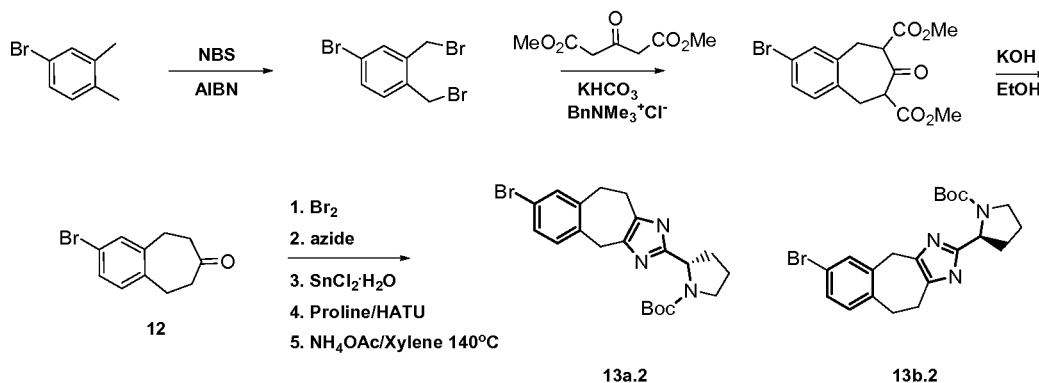
11a

Cold 4N HCl in dioxane (0.871 mL, 3.49 mmol) was added to a solution of 10a.3 (1R,3S,5R)-tert-butyl 3-(7-bromo-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1.5 g, 3.49 mmol) in MeOH (20 mL) and the reaction was stirred for 2h at room temperature. Concentration yielded a tan solid which was taken up in dioxane (20 mL) / water (20 mL) and cooled to 0°C. Na₂CO₃ (0.369 g, 3.49 mmol) and CBz-Cl (0.498 mL, 3.49 mmol) were added and the reaction mixture was stirred as it warmed to room temperature over 5h before

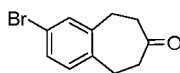
being partitioned between EtOAc and sat'd NaHCO₃ soln. The organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was charged (CH₂Cl₂) to a 110 g Thompson[®] silica gel cartridge and eluted 20% - 100% B over 1.5 L (A/B = hexanes/EtOAc). The combined yield of 11a (1R,3S,5R)-benzyl 3-(7-bromo-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]
 5 hexane-2-carboxylate from three fractions of various purities was 1.4 g (75%).
 LCMS Calcd for C₂₄H₂₃BrN₃O₂ (M+H)⁺ 464.10 and 466.10; found: 463.95 and 465.98.

Example 11b (Derived from Example 10a.5)		RT = 2.01 minutes (condition 2); LCMS: Anal. Calcd. For C ₂₄ H ₂₃ BrN ₃ O ₂ : 464.10, 466.10; found: 464.11, 466.11 (M+H) ⁺ .
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10 *Synthetic route 7.*



Reference: *J.Chem.Soc. Perkin Trans 2* (1993) p 1305.



12

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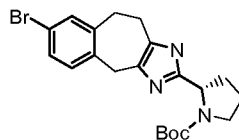
AIBN (98 mg, 0.59 mmol) was added to 4-bromo-1,2-dimethylbenzene (11 g, 59.4 mmol) and freshly recrystallized N-bromosuccinimide (21.1 g, 119 mmol) in CCl₄ (50 ml). The reaction mixture was heated at reflux for 2 hours under nitrogen.

After being cooled to room temperature, the solution was filtered and concentrated by rotary evaporation to give 21 g of a mixture containing approximately (75%) 4-bromo-1,2-bis(bromomethyl)benzene along with 3-bromo-1,2-bis(bromomethyl)benzene. [NOTE: The starting material was contaminated with
5 25% 3-bromo-1,2-dimethylbenzene]. RT = 2.2/2.3 min (condition 1).

The crude mixture of 4- and 3-bromo-1,2-bis(bromomethyl)benzene (21 g) was taken up in CH₂Cl₂ (313 ml) and dimethyl 3-oxopentanedioate (12.8 g, 73.5 mmol) was added and the solution was diluted with a 20% solution of KHCO₃ (64 g, 0.64 mol) in water (250 ml). Phase transfer catalyst benzyltrimethylammonium
10 chloride (1.7 g, 9.19 mmol) was added and the reaction mixture was stirred 18h under nitrogen at 50 °C. After separation of the organic phase, the aqueous phase was extracted with CH₂Cl₂ and the combined organic layers were washed with brine. Concentration gave 23 g of a complex mixture (both regio isomers and ester diastereomers) containing dimethyl 2-bromo-7-oxo-6,7,8,9-tetrahydro-5H-
15 benzo[7]annulene-6,8-dicarboxylate which was carried forward without purification. RT = 1.87 min (condition 1); LCMS: Anal. Calcd. for C₁₅H₁₅BrO₅: 377.01; found 377.05 [M+Na].

The 23 g mixture of crude dimethyl 2-bromo-7-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-6,8-dicarboxylate (contained ~ 8g, 22.5 mmol) was placed in a 1 L
20 round-bottomed flask fitted with a reflux condenser and dissolved in ethanol (250 ml). A solution of KOH (8.8 g, 0.23 mol) dissolved in water (250 ml) was added and the initially tan suspension turned black upon heating at reflux for 16 hours. The reaction mixture was poured onto EtOAc (1 vol) and the organic phase separated. Brine (1/4 vol) was added to the aqueous layer which was extracted with EtOAc, and
25 the combined organic layers were washed with brine. After being concentrated by rotary evaporation, the residue was charged (CH₂Cl₂) to a 40 (M) Biotage[®] silica gel column (apply vacuum from beneath column to aid adsorption) and gradient eluted 10-100% B (A = Hexanes; B = EtOAc) to give a 4:1 mixture of bromides which favored Example 12, 2-bromo-8,9-dihydro-5H-benzo[7]annulen-7(6H)-one and
30 contained 1-bromo-8,9-dihydro-5H-benzo[7]annulen-7(6H)-one, 8.3 g (61%). The mixture was carried forward without further purification, but a pure sample of Example 12 was obtained upon crystallization by allowing the mixture to stand for 3 weeks at -5°C. ¹H NMR (500 MHz, CDCl₃) δ 7.37 (d, *J* = 2.1 Hz, 1H), 7.33 (dd, *J* =

7.9, 2.1 Hz, 1H), 7.09 (d, $J = 7.9$ Hz, 1H), 2.87-2.84 (m, 4H), 2.61-2.57 (m, 4H). RT = 1.96 minutes (condition 1). LCMS: Anal. Calcd. for $C_{11}H_{11}BrO$: 239.0; found: 239.04 (M+H).



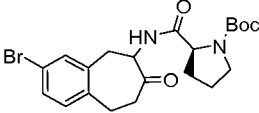
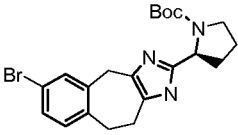
13a.2

5 Bromine (1.4 mL, 26.8 mmol) was added to a solution of the 4:1 mixture, respectively, of 2- and 1-bromo-8,9-dihydro-5H-benzo[7]annulen-7(6H)-one (6.4 g, 26.8 mmol) in diethyl ether (250 mL). The reaction was stirred for 4 h, concentrated, and the crude α -bromo ketones were taken up in acetonitrile (200 mL). Sodium
10 azide (1.7 g, 26.8 mmol) was added and the reaction was stirred 16 h before being concentrated. The residue was partitioned between EtOAc and sat'd $NaHCO_3$ soln, and the organic layer was washed with water, brine, and concentrated. RT = 2.0 minutes (broad peak, condition 1).

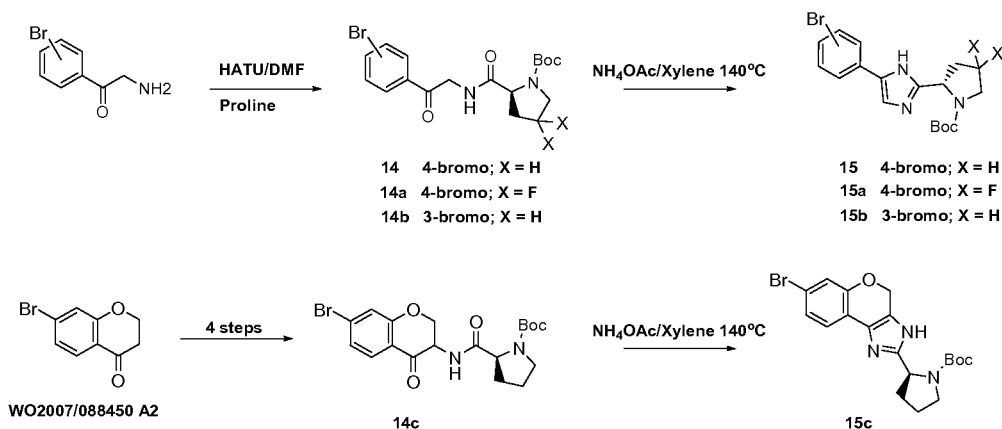
The crude α -keto azides were dissolved in CH_3OH (350 mL) and tin (II) chloride dihydrate (13.2 g, 69.6 mmol) added and the reaction mixture was stirred for
15 3.5 hours at 65 °C, concentrated by rotory evaporation, and dried under high vacuum for 18 hours.

The crude α -amino ketones were taken up in DMF (300 mL), Hunig's base (24.41 g, 189 mmol), (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (4.07 g, 18.89 mmol), and HATU (7.18 g, 18.89 mmol) was added in one portion with
20 vigorous stirring. After 8 hours the reaction was concentrated to 1/3 volume *in vacuo*, and partitioned between EtOAc (1 L) and 0.1N HCl (150 mL). The tin salts were removed by filtration through diatomaceous earth (Celite[®]), and the organic layer was washed with brine and concentrated. The crude product was charged (CH_2Cl_2) to a 40M Biotage[®] silica gel cartridge (divided into two runs). Gradient
25 elution from 15% to 100% B over 1.5 L (A = Hexanes; B = Ethyl Acetate) to give Examples 13a.1 and 13b.1 (3.8 g, 35.7% combined yield) each as a mixture of diastereomers. Example 13a.1: RT = 1.58/1.51 min (condition 5). LCMS: Anal. Calcd. for $C_{21}H_{27}BrN_2O_4$: 451.12; found: 450.87 (M+H).

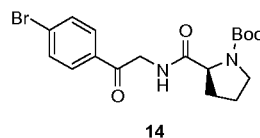
Ammonium acetate (4.4 g, 73.1 mmol) was added to a solution of the amides 13a.1 and 13b.1 (3.3 g, 7.31 mmol) in xylene (75 mL) and stirred in a pressure vessel heated at 140 °C for 4 hours. After being cooled, the reaction mixture was diluted with EtOAc (500 mL), washed with sat'd NaHCO₃, brine, and the organic phase was concentrated. The crude product was charged (CH₂Cl₂) to a 40S Biotage[®] silica gel cartridge. Gradient elution from 15% to 100% B over 750 mL (A = CH₂Cl₂; B = EtOAc) gave 2.49 g of a mixture that was subjected to a second chromatography; 40S Biotage[®] silica gel cartridge, elution 5% - 80% B over 1L (A = 1:1 Hex/CH₂Cl₂; B = 10% CH₃OH/EtOAc) and provided a mixture of Examples 13a.2 and 13b.2, 1.1 g (34.8%). A sample of the product was applied to semi-prep normal phase HPLC (Chiralcel OD Column, 20x250mm, 10um; 98:2 Heptane/EtOH @ 10 mL/min; UV 220/254 nm) and collect Example 13a.2 eluting at 35-36 min. ¹H NMR (500 MHz, CD₃OD) δ 7.44 (s, 1H), 7.28 (dd, *J* = 7.9, 2.1 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 4.73-4.69 (m, 1H), 3.91 (s, 2H), 3.64-3.61 (m, 1H), 3.48-3.44 (m, 1H), 3.09 (t, *J* = 4.6 Hz, 2H), 2.80 (t, *J* = 5.8 Hz, 2H), 2.31-2.11 (m, 1H), 2.01-1.88 (m, 3H), 1.46/1.48 (s, 9H). RT = 1.7 minutes (condition 1). HRMS: Anal. Calcd. for C₂₁H₂₆BrN₃O₂: 432.1281; found: 432.1268 (M+H).

Example 13b.1		RT = 1.59 minutes (condition 5); LCMS: Anal. Calcd. for C ₂₁ H ₂₇ BrN ₂ O ₄ : 451.12; found: 450.98 (M+H).
Example 13b.2		RT = 1.7 minutes (condition 1). LCMS: Anal. Calcd. for C ₂₁ H ₂₆ BrN ₃ O ₂ : 432; found: 432 (M+H).

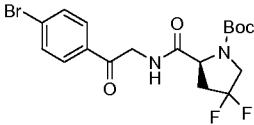
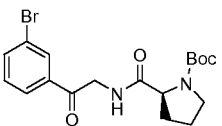
Synthetic route 8.



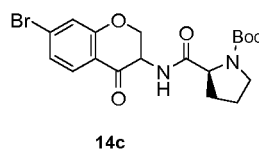
Example 14



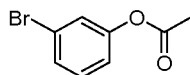
- 5 N,N-Diisopropylethylamine (18 mL, 103.3 mmol) was added dropwise, over
 15 minutes, to a heterogeneous mixture of N-Boc-L-proline (7.139 g, 33.17 mmol),
 HATU (13.324 g, 35.04 mmol), the HCl salt of 2-amino-1-(4-bromo-
 phenyl)ethanone (8.127 g, 32.44 mmol), in DMF (105 mL) and stirred at ambient
 condition for 55 minutes. DMF was removed *in vacuo*, and the resulting residue was
 10 partitioned between ethyl acetate (300 mL) and water (200 mL). The organic layer
 was washed with water (200 mL) and brine, dried (MgSO₄), filtered, and
 concentrated. A silica gel mesh was prepared from the residue and submitted to flash
 chromatography (silica gel; 50-60 % ethyl acetate/hexanes) to provide Example 14,
 (S)-tert-butyl 2-(2-(4-bromophenyl)-2-oxoethylcarbamoyl)pyrrolidine-1-carboxylate
 15 as a white solid (12.8 g). ¹H NMR (DMSO-d₆, δ = 2.5 ppm, 400 MHz): δ 8.25-8.14
 (m, 1H), 7.92 (br d, *J* = 8.0, 2H), 7.75 (br d, *J* = 8.6, 2H), 4.61 (dd, *J* = 18.3, 5.7,
 1H), 4.53 (dd, *J* = 18.1, 5.6, 1H), 4.22-4.12 (m, 1H), 3.43-3.35 (m, 1H), 3.30-3.23
 (m, 1H), 2.18-2.20 (m, 1H), 1.90-1.70 (m, 3H), 1.40/1.34 (two app br s, 9H). RT =
 1.70 min (condition 1); LCMS: Anal. Calcd. for C₁₈H₂₃BrN₂NaO₄: 433.07; found
 20 433.09 [M+Na]⁺.

Example 14a		RT = 1.59 minutes (condition 4); LCMS: Anal. Calcd. for $C_{18}H_{21}BrF_2N_2O_4$: 446.06; found: 445.43 (M-H)-.
Example 14b		LCMS: Anal. Calcd. for $C_{18}H_{23}BrN_2O_4$: (M+Na)+ = 433.08; found: 433.12

Example 14c



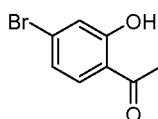
Example 14c; step 1:



5

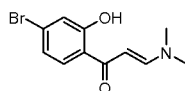
Acetyl chloride (10.2 mL, 144 mmol) was added in a dropwise manner over 1 h to a cold (ice bath) solution of 3-bromophenol (25 g, 144 mmol) and pyridine (10.8 mL, 144 mmol) in dichloromethane (100 mL), and the reaction was stirred 18 hr at room temperature. Water (150 mL) was added and the organic layer was extracted with dichloromethane. The combined organic layers were washed with 2.5N NaHSO₄, 3N NaOH, water, brine, and dried over Na₂SO₄, and filtered. Concentration gave the 3-bromophenyl acetate as a pink liquid (28 g, 96%). GC-MS data: 214 (M⁺); ¹H NMR (DMSO-d₆): 7.37-7.39 (d, 1H), 7.26-7.30 (m, 2H), 7.04-7.07 (t, 1H), 2.30 (s, 3H).

15 Example 14c; step 2:



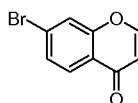
3-Bromophenyl acetate (36 g, 167 mmol) and anhydrous AlCl_3 (33.5g, 251 mmol) were heated at 140-150 °C for 2 hrs. After cooling, 5% HCl soln (100ml) was added and the mixture was heated (steam bath) until solid materials dissolved. A brown oil separated and was extracted into dichloromethane. To the extract was
5 added 5N NaOH (300 mL) and enough water to dissolve the resulting precipitate. The aqueous layer was separated, acidified (pH 2.0), and extracted with ethyl acetate. The extract was dried over Na_2SO_4 , filtered, and concentrated to give 1-(4-bromo-2-hydroxyphenyl)ethanone the crystals (35.8 g, 99%). GC-MS (214 M^+); ^1H NMR (DMSO- d_6) 11.99 (s, 1H, OH), 7.77-7.80 (d, 1H), 7.20 (s, 1H), 7.13-7.15 (dd, 1H),
10 2.6 (s, 3H).

Example 14c; step 3:



To 1-(4-bromo-2-hydroxyphenyl)ethanone (35.8g, 167 mmol) in dry benzene (800 mL) was added N,N-dimethylformamide dimethylacetal (44 mL, 333 mmol)
15 and the solution was heated at reflux for 4 hrs and concentrated to dryness. The resulting residue was dissolved in dichloromethane (300 mL) and filtered over SiO_2 . The organic layer was concentrated to afford (E)-1-(4-bromo-2-hydroxyphenyl)-3-(dimethylamino)prop-2-en-1-one as a bright yellow solid (31.9 g, 71%). LCMS 270 ($\text{M}+\text{H}$); ^1H NMR (DMSO- d_6) 14.96 (s, 1H), 7.86-7.94 (m, 2H), 6.96-7.02 (dd, 2H),
20 5.92-5.96 (d, 1H), 3.32 (s, 3H), 3.20 (s, 3H).

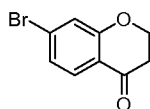
Example 14c; step 4:



Conc. HCl (100 mL) was added to a solution of (E)-1-(4-bromo-2-hydroxyphenyl)-3-(dimethylamino)prop-2-en-1-one (31.9 g, 118 mmol) in
25 dichloromethane (900 mL) and the reaction mixture was heated at reflux 40 min with vigorous stirring. After being cooled to room temperature, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with 3M potassium carbonate soln, water, and dried over Na_2SO_4 . Filtration and concentration gave 7-bromo-4H-chromen-4-one as a pale

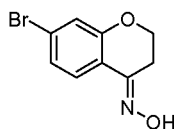
yellow solid. LCMS 224.9 (M+H); ¹H NMR (DMSO-d₆) 8.29-8.31 (d, 1H), 7.92-7.99 (m, 2H), 7.64-7.66 (dd, 1H), 6.37-6.39 (d, 1H).

Example 14c; step 5:



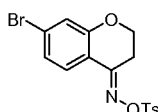
- 5 A solution of 7-bromo-4H-chromen-4-one (26 g, 116 mmol) in dry THF (500 mL) under nitrogen for 1 hr, cooled to -80 °C, and 173 mL of diisobutylaluminium hydride (2M in Toluene) was added over 30 minutes. The reaction was stirred at the same temperature for 30 min, quenched with a SiO₂ (52g) / water (52mL) suspension, and allowed to warm to 0 °C. The solution was filtered, the SiO₂ washed with
- 10 EtOAc, and the combined filtrate was concentrated to dryness. The residue was dissolved in CHCl₃ (400 mL), washed with 1N NaOH (300 mL), dried over Na₂SO₄ and concentrated. Purification by chromatography on SiO₂ (60-120 mesh) EtOAc/Pet ether (gradient elution 0-15%) afforded 7-bromochroman-4-one 18.1 g (69%) a pale yellow solid. LCMS 229.0 (M+2H); ¹H NMR (DMSO-d₆) 7.64-7.67
- 15 (d, 1H), 7.32 (s, 1H), 7.22-7.25(d, 1H), 4.53-4.57 (t, 2H), 2.76-2.80 (t, 2H).

Example 14c; step 6:



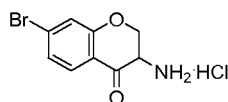
- NaOAc (3.78 g, 46.2 mmol) in H₂O (30 mL) was added to a soln of 7-bromo 4-chromanone (3.5 g, 15.4 mmol) and hydroxyl-amine hydrochloride (1.75 g, 23.1
- 20 mmol) in EtOH (70 ml). The reaction was heated at reflux for 2 h, cooled to room temperature, and concentrated. The residue was diluted with H₂O and a precipitate was filtered to give 7-bromochroman-4-one oxime obtained as the needle like crystals 3.5g (98%). LCMS 244 (M+2H) RT = 1.7 min (Condition 2); ¹H NMR (DMSO-d₆) 11.37 (s, OH, 1H), 7.76-7.70 (d, 1H), 7.09-7.13 (d, 2H), 4.16- 4.20 (t,
- 25 2H), 2.79-2.83 (t, 2H).

Example 14c; step 7:



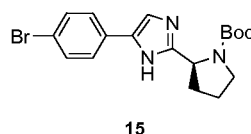
p-Toluenesulfonic anhydride (5 g, 16 mmol) was added to a solution of 7-bromochroman-4-one oxime (3.5g, 14.46 mmol) and triethylamine (2.4ml, 17.35 mmol) in dichloromethane (125 ml). The mixture was stirred for 3 h at room temperature and washed with water, brine, and dried (Na₂SO₄). Filtration and concentration under reduced pressure to afforded 7-bromochroman-4-one-O-p-toluenesulfoxime 5.5 g (96 %) as an off-white solid which was used without further purification. LCMS 398 (M+2H) RT = 1.92 min (Condition 1). ¹H NMR (DMSO-d₆) 7.89-7.91 (d, 2H), 7.56-7.58 (d, 1H), 7.48-7.50 (d, 2H), 7.22 (s, 1H), 7.16-7.18 (d, 1H), 4.20-4.23 (t, 2H), 2.97-3.00 (t, 2H), 2.40 (s, 1H).

Example 14c; step 8:



A solution of potassium ethoxide (1.27 g, 15.11 mmol) in ethanol (35 ml) was added to a solution of 7-bromochroman-4-one-O-p-toluenesulfoxime (5.7 g, 14.3 mmol) in toluene (60 ml) and the mixture was stirred for 15 h at room temperature. A precipitate (potassium tosylate) was removed by filtration and washed with diethyl ether. To the combined filtrates was added 3N HCl (20 ml) in methanol and the solution was stirred 2 h at room temperature to form the HCl salt. After removal of the solvent, the residue was triturated with diethyl ether. The resulting solid was filtered, washed with ether, and dried to afford 7-bromo-3-amino-chroman-4-one hydrochloride 2.8 g, (80 %) as off-white power. LCMS 244 (M+2H) RT = 3.77 (Condition 2); ¹H NMR (DMSO-d₆) 8.79 (bs, 2H), 7.71-7.74 (d, 1H), 7.45 (s, 1H), 7.34-7.37 (d, 1H), 4.67-4.80 (m, 2H), 4.43-4.51 (t, 1H).

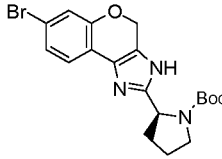
Example 14c (Prepared as described in Example 14, and derived from product of step 8)		RT = 1.76 minutes (condition 2); LCMS: Anal. Calcd. for C₁₉H₂₄BrN₂O₅: 439.09; found: 439 (M+H)
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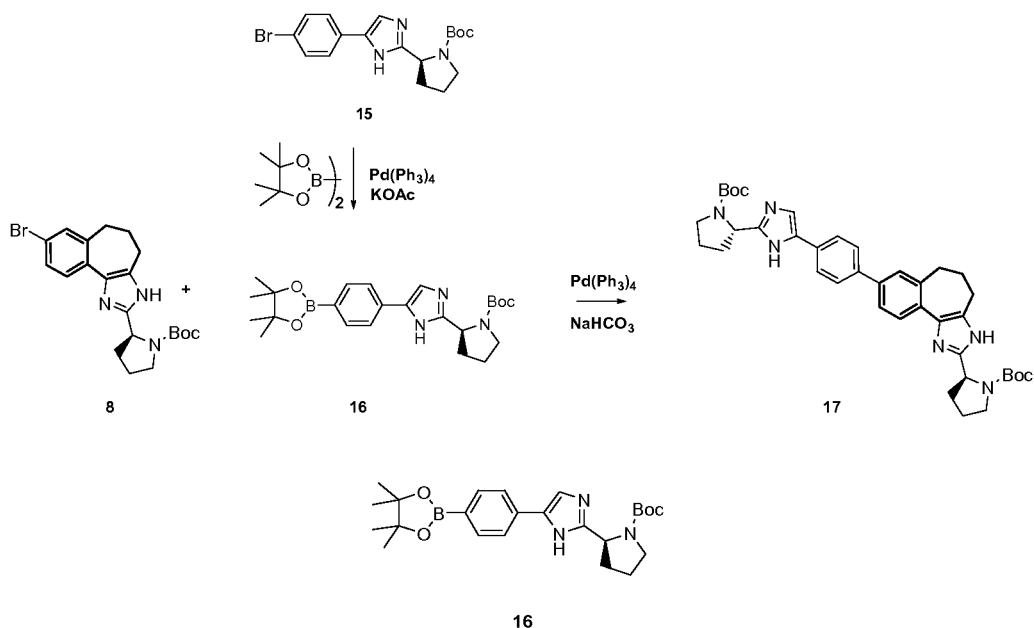
A mixture Example 14, (S)-tert-butyl 2-(2-(4-bromophenyl)-2-oxoethylcarbamoyl)-pyrrolidine-1-carboxylate (12.8 g, 31.12 mmol) and NH_4OAc (12.0 g, 155.7 mmol) in xylenes (155 mL) was heated in a sealed tube at 140 °C for 2 hours. The volatile component was removed *in vacuo*, and the residue was partitioned carefully between ethyl acetate and water, whereby enough saturated NaHCO_3 solution was added so as to make the pH of the aqueous phase slightly basic after the shaking of the biphasic system. The layers were separated, and the aqueous layer was extracted with an additional ethyl acetate. The combined organic phase was washed with brine, dried (MgSO_4), filtered, and concentrated. The resulting material was recrystallized from ethyl acetate/hexanes to provide two crops of Example 15, (S)-tert-butyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate 5.85 g. The mother liquor was concentrated *in vacuo* and submitted to a flash chromatography (silica gel; 30% ethyl acetate/hexanes) to provide an additional 2.23 g. ^1H NMR (DMSO-d_6 , δ = 2.5 ppm, 400 MHz): δ 12.17/11.92/11.86 (m, 1H), 7.72-7.46/7.28 (m, 5H), 4.86-4.70 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.30-1.75 (m, 4H), 1.40/1.15 (app br s, 9H). RT = 1.71 min (condition 1); LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{18}\text{H}_{23}\text{BrN}_3\text{O}_2$: 392.10; found 391.96; HRMS: Anal. Calcd. for $\text{C}_{18}\text{H}_{23}\text{BrN}_3\text{O}_2$: 392.0974; found 392.0959 $[\text{M}+\text{H}]$.

20

Example 15a (Derived from Example 14a)		RT = 1.59 minutes (condition 4); LRMS: Anal. Calcd. for $\text{C}_{18}\text{H}_{20}\text{BrF}_2\text{N}_3\text{O}_2$: 428.27; found: 428.02 (M+H).
Example 15b (Derived from Example 14b)		LRMS Anal. Calcd. for $\text{C}_{18}\text{H}_{22}\text{BrN}_3\text{O}_2$: 392.10; found: 391.96 (M+H).

Example 15c (Derived from Example 14c)		RT = 1.6 min (condition 1); LCMS: Anal. Calcd. for C₁₉H₂₂BrN₃O₃: 420.33; found 422.2 (M+2H).
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Synthetic route 9.

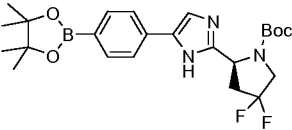
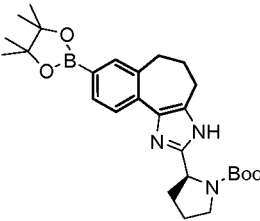
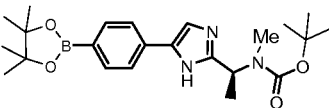
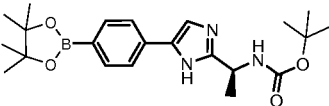


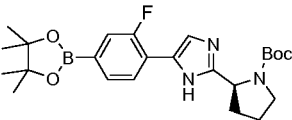
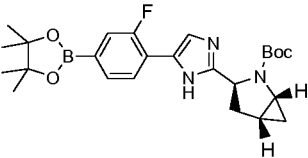
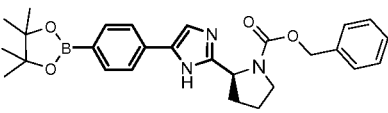
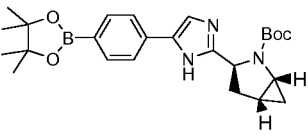
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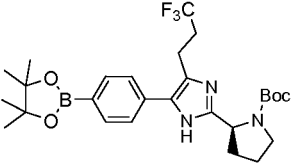
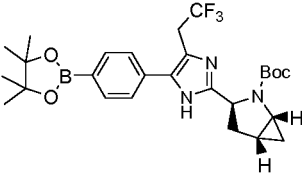
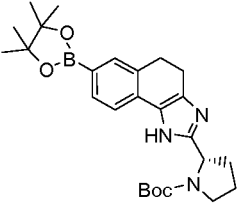
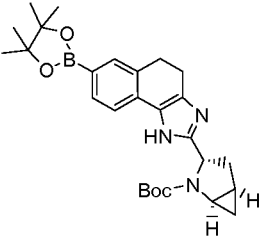
16

- Pd(Ph₃P)₄ (469 mg, 0.406 mmol) was added to a screw cap pressure tube containing a mixture of Example 15, (S)-tert-butyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (4 g, 10.22 mmol), bis(pinacolato)diboron (5.4 g, 21.35 mmol), potassium acetate (2.6 g, 26.21 mmol) and 1,4-dioxane (80 mL).
- The reaction flask was purged with nitrogen, capped and heated (oil bath 80°C) for 16 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was partitioned carefully between CH₂Cl₂ (150 mL) and an aqueous medium (50 mL water + 10 mL saturated NaHCO₃ solution). The aqueous layer was extracted with CH₂Cl₂, and the combined organic phase was dried (MgSO₄), filtered, and concentrated *in vacuo*. The resulting material was purified with flash chromatography (sample was loaded with eluting solvent; 20-35% ethyl acetate/CH₂Cl₂) to provide Example 16, (S)-tert-butyl 2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate,

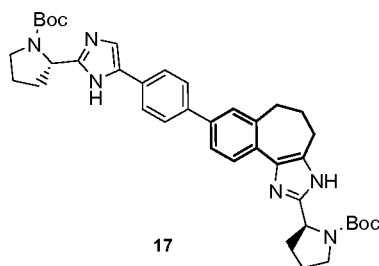
contaminated with pinacol, as an off-white dense solid; the relative mole ratio of Example 16 to pinacol was about 10:1 (^1H NMR). The sample weighed 3.9 g after ~2.5 days exposure to high vacuum. ^1H NMR (DMSO- d_6 , δ = 2.5 ppm, 400 MHz): 12.22/11.94/ 11.87 (m, 1H), 7.79-7.50/ 7.34-7.27 (m, 5H), 4.86-4.70 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.27-1.77 (m, 4H), 1.45-1.10 (m, 21H). RT = 1.64 min (condition 1); LC/MS: Anal. Calcd. for $[\text{M}+\text{H}]$ $\text{C}_{24}\text{H}_{35}\text{BN}_3\text{O}_4$: 440.27; found 440.23.

Example 16a (Derived from Example 15a)		RT = 1.62 minutes (condition 3); LCMS: Anal. Calcd. for $\text{C}_{34}\text{H}_{32}\text{BF}_2\text{N}_3\text{O}_4$: 475.34; found: 474.78 (M-H).
Example 16b (Derived from Example 8)		RT = 1.9 minutes (condition 1); LCMS: Anal. Calcd. for $\text{C}_{27}\text{H}_{38}\text{BN}_3\text{O}_4$: 497.3; found: 479 (M+H).
Example 16c (Derived from Example 10b).		RT = 1.83 minutes (condition 1); LCMS: Anal. Calcd. for $\text{C}_{23}\text{H}_{34}\text{BN}_3\text{O}_4$ 427; found: 427 (M+H).
Example 16d (Derived from Example 10b.1)		RT = 1.84 minutes (condition 1); LCMS: Anal. Calcd. for

		$C_{22}H_{32}BN_3O_4$ 413; found: 414 (M+H).
Example 16e (Derived from Example 10b.5)		RT = 2.62 minutes (condition 2); LRMS: Anal. Calcd. for $C_{24}H_{34}BFN_3O_4$ 458.26; found: 458.23 (M+H).
Example 16e.1 (Derived from Example 10b.6)		RT = 2.46 minutes (condition 2); LRMS: Anal. Calcd. for $C_{25}H_{34}BFN_3O_4$ 470.26; found: 470.19 (M+H).
Example 16f (Derived from Example 10b.4)		RT = 1.84 minutes (condition 2); LCMS: Anal. Calcd. for $C_{27}H_{32}BN_3O_4$ 473; found: 474 (M+H).
Example 16g (Derived from Example 10b.7)		RT = 1.59 minutes (condition 1); LCMS: Anal. Calcd. for $C_{25}H_{35}BN_3O_4$ 452.27; found: 452.23 (M+H).

Example 16h (Derived from Example 8c)		RT = 1.9 minutes (condition 1); LCMS: Anal. Calcd. for $C_{27}H_{38}BF_3N_3O_4$ 536.29; found: 536.37 (M+H).
Example 16i (Derived from Example 10b.3)		RT = 1.9 minutes (condition 1); LCMS: Anal. Calcd. for $C_{27}H_{36}BF_3N_3O_4$ 534.27; found: 534.21 (M+H)⁺.
Example 16j (Derived from Example 10a.3)		RT = 2.46 minutes (condition 2); LRMS: Anal. Calcd. for $C_{26}H_{37}BN_3O_4$ 466.29; found: 466.27 (M+H)⁺.
Example 16k (Derived from Example 10a.5)		RT = 2.48 minutes (condition 2); LRMS: Anal. Calcd. for $C_{27}H_{37}BN_3O_4$ 478.29; found: 478.27 (M+H)⁺.

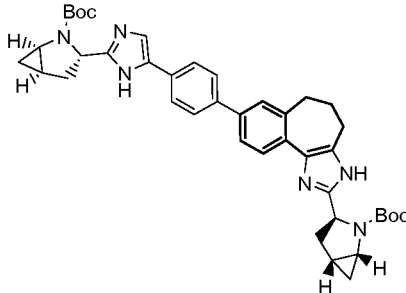
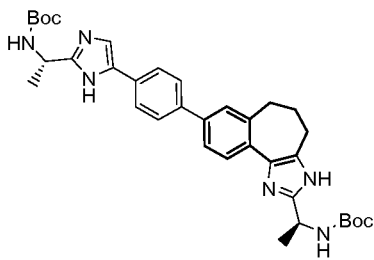
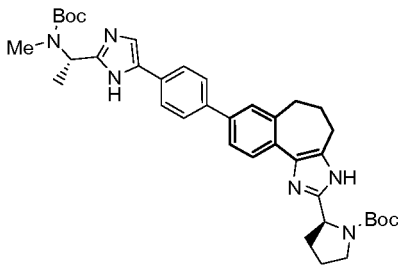
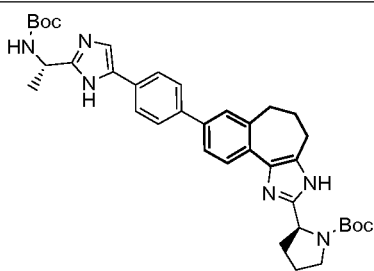
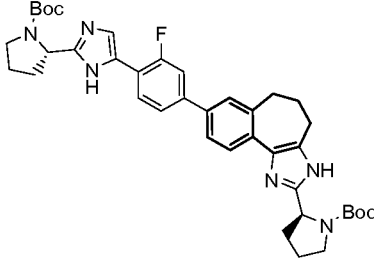
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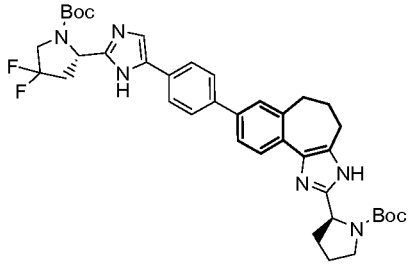
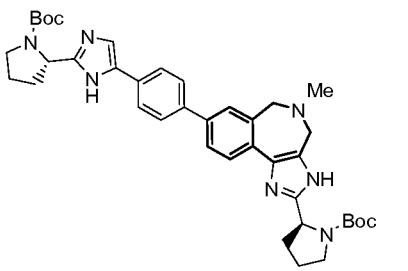
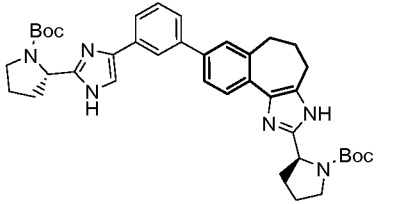
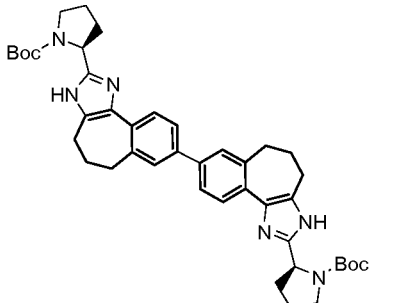
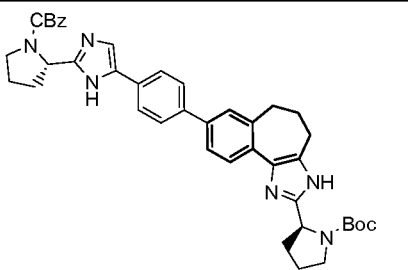


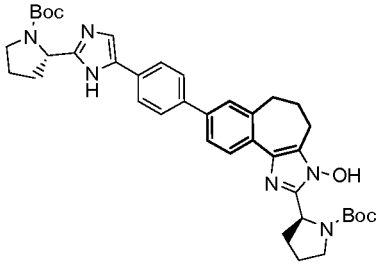
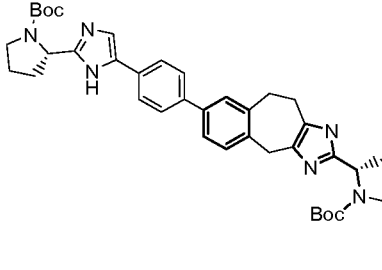
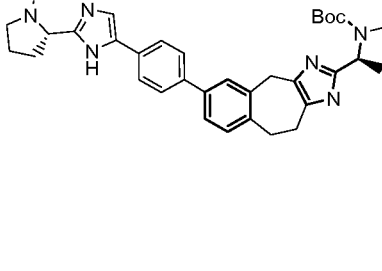
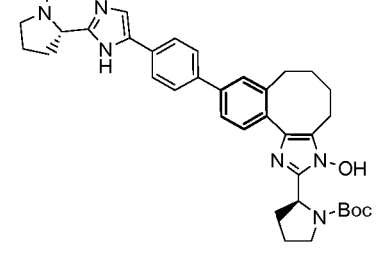
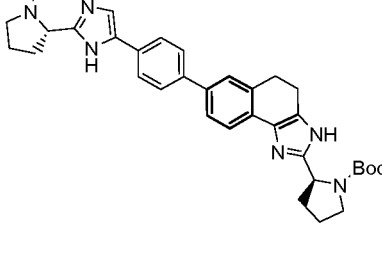
Example 8, (950 mg, 2.19 mmol); Example 16, (S)-tert-butyl 2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (965 mg, 2.2 mmol), and NaHCO₃ (462 mg, 5.5 mmol) were dissolved in 1,2-dimethoxyethane (25 mL) and water (4 mL) was added. The reaction mixture was evacuated and flushed with nitrogen (3x), Pd(Ph₃P)₄ (127 mg, 0.11 mmol) was added, and the mixture heated (oil bath at 80°C) in a capped 100 mL pressure vessel for 8 hours. Additional catalyst (35 mg) was added and heating continued for 16 hours. After being cooled, the solution was partitioned in EtOAc/water and the organic layer washed with brine. The crude product was applied (CH₂Cl₂) to a 40 (S) Biotage[®] silica gel column, and gradient eluted from 20-100% B (A = CH₂Cl₂; B = EtOAc) over 1 L gave Example 17, 680 mg (49%). ¹H NMR (300 MHz, DMSO-d₆) δ 8.05 (br s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.53-7.45 (m, 3H), 4.86-4.70 (m, 2H), 3.57-3.51 (m, 2H), 3.17 - 3.16 (m, 2H), 2.89-2.85 (m, 4H), 2.27-2.18 (m, 2H), 1.99-1.83 (m, 8H), 1.40/1.16 (s, 9H). RT = 1.7 minutes (condition 1). LRMS: Anal. Calcd. for C₃₉H₄₈N₆O₄: 665.38; found: 665.39 (M+H). HRMS: Anal. Calcd. for C₃₉H₄₈N₆O₄: 665.3815; found: 665.33845 (M+H).

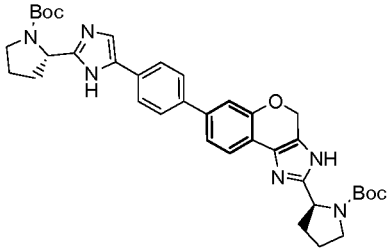
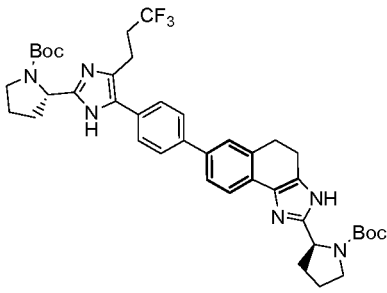
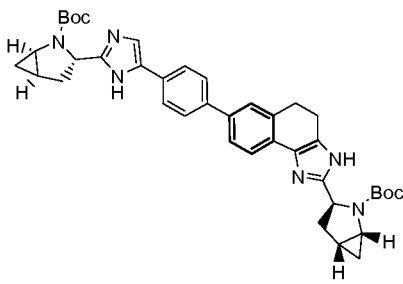
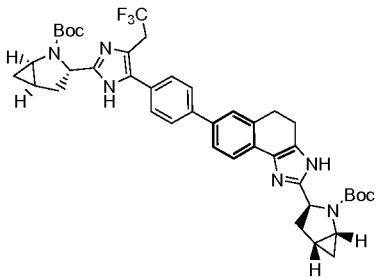
Example 17a (Derived from Example 16 and Example 8b)		RT = 2.38 minutes (Condition 2) LCMS: Anal. Calcd. for C₃₈H₄₆N₆O₅: 666.80; found: 665.2 (M-H).
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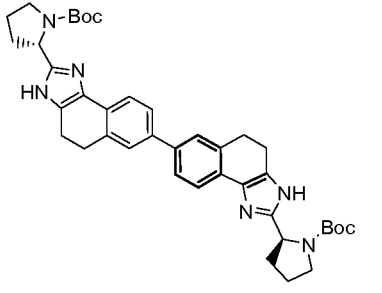
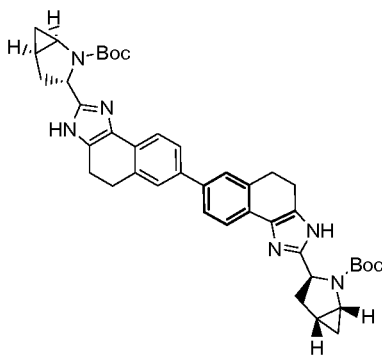
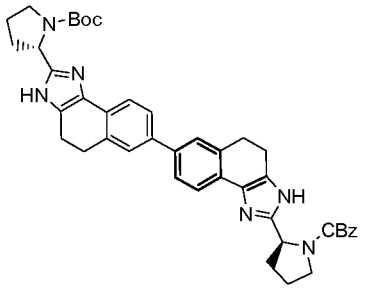
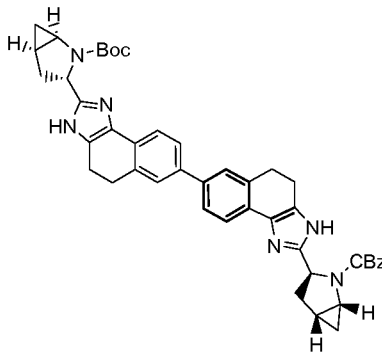
Example 17a.1 (Derived from Example 16b and Example 10b.2)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{41}H_{50}F_3N_6O_4$: 747.38; found: 747.33 (M+H).
Example 17a.2 (Derived from Example 16b and Example 8c)		RT = 1.7 minutes (condition 1); HRMS: Anal. Calcd. for $C_{42}H_{52}F_3N_6O_4$: 761.3997; found: 761.4005 (M+H).
Example 17b (Derived from Example 16 and Example 10)		RT = 1.8 minutes (condition 1); LRMS: Anal. Calcd. for $C_{38}H_{48}N_6O_4$: 675.37; found: 675.35 (M+Na).
Example 17b.1 (Derived from Example 16 and Example 10a.1)		RT = 1.65 minutes (Condition 1) LCMS: Anal. Calcd. for $C_{37}H_{46}N_6O_5$: 654.82; found: 655.4 (M+H).
Example 17c (Derived from Example 16 and Example 10a)		RT = 1.8 minutes (condition 1); LRMS: Anal. Calcd. for $C_{37}H_{46}N_6O_4$: 639.37; found: 639.32 (M+H).

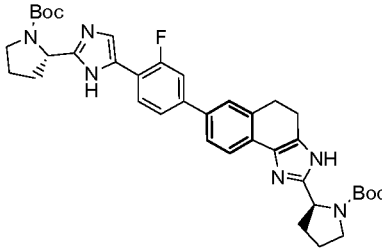
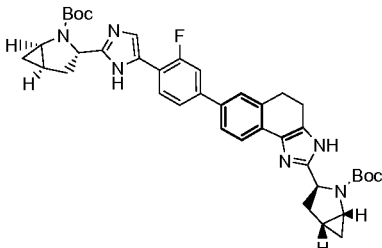
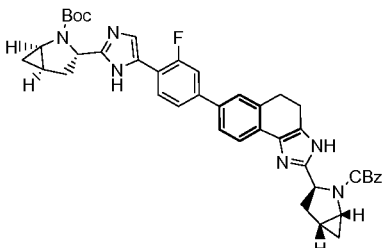
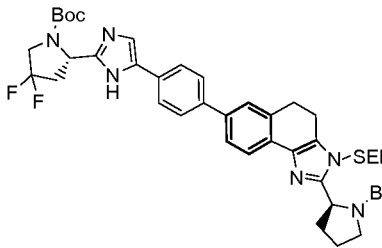
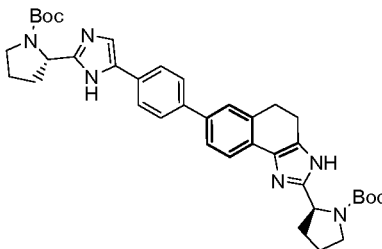
Example 17c.1 (Derived from Example 16g and Example 10a.2)		RT = 1.6 minutes (condition 1); LRMS: Anal. Calcd. for $C_{41}H_{49}N_6O_4$: 689.38; found: 689.43 (M+H).
Example 17d (Derived from Example 16d and Example 10a)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{35}H_{44}N_6O_4$: 613.34; found: 613.28 (M+H).
Example 17e (Derived from Example 16c and Example 8)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{38}H_{48}N_6O_4$: 653.38; found: 653.50 (M+H).
Example 17f (Derived from Example 16d and Example 8)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{37}H_{46}N_6O_4$: 639.37; found: 639.50 (M+H).
Example 17g (Derived from Example 16c and Example 8)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{39}H_{47}FN_6O_4$: 683.37; found: 683.18 (M+H).

Example 17h (Derived from Example 16a and Example 8)		RT = 2.31 minutes (condition 2); LRMS: Anal. Calcd. for $C_{39}H_{47}F_2N_6O_4$: 701.35; found: 701.69 (M+H).
Example 17i (Derived from Example 16 and Example 8a)		RT = 2.02 minutes (condition 2); HRMS: Anal. Calcd. for $C_{39}H_{50}N_7O_4$: 680.3924; found: 680.3957 (M+H).
Example 17j (Derived from Example 16b and Example 15b)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{39}H_{48}N_6O_4$: 665.38; found: 665.37 (M+H).
Example 17k (Derived from Example 16b and Example 8)		RT = 1.8 minutes (condition 1); LRMS: Anal. Calcd. for $C_{42}H_{52}N_6O_4$: 705.41; found: 705.40 (M+H).
Example 17m (Derived from Example 16f and Example 8)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for $C_{42}H_{46}N_6O_4$: 699.37; found: 699.47 (M+H).

Example 17n (Derived from Example 16 and Example 7)		RT = 2.41 minutes (condition 2); LRMS: Anal. Calcd. for $C_{39}H_{49}N_6O_5$ 681.38; found: 681.49 (M+H).
Example 17o (Derived from Example 16 and Example 13a.2)		RT = 1.7 minutes (condition 1); HRMS: Anal. Calcd. for $C_{39}H_{38}N_6O_4$ 665.3810; found: 655.3789 (M+H).
Example 17p (Derived from Example 16 and Example 13b.2)		RT = 1.7 minutes (condition 1); LCMS: Anal. Calcd. for $C_{39}H_{38}N_6O_4$ 665; found: 655 (M+H).
Example 17q (Derived from Example 16 and Example 7c)		RT = 2.43 minutes (condition 2); LRMS: Anal. Calcd. for $C_{40}H_{51}N_6O_5$ 695.39; found: 695.55 (M+H).
Example 17r (Derived from Example 16 and Example 10a.3)		RT = 2.25 minutes (condition 2); LRMS: Anal. Calcd. for $C_{38}H_{47}N_6O_4$ 651.37; found: 651.33 (M+H).

Example 17r.a (Derived from Example 16 and Example 15c)		RT = 2.05 minutes (Condition 2) LCMS: Anal. Calcd. for $C_{37}H_{44}N_6O_5$: 652.78; found: 653.4 (M+H).
Example 17r.1 (Derived from Example 16h and Example 10a.3)		RT = 1.73 minutes (condition 1); LRMS: Anal. Calcd. for $C_{41}H_{50}F_3N_6O_4$ 747.38; found: 747.46 (M+H).
Example 17r.2 (Derived from Example 16g and Example 10a.5)		RT = 2.17 minutes (condition 2); LRMS: Anal. Calcd. for $C_{40}H_{47}N_6O_4$ 675.37; found: 675.39 (M+H). HRMS: Anal. Calcd. for $C_{40}H_{47}N_6O_4$ 675.3653; found: 675.3680 (M+H).
Example 17r.3 (Derived from Example 16i and Example 10a.5)		RT = 1.72 minutes (condition 1). HRMS: Anal. Calcd. for $C_{42}H_{48}F_3N_6O_4$ 757.3684; found: 757.3684 (M+H).

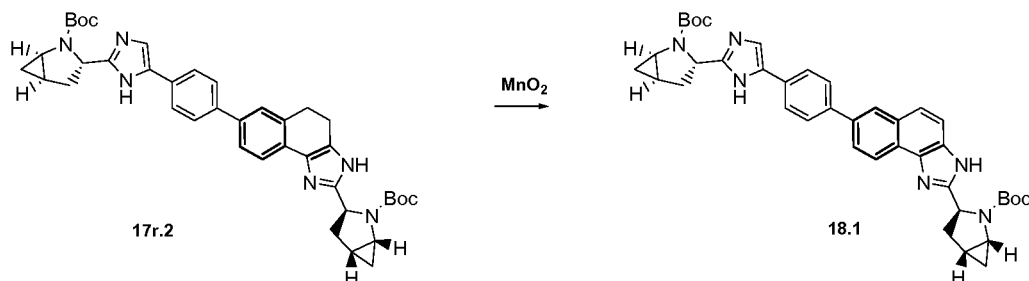
Example 17r.4 (Derived from Example 16j and Example 10a.3)		RT = 2.21 minutes (condition 2); LRMS: Anal. Calcd. for $C_{40}H_{49}N_6O_4$ 677.38; found: 677.36 (M+H). HRMS: Anal. Calcd. for $C_{40}H_{49}N_6O_4$ 677.3810; found: 677.3803 (M+H).
Example 17r.5 (Derived from Example 16k and Example 10a.5)		RT = 2.25 minutes (condition 2); LRMS: Anal. Calcd. for $C_{42}H_{49}N_6O_4$ 701.38; found: 701.36 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{49}N_6O_4$ 701.3810; found: 701.3798 (M+H).
Example 17r.6 (Derived from Example 16j and Example 11a)		RT = 2.21 minutes (condition 2); LRMS: Anal. Calcd. for $C_{43}H_{47}N_6O_4$ 711.37; found: 711.52 (M+H).
Example 17r.7 (Derived from Example 16k and Example 11b)		RT = 2.06 minutes (condition 2); LRMS: Anal. Calcd. for $C_{45}H_{47}N_6O_4$ 735.37; found: 735.38 (M+H).

Example 17s (Derived from Example 16e and Example 10a.3)		RT = 2.31 minutes (condition 2); LRMS: Anal. Calcd. for C ₃₈ H ₄₆ FN ₆ O ₄ 669.36; found: 669.60 (M+H).
Example 17s.1 (Derived from Example 16e.1 and Example 10a.5)		RT = 2.22 minutes (condition 2); LRMS: Anal. Calcd. for C ₄₀ H ₄₆ FN ₆ O ₄ 693.36; found: 693.36 (M+H). HRMS: Anal. Calcd. for C ₄₀ H ₄₆ FN ₆ O ₄ 693.3559; found: 693.3584 (M+H).
Example 17s.2 (Derived from Example 16e.1 and Example 11b)		RT = 2.2 minutes (condition 2); LRMS: Anal. Calcd. for C ₄₃ H ₄₄ FN ₆ O ₄ 727.34; found: 727.35 (M+H).
Example 17t (Derived from Example 16a and Example 11)		RT = 2.71 minutes (condition 2); LRMS: Anal. Calcd. for C ₄₄ H ₅₉ F ₂ N ₆ O ₅ Si 817.42; found: 817.71 (M+H).
Example 17t.1 (Derived from Example 16 and Example 10a.4)		RT = 2.25 minutes (condition 2); HRMS: Anal. Calcd. for C ₃₈ H ₄₅ F ₂ N ₆ O ₄ 687.3465; found: 687.3497 (M+H).

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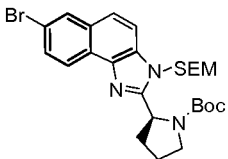
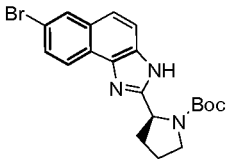
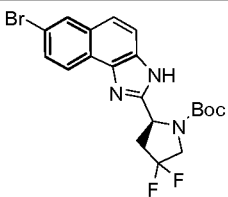
Synthetic route 10.

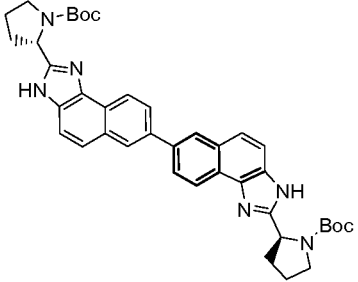
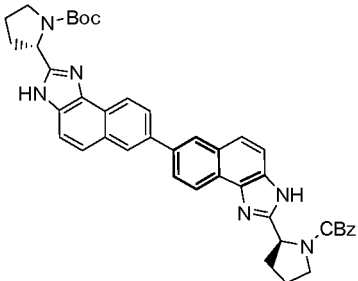
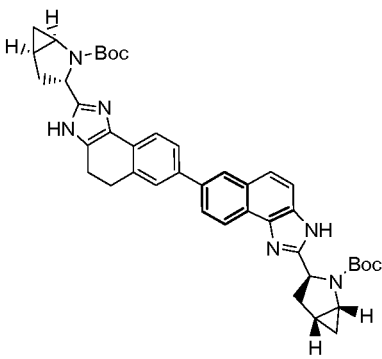
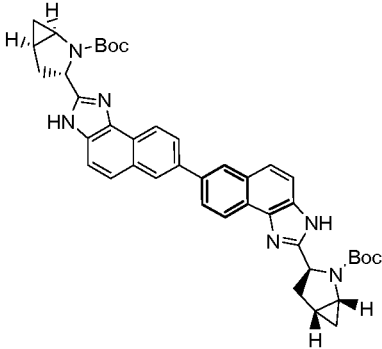
- DDQ (116 mg, 0.51 mmol) was added to a solution of Example 17r (S)-tert-butyl 2-(7-(4-(5-((S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-2-yl)phenyl)-4,5-dihydro-1H-naphtho[1,2d]imidazol-2-yl)pyrrolidine-1-carboxylate (332 mg, 0.51 mmol) in benzene (5 mL) under nitrogen atmosphere and the dark brown mixture was heated at reflux for 2 hours. The solvent was removed *in vacuo* and the residue was charged (CH₂Cl₂) to a 25 (M) Biotage[®] silica gel column.
- Segment 1; Gradient eluted from 50-100% B over 720 mL (A = CH₂Cl₂; B = 20% CH₃OH in CH₂Cl₂) Segment 2; Gradient eluted from 0-50% B over 720 mL (A = CH₂Cl₂; B = CH₃OH) gave Example 18, 261 mg (79%). ¹H NMR (500 MHz, DMSO-d₆) δ 8.46 (br s, 1H), 8.31 (s, 1H), 7.95-7.55 (m, 8H), 5.1-4.8 (rotomers, 2H), 3.67 (br.s, 1H), 3.57 (br.s, 1H), 3.48-3.47 (m, 1H), 3.39 - 3.38 (m, 1H), 2.42-1.89 (m, 8H), 1.42/1.18 (s, 9H). RT = 2.24 minutes (condition 2). LRMS: Anal. Calcd. for C₃₈H₄₄N₆O₄: 649.35; found: 649.65 (M+H).

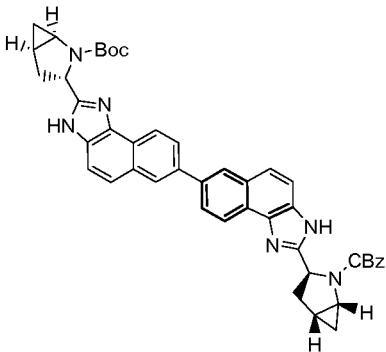
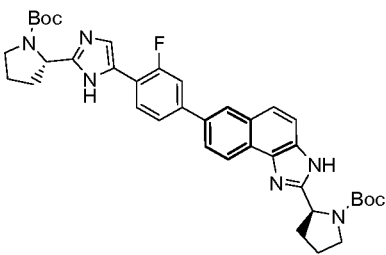
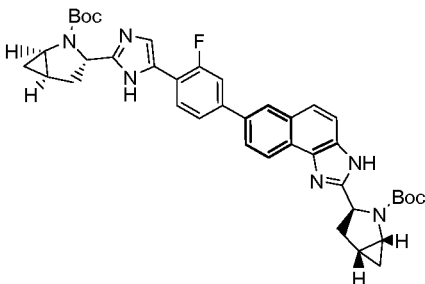
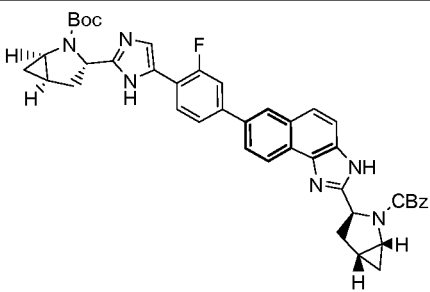
Synthetic route 10a.

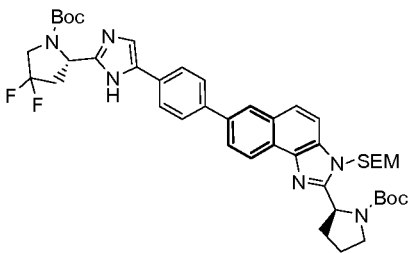
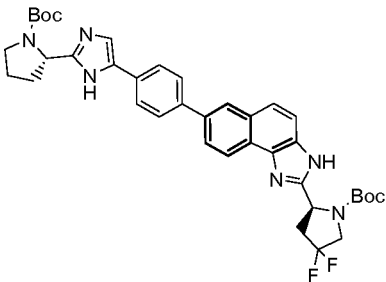
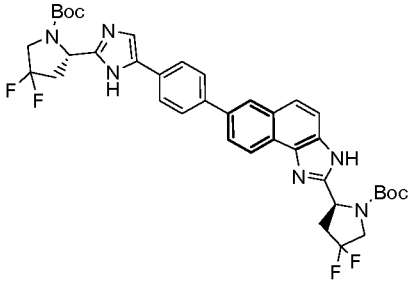
- Activated MnO₂ (77 mg, 0.889 mmol) was added in one portion to a stirred solution of Example 17r.2 (200 mg, 0.296 mmol) in dry CH₂Cl₂ (2 mL), and the suspension was stirred for 4h. Additional MnO₂ (300 mg) was added and the

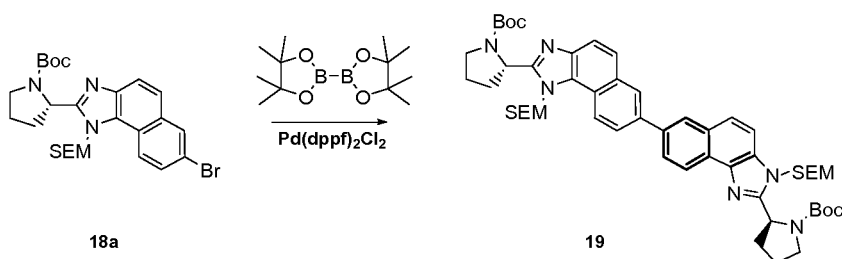
mixture stirred 16h. This sequence was repeated until LCMS revealed no remaining starting material. The reaction mixture was filtered through diatomaceous earth (Celite[®]), concentrated, and dried under high vacuum for 1h to give Example 18.1 (185.8 mg, 92 %) as a yellowish-orange solid. LCMS: RT = 2.24 minutes, Calcd. for C₄₀H₄₅N₆O₄ 673.35; found: 673.36 (M+H). HRMS: Calcd for C₄₀H₄₅N₆O₄ 673.3497; found: 673.3525 (M+H).

Example 18a (Derived from Example 11)		RT = 3.5 minutes (condition 2); LCMS: Anal. Calcd. for C ₂₆ H ₃₇ BrN ₃ O ₃ Si 546.18; found: 546.21 (M+H).
Example 18b (Derived from Example 10a.3)		RT = 2.74 minutes (condition 2); LCMS: Anal. Calcd. for C ₂₀ H ₂₃ BrN ₃ O ₂ 416.08; found: 416.08 (M+H).
Example 18b.1 (Derived from Example 10a.4)		RT = 2.62 minutes (condition 2); LCMS: Anal. Calcd. for C ₂₀ H ₂₁ BrF ₂ N ₃ O ₂ 454.08 and 452.08; found: 454.01 and 454.01 (M+H).

Example 18b.2 (Derived from Example 17r.4)		RT = 2.28 minutes (condition 2); LRMS: Anal. Calcd. for C₄₀H₄₅N₆O₄ 673.35; found: 673.36 (M+H). HRMS: Anal. Calcd. for C₄₀H₄₅N₆O₄ 673.3497; found: 673.3498 (M+H).
Example 18b.3 (Derived from Example 17r.6)		RT = 2.30 minutes (condition 2); LRMS: Anal. Calcd. for C₄₃H₄₃N₆O₄ 707.34; found: 707.52 (M+H).
Example 18b.4 (Derived from Example 17r.5)		Example not characterized.
Example 18b.5 (Derived from Example 17r.5)		RT = 2.32 minutes (condition 2); LRMS: Anal. Calcd. for C₄₂H₄₅N₆O₄ 697.35; found: 697.36 (M+H). HRMS: Anal. Calcd. for C₄₂H₄₅N₆O₄ 697.3497; found:

		697.3488 (M+H).
Example 18b.6 (Derived from Example 17r.7)		RT = 2.13 minutes (condition 2); LRMS: Anal. Calcd. for C ₄₅ H ₄₃ N ₆ O ₄ 731.34; found: 731.32 (M+H).
Example 18c (Derived from Example 17s)		RT = 2.3 minutes (condition 2). HRMS: Anal. Calcd. for C ₃₈ H ₄₄ FN ₆ O ₄ 667.3403; found: 667.3419 (M+H).
Example 18c.1 (Derived from Example 17s.1)		RT = 2.29 minutes (condition 2); LRMS: Anal. Calcd. for C ₄₀ H ₄₄ FN ₆ O ₄ 691.34; found: 691.33 (M+H). HRMS: Anal. Calcd. for C ₄₀ H ₄₄ FN ₆ O ₄ 691.3403; found: 691.3420 (M+H).
Example 18c.2 (Derived from Example 17s.2)		RT = 2.05 minutes (condition 2); LRMS: Anal. Calcd. for C ₄₃ H ₄₂ FN ₆ O ₄ 725.32; found: 725.25 (M+H).

Example 18d (Derived from Example 17t)		RT = 2.87 minutes (condition 2); HRMS: Anal. Calcd. for C ₄₄ H ₅₇ F ₂ N ₆ O ₄ Si 815.4122; found: 815.4149 (M+H).
Example 18e (Derived from Example 17t.1)		RT = 2.34 minutes (condition 2); HRMS: Anal. Calcd. for C ₃₈ H ₄₃ F ₂ N ₆ O ₄ 685.3308; found: 685.3342 (M+H).
Example 18f (Derived from Examples 16a and 18b.1 according to the procedure described for Example 17)		RT = 2.34 minutes (condition 2); HRMS: Anal. Calcd. for C ₃₈ H ₄₁ F ₄ N ₆ O ₄ 721.3120; found: 721.3128 (M+H).

Synthetic route 11

[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(ii)complex with
 5 dichloromethane (11.2 mg, 0.014 mmol) was added to a stirred solution of Example
 18a (150 mg, 0.274 mmol), bis-pinacol diborane (34.8 mg, 0.137 mmol), dppf (7.61
 mg, 0.014 mmol), and K₂CO₃ (114 mg, 0.823 mmol) in DMSO (2.5 mL) under argon
 atmosphere in a screw top pressure vessel. The solution was flushed thoroughly with
 argon, sealed, and immersed in an oil bath preheated at 80 °C and stirred 18 hours.

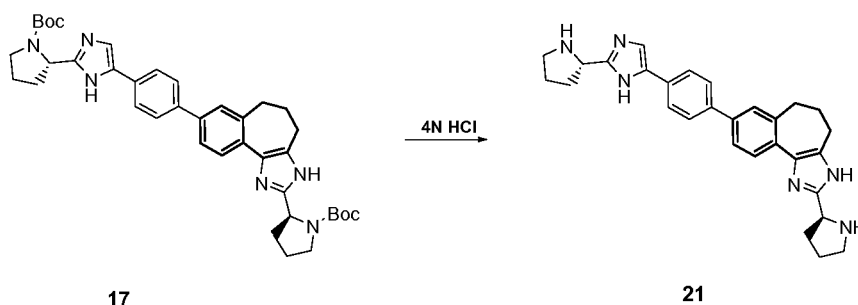
The mixture was cooled, diluted with EtOAc and washed with sat'd NaHCO₃ solution, brine, and dried (Na₂SO₄) and filtered. Solvent was removed *in vacuo* and the residue was charged (CH₂Cl₂) to a 25 (M) Biotage[®] silica gel column: Segment 1. 10% B for 75 mL; Segment 2. Gradient eluted from 10-100% B over 1.8 L; (A =
 5 Hexanes; B = EtOAc) gave Example 19, 88.7 mg (33%). ¹H NMR (500 MHz, DMSO-d₆) δ 8.56-8.54 (m, 2H), 8.48 (s, 2H), 8.12-8.10 (m, 2H), 7.95-7.91 (m, 4H), 5.83-5.76 (m, 4H), 5.30-5.22 (m, 2H), 3.72-3.61 (m, 4H), 3.53 (t, *J* = 7.3 Hz, 4H), 2.44-2.18 (m, 4H) 2.11-2.08 (m, 2H), 2.0-1.94 (m, 2H), 1.38/1.08 (s, 18H), 0.91-0.81 (m, 4H), -0.06 (s, 18H). RT = 3.2 minutes (condition 2); HRMS: Anal. Calcd. for
 10 C₅₂H₇₃N₆O₆Si₂ 933.5125; found: 933.5132 (M+H).

Synthetic route 12

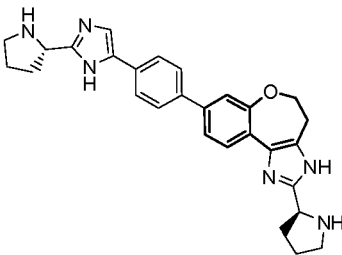
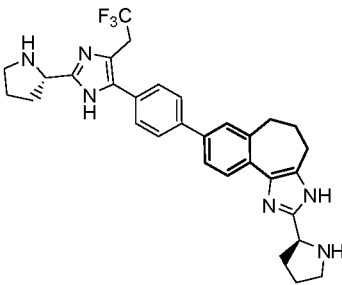
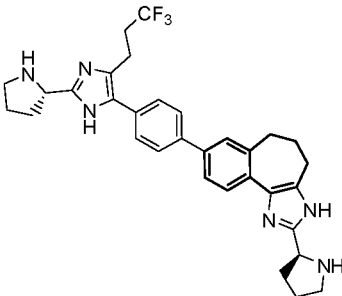


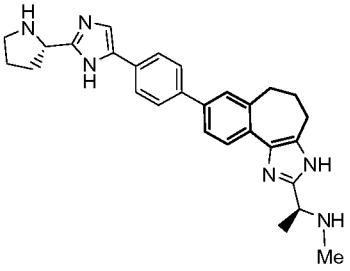
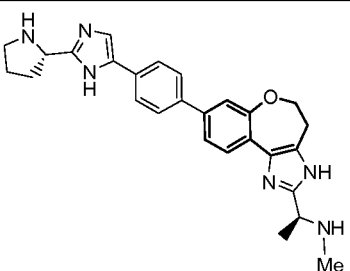
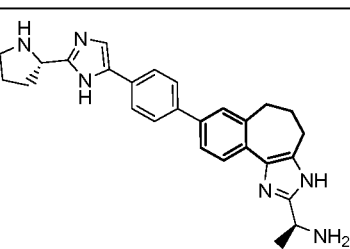
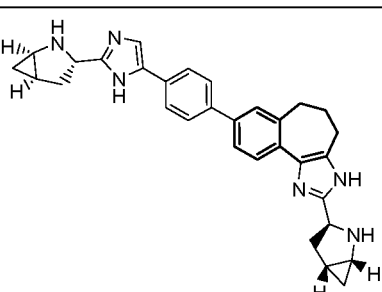
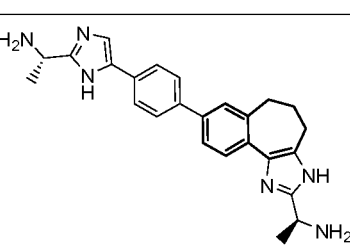
Triethylphosphite (0.257 mL, 1.48 mmol) was added to Example 17q, (340 mg, 0.489 mmol) in DMF (5 mL) and stirred at 80°C for 16 hours. Additional
 15 triethylphosphite (0.3 mL and 0.6 mL) was added at 8 hours intervals until LCMS indicated the reaction was complete. The solvent was removed *in vacuo* and the residue was charged (CH₂Cl₂) to a 25 (M) Biotage[®] silica gel column. Segment 1. 0% B for 300 mL; Segment 2. Gradient eluted from 0-50% B over 1440 mL; Segment 3. Gradient eluted 50-100% B over 600 mL (A = CH₂Cl₂; B = 20% CH₃OH
 20 in CH₂Cl₂) gave Example 20, 286 mg (82%). ¹H NMR (500 MHz, DMSO-d₆) δ 7.84-7.80 (m, 8H), 4.87-4.68 (m, 2H), 3.55-3.54 (m, 2H), 3.40-3.30 (m, 6H), 2.82-2.76 (m, 2H), 2.25-1.82 (m, 8H), 1.63-1.57 (m, 2H), 1.42/1.18 (s, 9H). RT = 2.32 minutes (condition 2); LRMS: Anal. Calcd. for C₄₀H₅₁N₆O₄ 679.40; found: 679.57 (M+H)⁺.

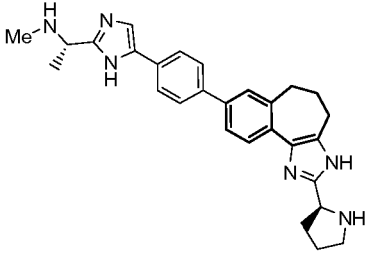
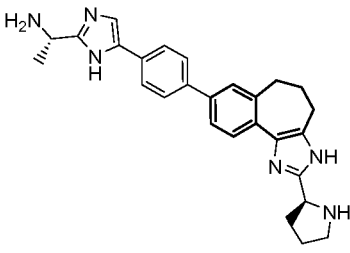
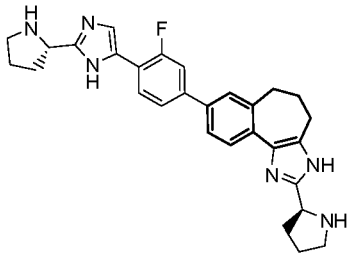
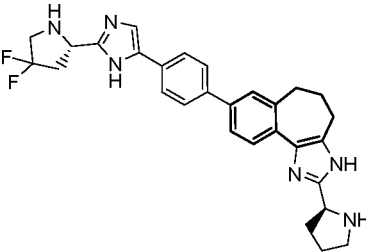
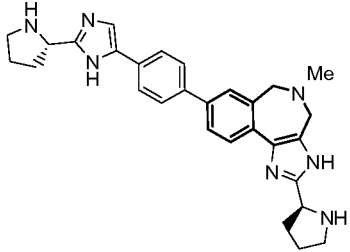
Synthetic route 13

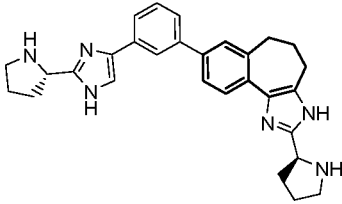
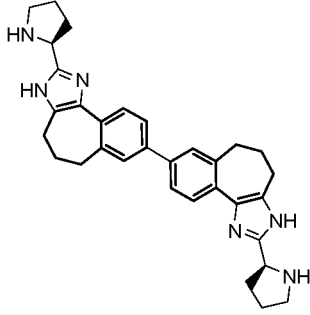
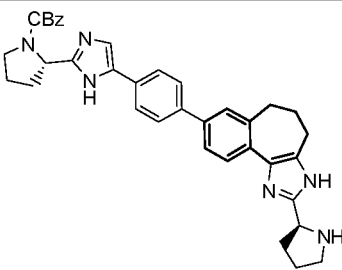
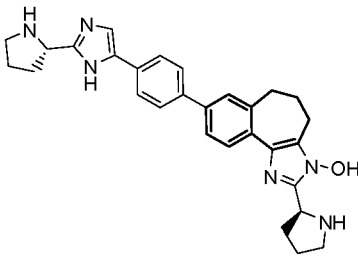
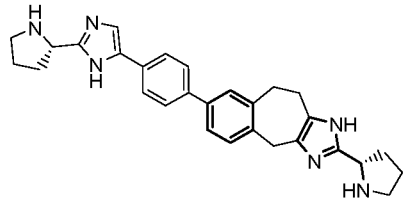


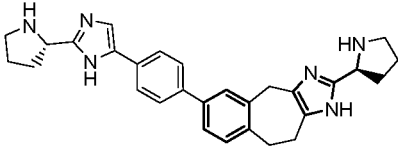
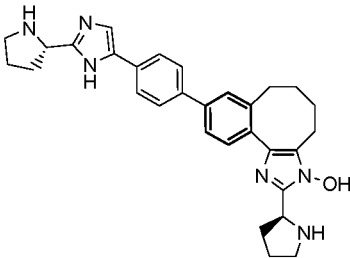
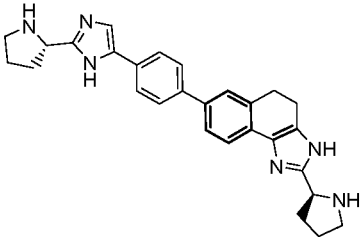
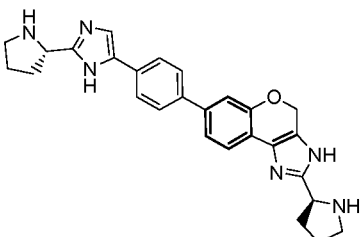
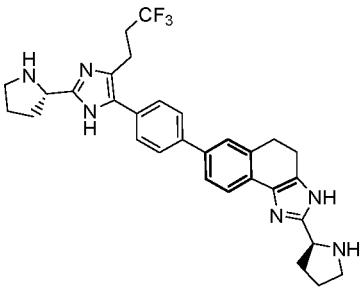
Example 17, (411 mg, 0.62 mmol) was dissolved in CH₃OH (20 mL) and HCl/Dioxane (100 mL of 4N) was added and the reaction was stirred 4 hr. The solvents were removed *in vacuo*, and the tetra HCl salt was exposed to high vacuum for 18 hours to give Example 21, 350 mg (94%) as an HCl salt which was used without further purification. RT = 1.3 minutes (condition 1). LCMS: Anal. Calcd. for C₂₉H₃₃N₆; 465; found: 465 (M+H).

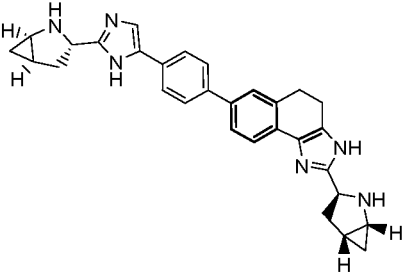
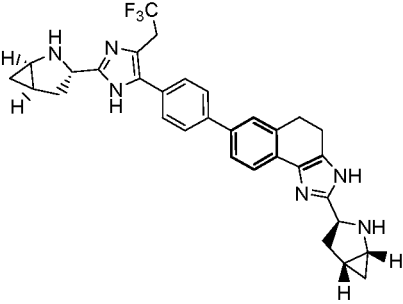
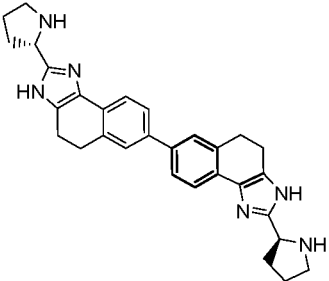
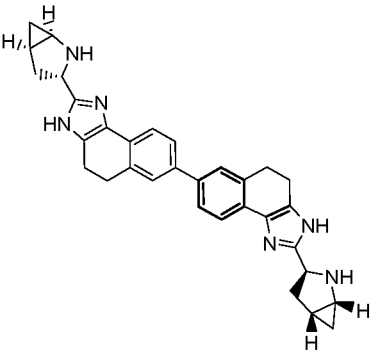
Example 21a (Derived from Example 17a)		RT = 2.99 minutes (condition 2); LCMS: Anal. Calcd. For C ₃₇ H ₄₆ N ₆ O ₅ : 466.57; found: 467.2.2 (M+H).
Example 21a.1 (Derived from Example 17a.1)		RT = 1.4 minutes (condition 1); LCMS: Anal. Calcd. for C ₃₁ H ₃₄ F ₃ N ₆ 547.28; found: 547.19 (M+H).
Example 21a.2 (Derived from Example 17a.2)		RT = 1.4 minutes (condition 1); LCMS: Anal. Calcd. for C ₃₂ H ₃₆ F ₃ N ₆ : 561.29; found: 561.36 (M+H).

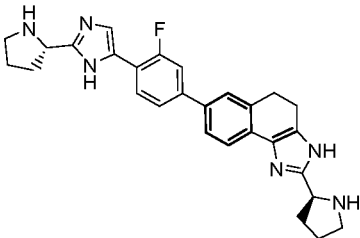
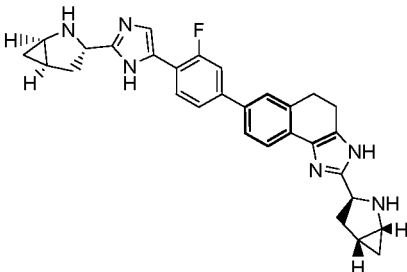
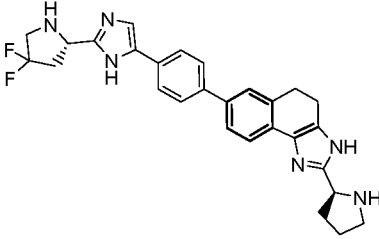
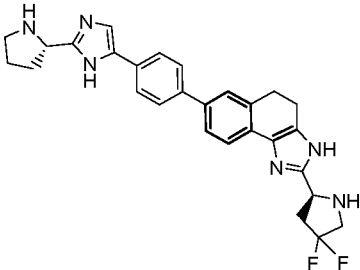
Example 21b (Derived from Example 17b)		RT = 1.3 minutes (condition 1); LCMS: Anal. Calcd. for $C_{28}H_{32}N_6$ 452; found: 452 (M+H).
Example 21b.1 (Derived from Example 17b.1)		RT = 1.2 minutes (condition 2); LCMS: Anal. Calcd. for $C_{37}H_{46}N_6O_5$ 454.25; found: 455.2 (M+H).
Example 21c (Derived from Example 17c)		RT = 1.3 minutes (condition 1); LCMS: Anal. Calcd. for $C_{27}H_{30}N_6$ 438; found: 438 (M+H).
Example 21c.1 (Derived from Example 17c.1)		RT = 1.2 minutes (condition 1); LCMS: Anal. Calcd. for $C_{31}H_{33}N_6$ 489.28; found: 489.28 (M+H).
Example 21d (Derived from Example 17d)		RT = 1.2 minutes (condition 1); LCMS: Anal. Calcd. for $C_{25}H_{28}N_6$ 412; found: 412 (M+H).

Example 21e (Derived from Example 17e)		RT = 1.4 minutes (condition 1); LCMS: Anal. Calcd. for $C_{28}H_{32}N_6$ 452; found: 452 (M+H).
Example 21f (Derived from Example 17f)		RT = 1.2 minutes (condition 1); LCMS: Anal. Calcd. for $C_{27}H_{30}N_6$ 438; found: 438 (M+H).
Example 21g (Derived from Example 17g)		RT = 1.3 minutes (condition 1); LCMS: Anal. Calcd. for $C_{29}H_{31}FN_6$ 483; found: 483 (M+H).
Example 21h (Derived from Example 17h)		RT = 1.7 minutes (condition 2); LCMS: Anal. Calcd. for $C_{29}H_{31}F_2N_6$ 501.25; found: 501.51 (M+H).
Example 21i (Derived from Example 17i)		RT = 1.5 minutes (condition 2); LRMS: Anal. Calcd. for $C_{29}H_{34}N_7$ 480.28; found: 480.26 (M+H).

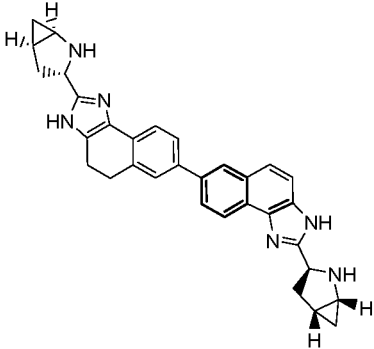
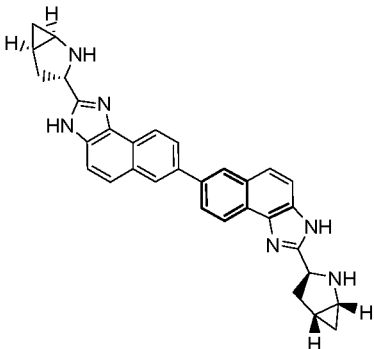
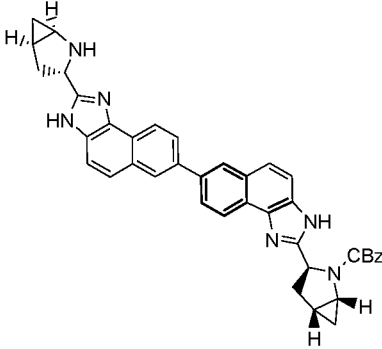
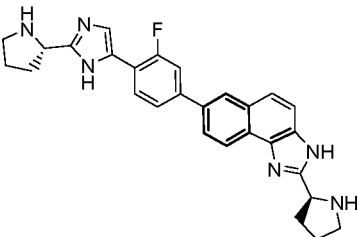
Example 21j (Derived from Example 17j)		RT = 1.3 minutes (condition 1); LRMS: Anal. Calcd. for $C_{29}H_{32}N_6$ 464; found: 464 (M+H).
Example 21k (Derived from Example 17k)		RT = 1.3 minutes (condition 1); LCMS: Anal. Calcd. for $C_{32}H_{36}N_6$ 505; found: 505 (M+H).
Example 21m (Derived from Example 17m)		RT = 1.5 minutes (condition 1); LRMS: Anal. Calcd. for $C_{37}H_{38}N_6O_2$ 598; found: 598 (M+H).
Example 21n (Derived from Example 17n)		RT = 1.7 minutes (condition 2) LCMS: Anal. Calcd. for $C_{29}H_{33}N_6O$ 481.26; found: 481.37 (M+H).
Example 21o (Derived from Example 17o)		RT = 2.1 minutes (condition 1) LCMS: Anal. Calcd. for $C_{29}H_{32}N_6$ 464; found: 464 (M+H).

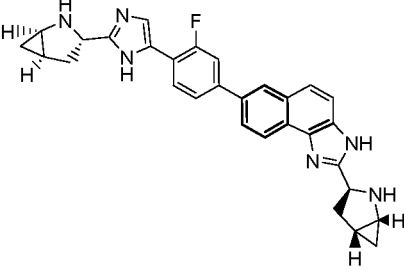
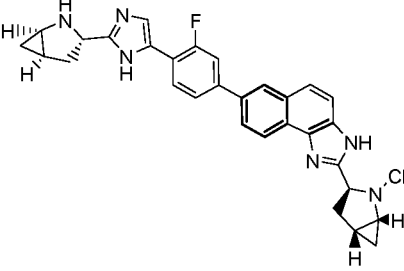
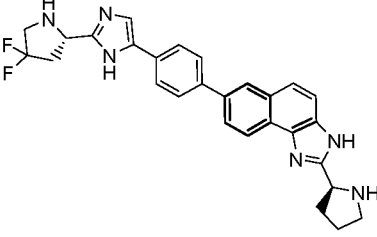
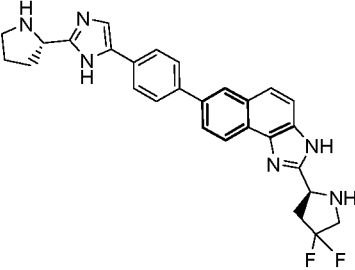
Example 21p (Derived from Example 17p)		RT = 2.0 minutes (condition 1) LCMS: Anal. Calcd. for C ₂₉ H ₃₂ N ₆ 464; found: 464 (M+H).
Example 21q (Derived from Example 17q)		RT = 1.7 minutes (condition 2) LCMS: Anal. Calcd. for C ₃₀ H ₃₅ N ₆ O 495.28; found: 495.37 (M+H).
Example 21r (Derived from Example 17r)		RT = 1.5 minutes (condition 2) LCMS: Anal. Calcd. for C ₂₈ H ₃₀ N ₆ 451.26; found: 451.33 (M+H) ⁺ .
Example 21r.a (Derived from Example 17r.a)		RT = 1.1 minutes (condition 1); LCMS: Anal. Calcd. for C ₃₇ H ₄₄ N ₆ O ₅ : 452.18; found: 453.2 (M+H).
Example 21r.1 (Derived from Example 17r.1)		RT = 1.4 minutes (condition 1) LCMS: Anal. Calcd. for C ₃₁ H ₃₄ F ₃ N ₆ 547.28; found: 547.26 (M+H) ⁺ .

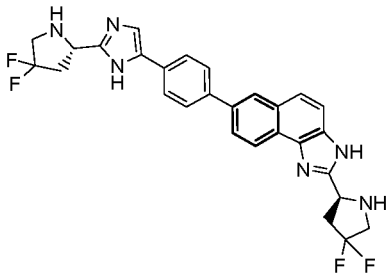
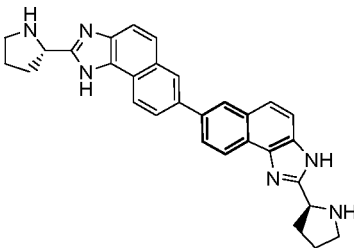
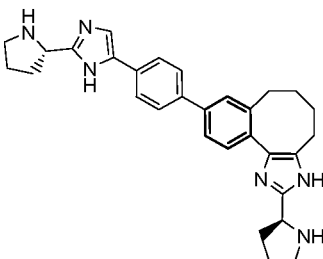
Example 21r.2 (Derived from Example 17r.2)		RT = 1.46 min, (condition 2), LCMS: Anal. Calcd for $C_{30}H_{31}N_6$ (M+H) 475.26; found: 475.25. HRMS: Anal. Calcd for $C_{30}H_{31}N_6$ 475.2605; found: 475.2616 (M+H).
Example 21r.3 (Derived from Example 17r.3)		RT = 1.4 minutes (condition 1) LCMS: Anal. Calcd. for $C_{32}H_{32}F_3N_6$ 557.26; found: 557.22 (M+H).
Example 21r.4 (Derived from Example 17r.4)		RT = 1.43 minutes (condition 2) LCMS: Anal. Calcd. for $C_{30}H_{33}N_6$ 477.28; found: 477.22 (M+H). HRMS: Calcd for $C_{30}H_{33}N_6$ 477.2761; found 477.2765 (M+H).
Example 21r.5 (Derived from Example 17r.5)		RT = 1.56 minutes (condition 2) LCMS: Anal. Calcd. for $C_{32}H_{33}N_6$ 501.28; found: 501.29 (M+H). HRMS: Calcd for $C_{32}H_{33}N_6$ 501.2761;

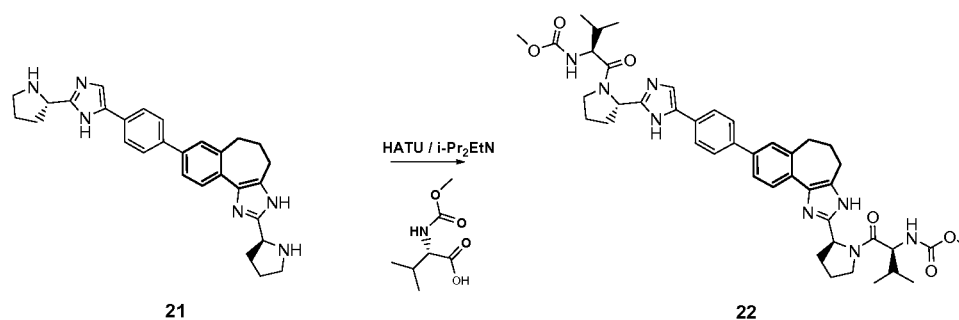
		found 501.2761 (M+H).
Example 21s (Derived from Example 17s)		RT = 1.7 minutes (condition 2) LCMS: Anal. Calcd. for C ₂₈ H ₃₀ FN ₆ 469.25; found: 469.47 (M+H) ⁺ .
Example 21s.1 (Derived from Example 17s.1)		RT = 1.62 min, (condition 2), LCMS: Anal. Calcd for C ₃₀ H ₃₀ FN ₆ 493.25; found: 493.28 (M+H). HRMS: Calcd for C ₃₀ H ₃₀ FN ₆ 493.2511; found 493.2520 (M+H).
Example 21t (Derived from Example 17t)		RT = 1.7 minutes (condition 2) LCMS: Anal. Calcd. for C ₂₈ H ₂₉ F ₂ N ₆ 487.23; found: 487.51 (M+H).
Example 21t.1 (Derived from Example 17t.1)		RT = 1.7 minutes (condition 2) LCMS: Anal. Calcd. for C ₂₈ H ₂₉ F ₂ N ₆ 487.24; found: 487.51 (M+H).

Example 21u (Derived from Example 18)		RT = 1.6 minutes (condition 2) LCMS: Anal. Calcd. for C ₂₈ H ₂₉ N ₆ 449.25; found: 449.46 (M+H).
Example 21u.1 (Derived from Example 18.1)		RT = 1.61 min, (condition 2), LCMS: Anal. Calcd for C ₃₀ H ₂₉ N ₆ 473.36; found: 473.28 (M+H). HRMS: Anal. Calcd. for C ₃₀ H ₂₉ N ₆ 473.2448; found: 473.2457 (M+H).
Example 21u.2 (Derived from Example 18b.2)		See Example 21x below for characterization.
Example 21u.3 (Derived from Example 18b.3)		RT = 2.10 min, (condition 2), LCMS: Anal. Calcd for C ₃₈ H ₃₅ N ₆ O ₂ 607.46; found: 607.46 (M+H).

Example 21u.4 (Derived from Example 18b.4)		Example not characterized.
Example 21u.5 (Derived from Example 18b.5)		RT = 1.82 minutes (condition 2); LRMS: Anal. Calcd. for $C_{32}H_{29}N_6$ 497.25; found: 497.29 (M+H). HRMS: Calcd for $C_{32}H_{29}N_6$ 497.2448; found 497.2448 (M+H).
Example 21u.6 (Derived from Example 18b.6)		RT = 1.91 min (condition 2); LCMS: Anal. Calcd. for $C_{40}H_{35}N_6O_2$ 631.28; found: 631.27 (M+H).
Example 21v (Derived from Example 18c)		RT = 1.8 minutes (condition 2) LCMS: Anal. Calcd. for $C_{28}H_{28}FN_6$ 467.24; found: 467.43 (M+H).

Example 21v.1 (Derived from Example 18c.1)		RT = 1.7 minutes (condition 2) LCMS: Anal. Calcd. for $C_{30}H_{28}FN_6$ 491.24; found: 491.25 (M+H). HRMS: Calcd. for $C_{30}H_{28}FN_6$ 491.2354; found 491.2364 (M+H).
Example 21v.2 (Derived from Example 18c.2)		RT = 1.76 minutes (condition 2) LCMS: Anal. Calcd. for $C_{38}H_{34}FN_6O_2$ 625.27; found: 625.19 (M+H).
Example 21w (Derived from Example 18d)		RT = 1.9 minutes (condition 2) LCMS: Anal. Calcd. for $C_{28}H_{27}F_2N_6$ 485.23; found: 485.46 (M+H).
Example 21w.1 (Derived from Example 18e)		RT = 1.8 minutes (condition 2) LCMS: Anal. Calcd. for $C_{28}H_{27}F_2N_6$ 485.23; found: 485.30 (M+H).

Example 21w.2 (Derived from Example 18f)		RT = 2.3 minutes (condition 2) LCMS: Anal. Calcd. for $C_{28}H_{25}F_4N_6$ 521.21; found: 521.28 (M+H).
Example 21x (Derived from Example 19) NOTE: Same as Example 21u.2		RT = 1.7 minutes (condition 2) LCMS: Anal. Calcd. for $C_{30}H_{29}N_6$ 473.24; found: 473.27 (M+H).
Example 21x.1 (Derived from Example 20)		RT = 1.6 minutes (condition 2) LCMS: Anal. Calcd. for $C_{30}H_{35}N_6$ 479.29; found: 479.39 (M+H).

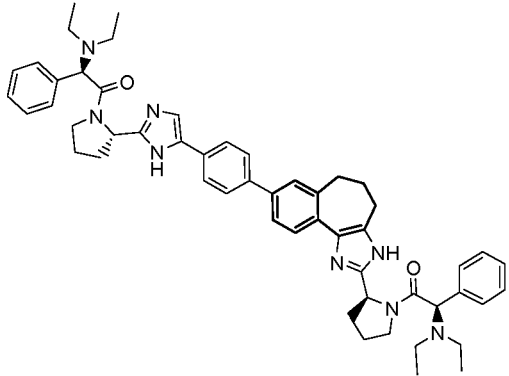
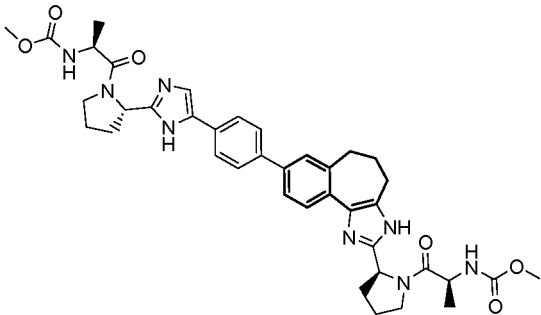
Synthetic route 14

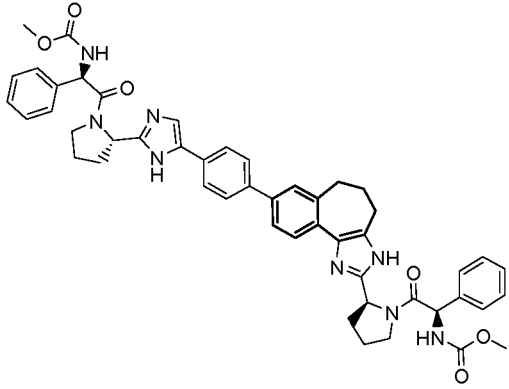
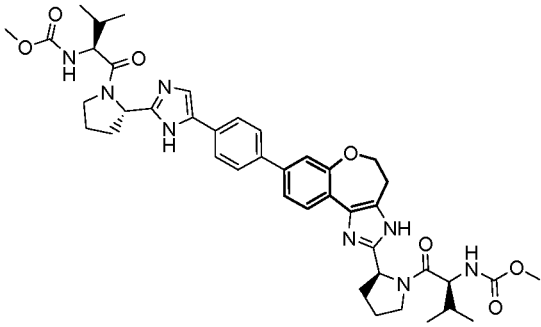
HATU (88 mg, 0.33 mmol) was added and rapidly stirred solution of

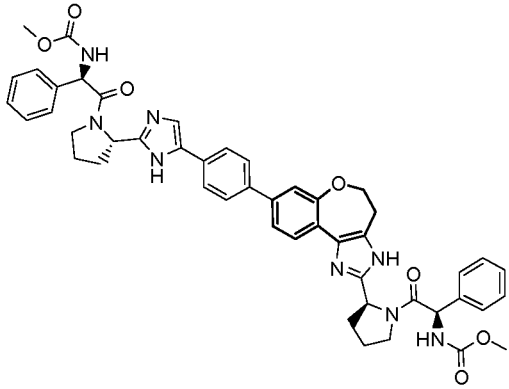
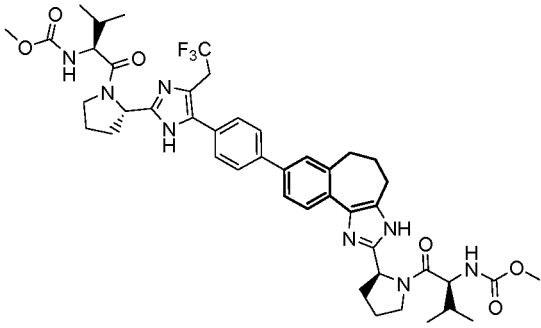
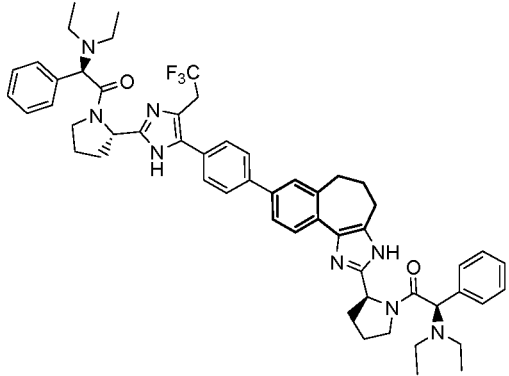
5 Example 21, (87.5 mg, 0.145 mmol), Cap-51: N-methoxycarbonyl-L-valine (63.3 mg, 0.36 mmol), and Hunig's base (0.23 mL, 1.25 mmol) in DMF (3.5 mL). The reaction mixture was stirred 16 hours before being diluted with CH₃OH (1 vol) and directly subjected to semi prep HPLC (4 injections at 2 mL each; Dynamax 60A prep C8 column; 25% - 100% B over 30 min; Flow Rate = 20 mL/min; Wavelength = 220

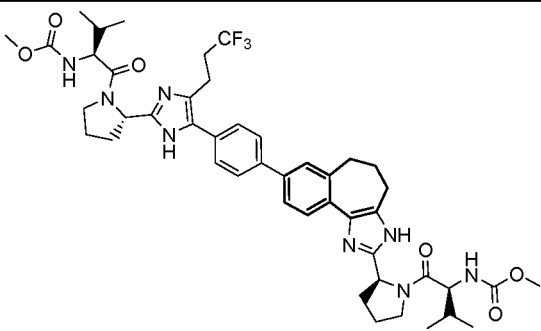
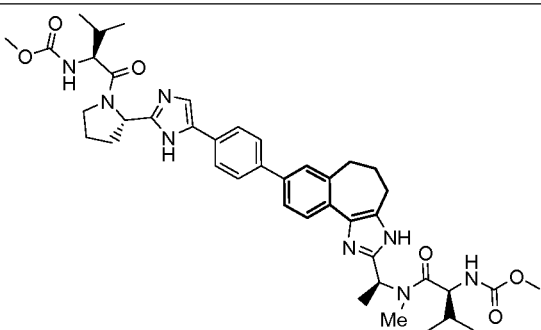
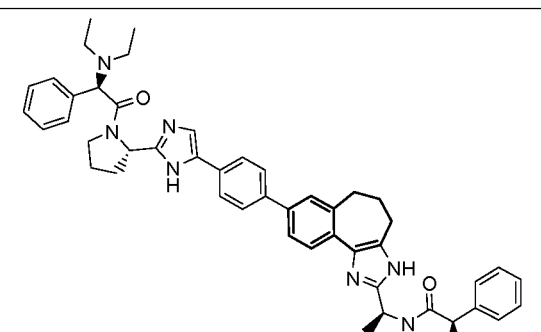
10 nm; Solvent A = 0.1% TFA in 10% methanol/90% H₂O; Solvent B = 0.1% TFA in

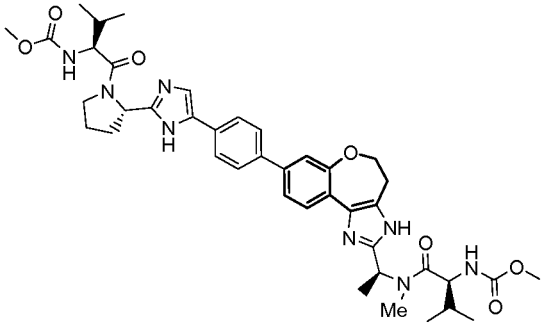
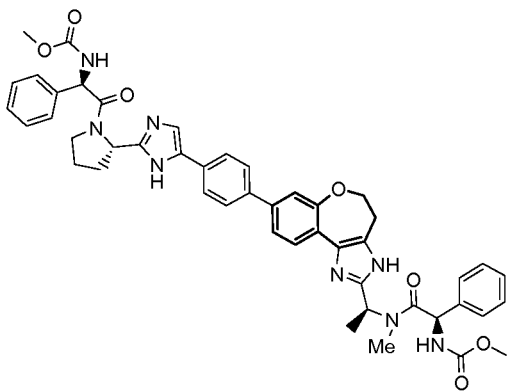
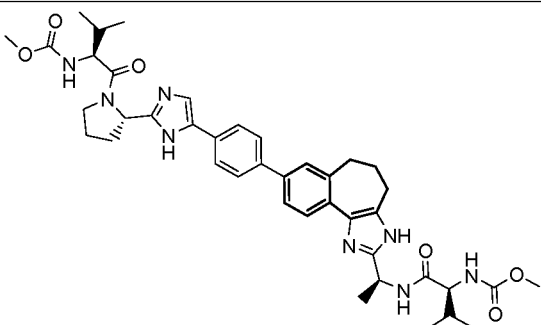
90% methanol/10% H₂O) to give Example 22, (TFA salt). ¹H NMR (300 MHz, DMSO-d₆) δ 8.04-8.02 (m, 1H), 7.78-7.58 (m, 4H), 7.49-7.41 (m, 3H), 7.30-7.24 (m, 2H), 5.09-5.01 (m, 2H), 4.1-4.03 (m, 2H), 3.81-3.79 (m, 4H), 3.54 (s, 6H), 2.92-2.84 (m, 4H), 2.17-2.09 (m, 4H), 2.00-1.87 (m, 8H), 0.79-0.81 (m, 12H). RT = 1.57 minutes (condition 1). LRMS: Anal. Calcd. for C₄₃H₅₅N₈O₆: 779.42; found: 779.48 (M+H). HRMS: Anal. Calcd. for C₄₃H₅₅N₈O₆: 779.4245; found: 779.4249 (M+H).

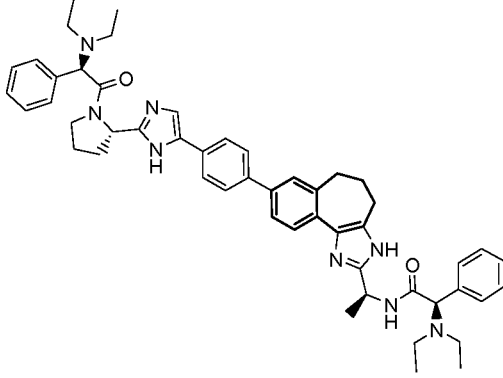
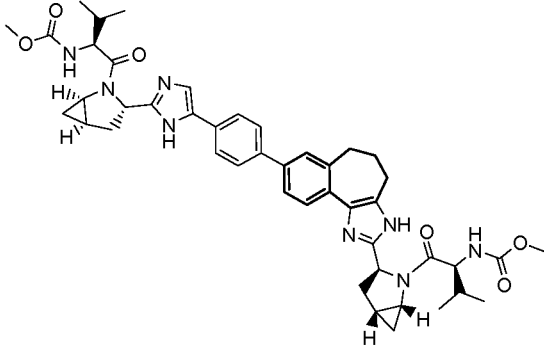
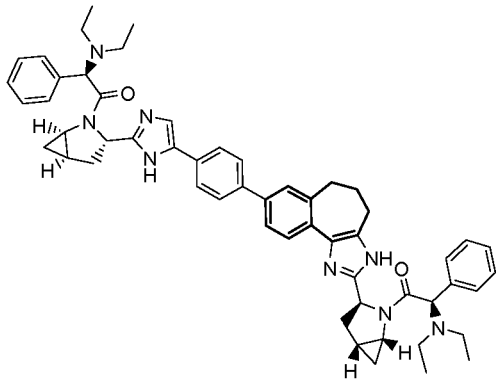
Example 22.1 (Derived from Example 21 and Cap-2)		RT = 1.4 minutes (condition 1); LRMS: Anal. Calcd. for C₅₃H₆₂N₈O₂ 843.51; found: 843.89 (M+H). HRMS: Anal. Calcd. for C₅₃H₆₂N₈O₂ 843.5047; found: 843.5099 (M+H).
Example 22.2 (Derived from Example 21 and Cap-52)		RT = 1.4 minutes (condition 1); LRMS: Anal. Calcd. for C₃₉H₄₆N₈O₆ 723.36; found: 723.39 (M+H). HRMS: Anal. Calcd. for C₃₉H₄₆N₈O₆

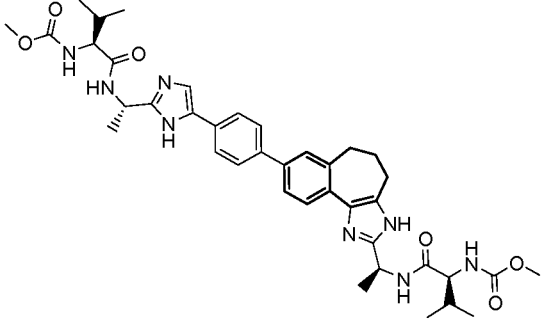
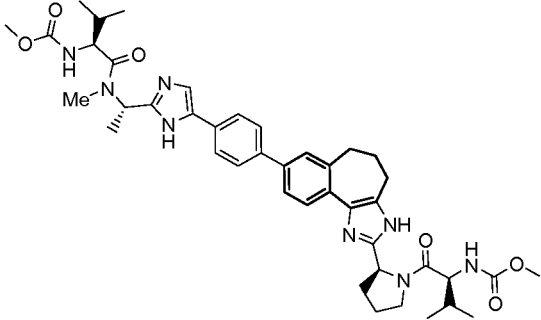
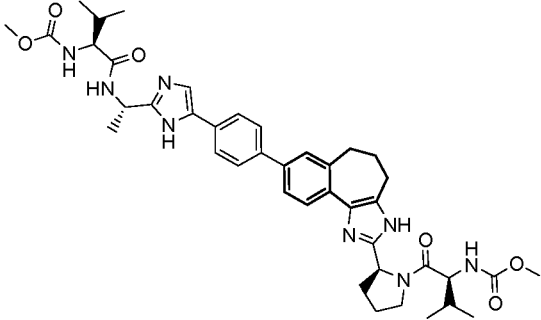
		723.3619; found: 723.3643 (M+H).
Example 22.3 (Derived from Example 21 and Cap-4)		RT = 1.7 minutes (condition 1); LRMS: Anal. Calcd. for C ₄₉ H ₅₀ N ₈ O ₆ 723.39; found: 723.40 (M+H). HRMS: Anal. Calcd. for C ₄₉ H ₅₀ N ₈ O ₆ 847.3932; found: 847.3953 (M+H).
Example 22a (Derived from Example 21a and Cap-51)		RT = 2.0 minutes (condition 4); LRMS: Anal. Calcd. for C ₄₂ H ₅₃ N ₈ O ₇ 781.41; found: 781.33 (M+H).

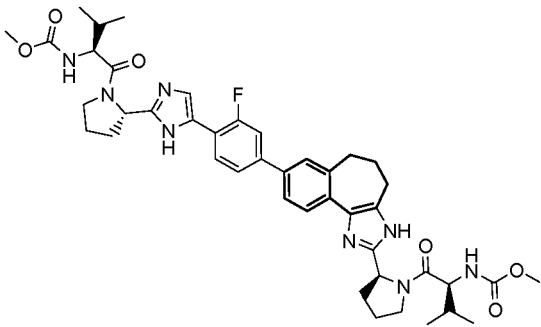
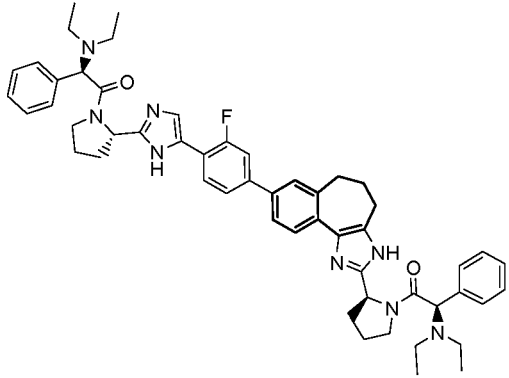
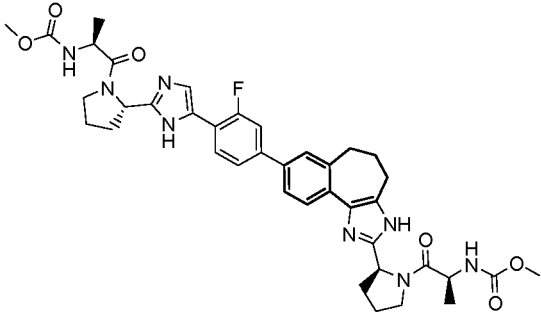
Example 22a.1 (Derived from Example 21a and Cap-4)		RT = 2.2 minutes (condition 4); LRMS: Anal. Calcd. for $C_{48}H_{49}N_8O_7$ 849.37; found: 849.25 (M+H).
Example 22a.2 (Derived from Example 21a.1 and Cap-51)		RT = 1.6 minutes (condition 1); HRMS: Anal. Calcd. for $C_{45}H_{56}F_3N_8O_6$ 861.4281; found: 861.4269 (M+H).
Example 22a.3 (Derived from Example 21a.1 and Cap-2)		RT = 1.4 minutes (condition 1); HRMS: Anal. Calcd. for $C_{55}H_{64}F_3N_8O_2$ 925.5099; found: 925.5096 (M+H).

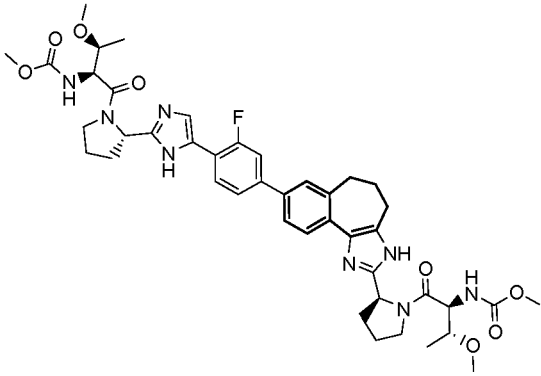
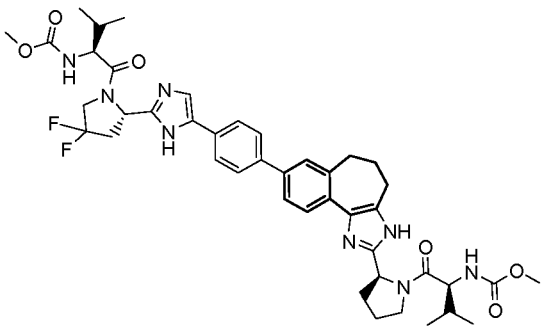
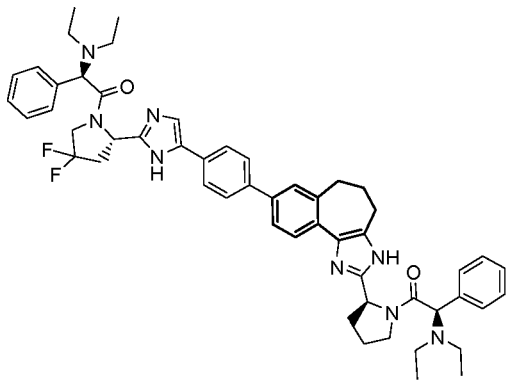
Example 22a.4 (Derived from Example 21a.2 and Cap-51)		RT = 1.6 minutes (condition 1); HRMS: Anal. Calcd. for $C_{46}H_{57}F_3N_8O_6$ 875.4426; found: 875.4406 (M+H).
Example 22b (Derived from Example 21b and Cap-51)		RT = 1.6 minutes (condition 1); LRMS: Anal. Calcd. for $C_{42}H_{54}N_8O_6$ 767.37; found: 767.42 (M+H).
Example 22b.1 (Derived from Example 21b and Cap-2)		RT = 1.4 minutes (condition 1); LRMS: Anal. Calcd. for $C_{52}H_{62}N_8O_2$ 831.50; found: 831.63 (M+H).

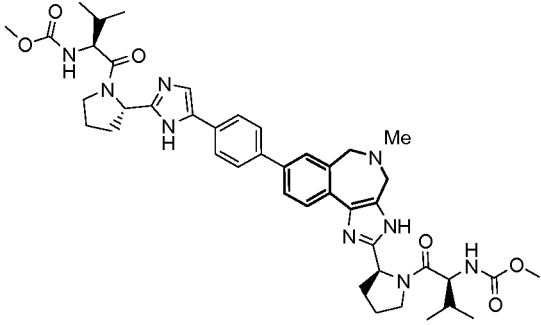
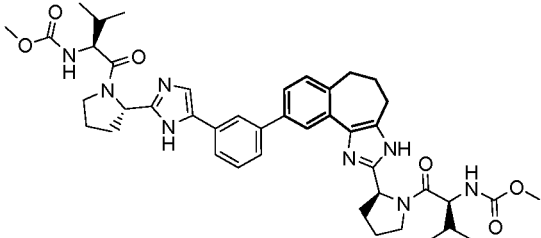
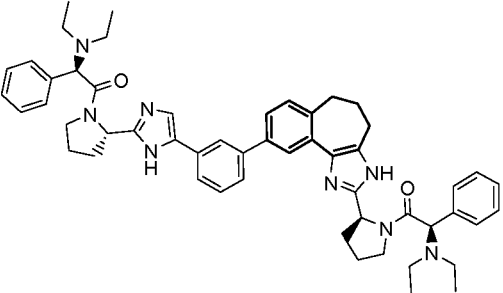
Example 22b.2 (Derived from Example 21b.1 and Cap-51)		RT = 2.1 minutes (condition 4); LRMS: Anal. Calcd. for $C_{41}H_{53}N_8O_7$ 769.40; found: 769.21 (M+H).
Example 22b.3 (Derived from Example 21b.1 and Cap-4)		RT = 2.2 minutes (condition 4); LRMS: Anal. Calcd. for $C_{47}H_{49}N_8O_7$ 837.37; found: 837.19 (M+H).
Example 22c (Derived from Example 21c and Cap-51)		RT = 1.5 minutes (condition 1); HRMS: Anal. Calcd. for $C_{41}H_{52}N_8O_6$ 753.4083; found: 753.4085 (M+H).

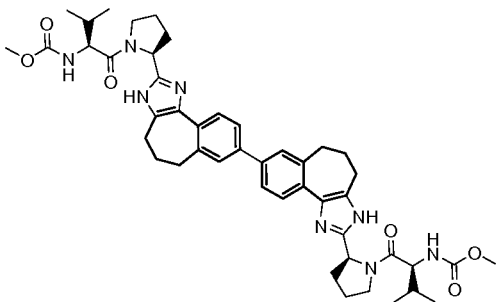
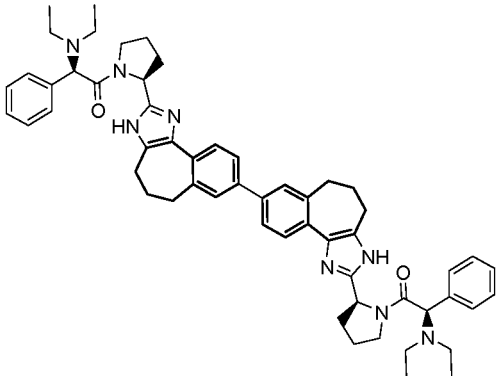
Example 22c.1 (Derived from Example 21c and Cap-2)		RT = 1.4 minutes (condition 1); LRMS: Anal. Calcd. for C ₅₁ H ₆₀ N ₈ O ₂ 817.49; found: 817.62 (M+H).
Example 22c.2 (Derived from Example 21c.1 and Cap-51)		RT = 1.5 minutes (condition 1); HRMS: Anal. Calcd. for C ₄₅ H ₅₅ N ₈ O ₆ 803.4239; found: 803.4236 (M+H).
Example 22c.3 (Derived from Example 21c.1 and Cap-2)		RT = 1.3 minutes (condition 1); HRMS: Anal. Calcd. for C ₅₅ H ₆₃ N ₈ O ₂ 867.5068; found: 867.5058 (M+H).

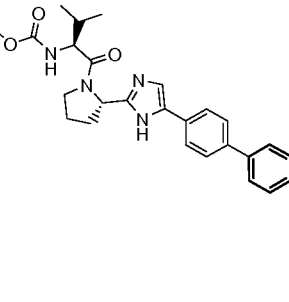
Example 22d (Derived from Example 21d and Cap-51)		RT = minutes (condition 1); LRMS: Anal. Calcd. for $C_{39}H_{50}N_8O_6$ 727.39; found: 727.32 (M+H).
Example 22e (Derived from Example 21e and Cap-51)		RT = 1.6 minutes (condition 1); HRMS: Anal. Calcd. for $C_{42}H_{54}N_8O_6$ 767.4239; found: 767.4240 (M+H).
Example 22f (Derived from Example 21f and Cap-51)		RT = 1.6 minutes (condition 1); HRMS: Anal. Calcd. for $C_{41}H_{52}N_8O_6$ 753.41; found: 753.54 (M+H).

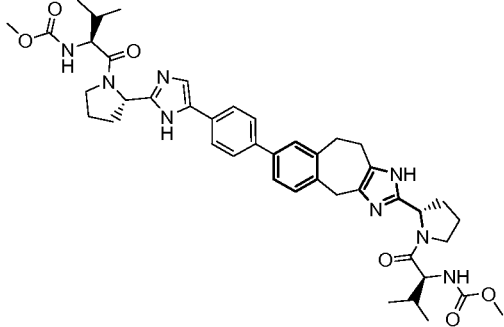
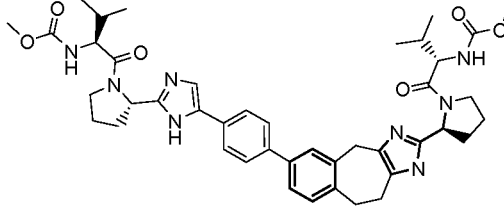
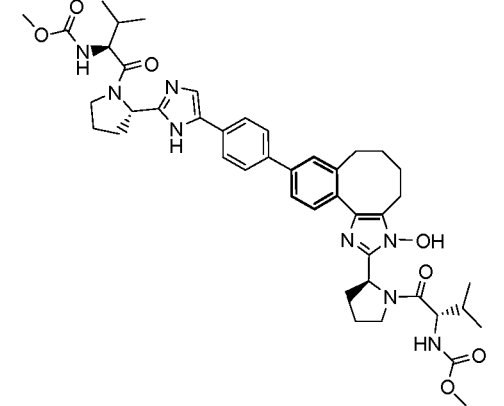
Example 22g (Derived from Example 21g and Cap-51)		RT = 1.5 minutes (condition 1); HRMS: Anal. Calcd. for $C_{43}H_{53}FN_8O_6$ 797.41; found: 797.21 (M+H).
Example 22g.1 (Derived from Example 21g and Cap-2)		RT = 1.4 minutes (condition 1); HRMS: Anal. Calcd. for $C_{53}H_{61}FN_8O_2$ 861.50; found: 861.31 (M+H).
Example 22g.2 (Derived from Example 21g and Cap-52)		RT = 1.4 minutes (condition 1); HRMS: Anal. Calcd. for $C_{39}H_{45}FN_8O_6$ 741.35; found: 741.19 (M+H).

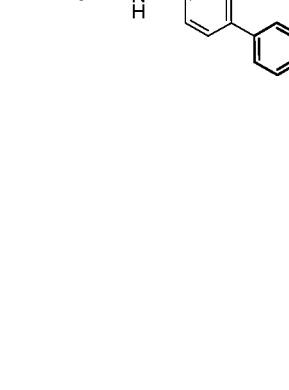
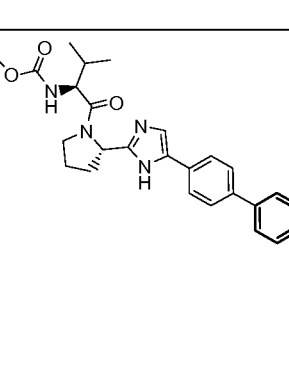
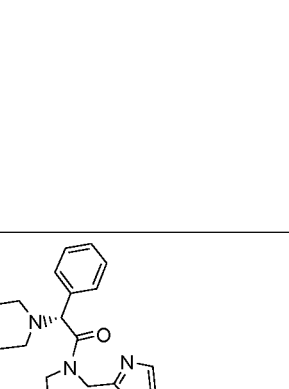
Example 22g.3 (Derived from Example 21g and Cap-86)		RT = 1.5 minutes (condition 1); HRMS: Anal. Calcd. for $C_{43}H_{53}FN_8O_6$ 829.41; found: 829.25 (M+H).
Example 22h (Derived from Example 21h and Cap-51)		RT = 2.05 minutes (condition 2); LCMS: Anal. Calcd. for $C_{43}H_{52}F_2N_8O_6$ 815.41; found: 815.79 (M+H). HRMS: Anal. Calcd. for $C_{43}H_{52}F_2N_8O_6$ 815.4056; found: 815.4032 (M+H).
Example 22h.1 (Derived from Example 21h and Cap-2)		RT= 1.8 minutes (condition 2); LCMS: Anal. Calcd. for $C_{53}H_{60}F_2N_8O_2$ 879.49; found: 879.86 (M+H). HRMS: Anal. Calcd. for

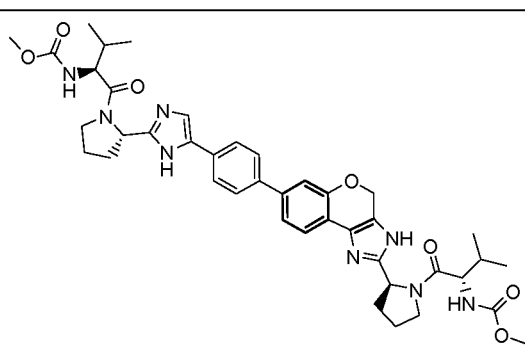
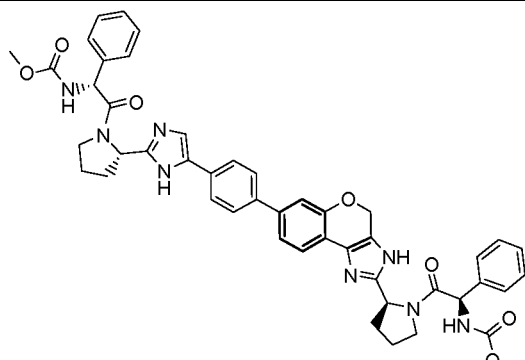
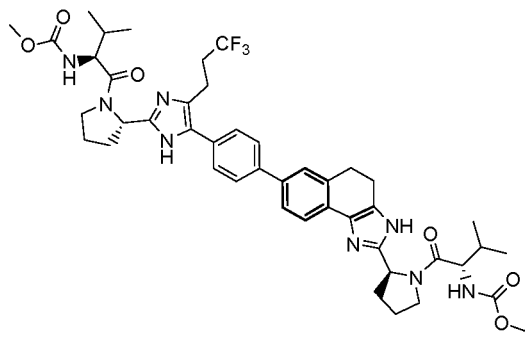
		$C_{53}H_{60}F_2N_8O_2$ 879.4886; found: 879.4855 (M+H).
Example 22i (Derived from Example 21i and Cap-51)		RT = 1.8 minutes (condition 2); LRMS: Anal. Calcd. for $C_{43}H_{56}N_9O$ 794.44; found: 794.41 (M+H). HRMS: Anal. Calcd. for $C_{43}H_{56}N_9O$ 794.4354; found: 794.4365 (M+H).
Example 22j (Derived from Example 21j and Cap-51)		RT= 1.6 minutes (condition 1); LCMS: Anal. Calcd. for $C_{43}H_{54}N_8O_6$ 779.42; found: 779.39 (M+H).
Example 22j.1 (Derived from Example 21j and Cap-2)		RT= 1.4 minutes (condition 1); LCMS: Anal. Calcd. for $C_{53}H_{62}N_8O_2$ 843.51; found:

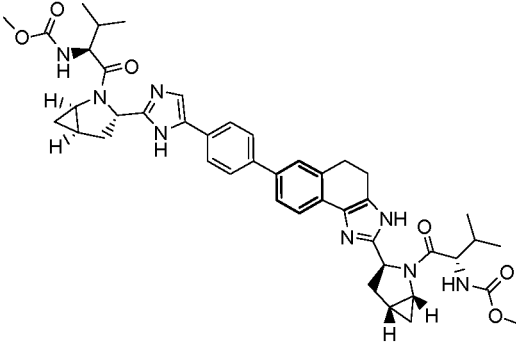
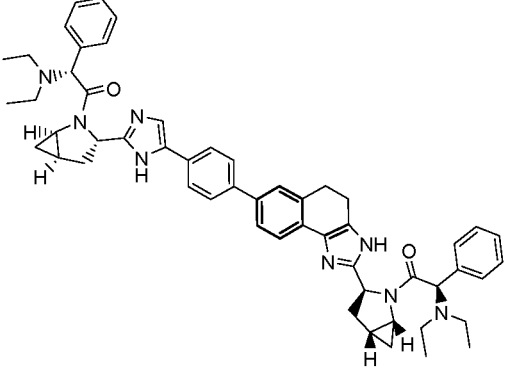
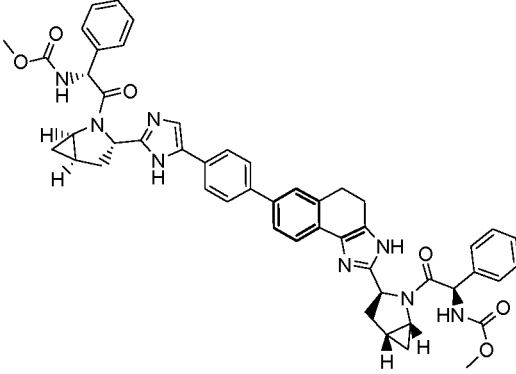
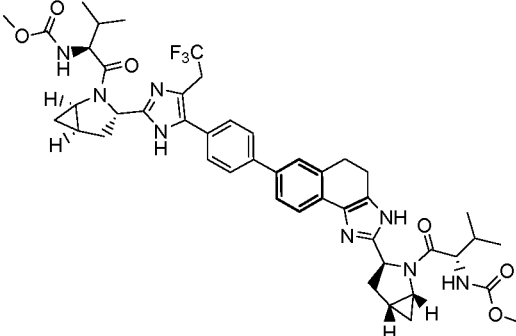
		843.48 (M+H). HRMS: Anal. Calcd. for $C_{53}H_{62}N_8O_4$ 843.5074; found: 843.5079 (M+H).
Example 22k (Derived from Example 21k and Cap-51)		RT= 1.7 minutes (condition 1); LCMS: Anal. Calcd. for $C_{46}H_{58}N_8O_6$ 819.46; found: 819.50 (M+H). HRMS: Anal. Calcd. for $C_{46}H_{58}N_8O_6$ 819.4558; found: 819.4547 (M+H).
Example 22k.1 (Derived from Example 21k and Cap-2)		RT= 1.4 minutes (condition 1); LCMS: Anal. Calcd. for $C_{56}H_{66}N_8O_2$ 883.54; found: 883.56 (M+H). HRMS: Anal. Calcd. for $C_{56}H_{66}N_8O_2$ 883.5387; found: 883.5353 (M+H).

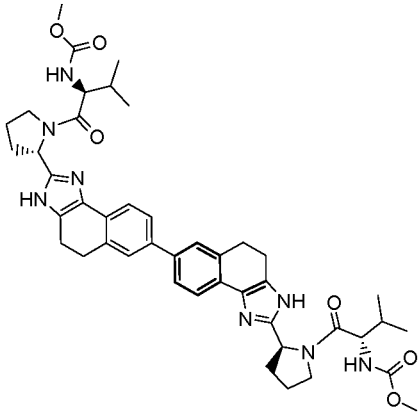
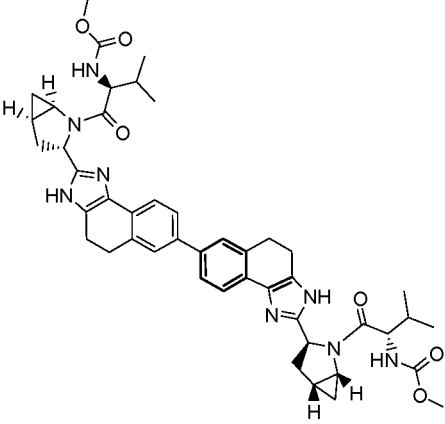
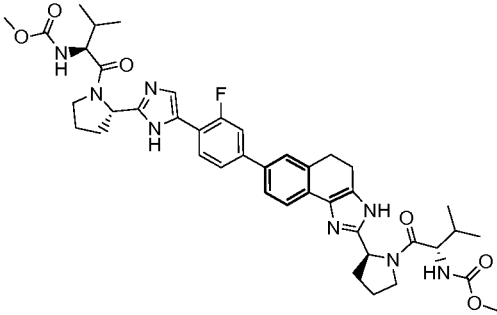
Example 22m (Derived from Example 21m and Cap-51)		RT = 1.6 minutes (condition 1); LRMS: Anal. Calcd. for C₄₄H₄₉N₇O₅ 756.39; found: 756.55 (M+H).
Example 22n (Derived from Example 21n and Cap-51)		RT = 2.1 minutes (condition 2); LRMS: Anal. Calcd. for C₄₃H₅₅N₈O₇ 795.41; found: 795.53 (M+H). HRMS: Anal. Calcd. for C₄₃H₅₅N₈O₇ 795.4188; found: 795.4188 (M+H).
Example 22n.1 (Derived from Example 21n and Cap-2)		RT= 1.9 minutes (condition 2); LRMS: Anal. Calcd. for C₅₃H₆₃N₈O₃ 859.49; found: 859.59 (M+H). HRMS: Anal. Calcd. for C₅₃H₆₃N₈O₃ 859.5018; found: 859.5015 (M+H).

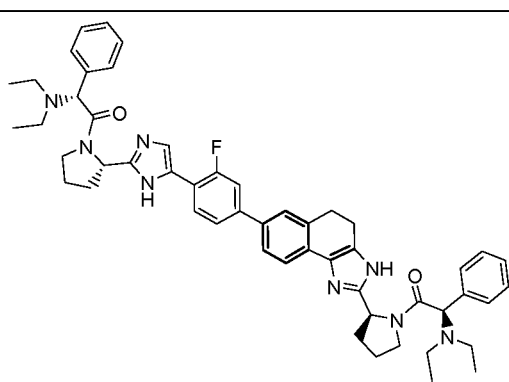
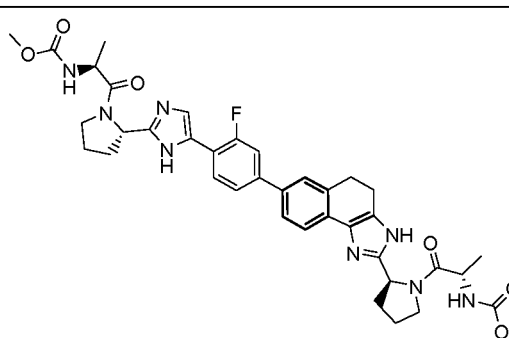
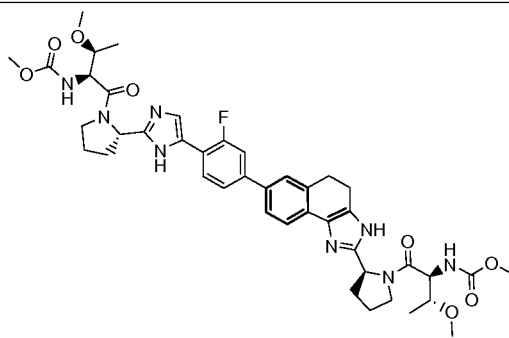
Example 22o (Derived from Example 21o and Cap-51)		RT = 1.5 minutes (condition 1); HRMS: Anal. Calcd. for $C_{43}H_{54}N_8O_5$ 779.4239; found: 779.4242 (M+H).
Example 22p (Derived from Example 21p and Cap-51)		RT = 1.5 minutes (condition 1); HRMS: Anal. Calcd. for $C_{43}H_{54}N_8O_5$ 779.4239; found: 779.4243 (M+H).
Example 22q (Derived from Example 21q and Cap-51)		RT = 2.2 minutes (condition 2); LRMS: Anal. Calcd. for $C_{44}H_{57}N_8O_7$ 809.43; found: 809.53 (M+H). HRMS: Anal. Calcd. for $C_{44}H_{57}N_8O_7$ 809.4345; found: 809.4345 (M+H)⁺.

Example 22q.1 (Derived from Example 21q and Cap-2)		RT = 1.9 minutes (condition 2); LRMS: Anal. Calcd. for $C_{54}H_{65}N_8O_3$ 873.51; found: 873.60 (M+H). HRMS: Anal. Calcd. for $C_{54}H_{65}N_8O_3$ 873.5174; found: 873.5171 (M+H).
Example 22r (Derived from Example 21r and Cap-51)		RT = 2.1 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{53}N_8O_6$ 765.41; found: 765.51 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{53}N_8O_6$ 765.4083; found: 765.4088 (M+H).
Example 22r.a (Derived from Example 21r and Cap-2)		RT = 1.8 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{61}N_8O_2$ 829.49; found: 829.65 (M+H). HRMS: Anal.

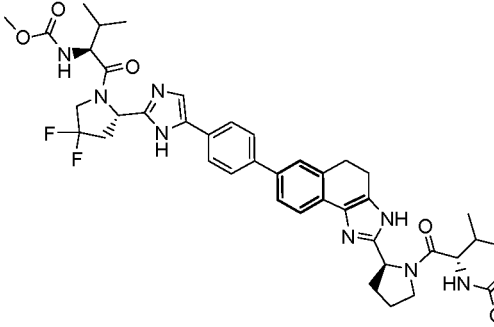
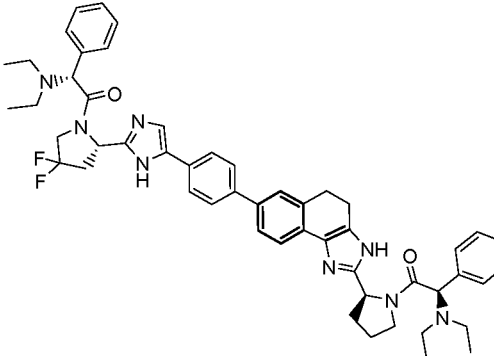
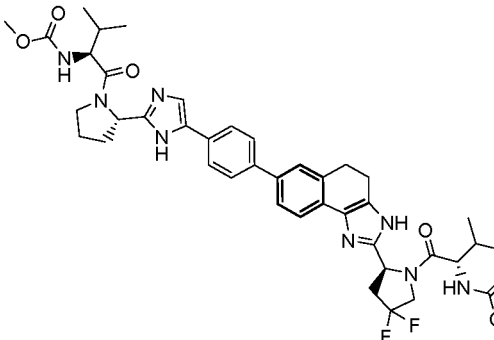
		Calcd. for $C_{52}H_{61}N_8O_2$ 829.4912; found: 829.4917 (M+H).
Example 22r.b (Derived from Example 21r.a and Cap-51)		RT = 2.1 minutes (condition 4); LCMS: Anal. Calcd. for $C_{41}H_{51}N_8O_7$ 767.67; found: 767.17 (M+H).
Example 22r.c (Derived from Example 21r.a and Cap-4)		RT = 2.2 minutes (condition 4); LCMS: Anal. Calcd. for $C_{47}H_{47}N_8O_7$ 835.35; found: parent not obs. (M+H).
Example 22r.1 (Derived from Example 21r.1 and Cap-51)		RT = 1.4 minutes (condition 1); LCMS: Anal. Calcd. for $C_{45}H_{56}N_8O_6$ 861.43; found: 861.61 (M+H).

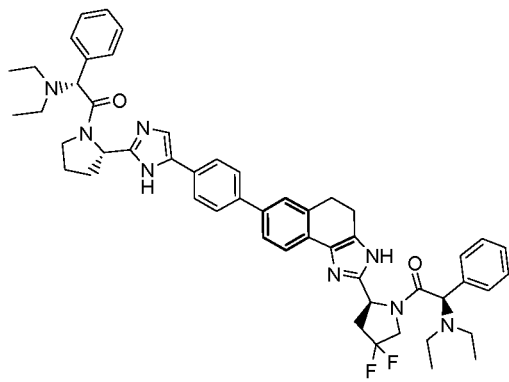
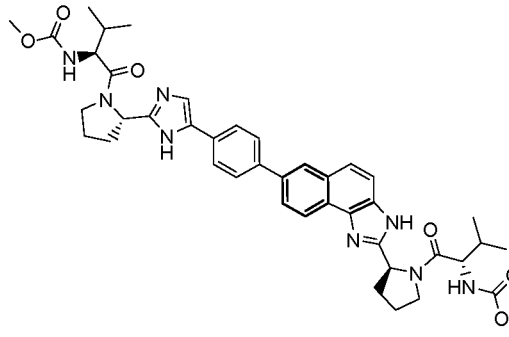
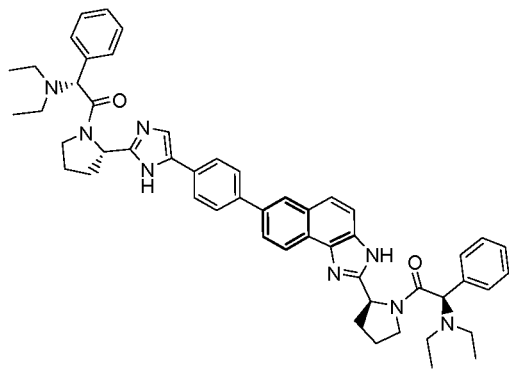
Example 22r.2 (Derived from Example 21r.2 and Cap-51)		RT = 1.95 min (condition 2). HRMS: Calcd for $C_{44}H_{53}N_8O_6$ 789.4083; found: 789.4098 (M+H).
Example 22r.2a (Derived from Example 21r.2 and Cap-2)		RT = 1.70 min (condition 2). HRMS: Calcd for $C_{54}H_{61}N_8O_2$ 853.4912; found: 853.4925 (M+H).
Example 22r.2b (Derived from Example 21r.2 and Cap-4)		RT = 1.85 min (condition 2); LCMS: Anal. Calcd for $C_{50}H_{49}N_8O_6$ 857.38; found: 857.41 (M+H).
Example 22r.3 (Derived from Example 21r.3 and Cap-51)		RT = 1.6 minutes (condition 1). HRMS: Anal. Calcd. for $C_{46}H_{54}F_3N_8O_6$ 871.4113; found: 871.4114 (M+H).

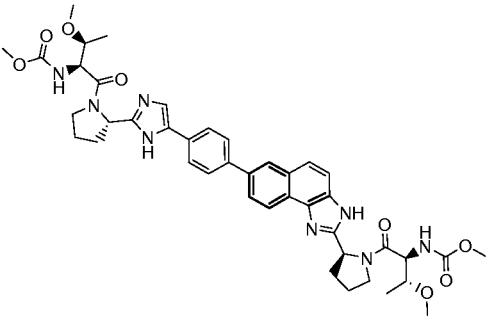
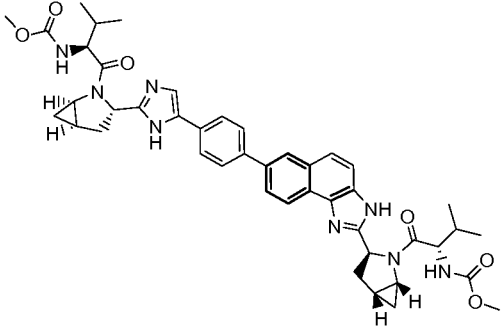
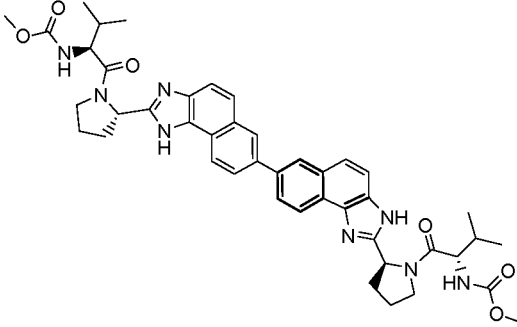
Example 22r.4 (Derived from Example 21r.4 and Cap-51)		RT = 1.97 min (condition 2). HRMS: Calcd for $C_{44}H_{55}N_8O_6$ 791.4239; found: 791.4329 (M+H).
Example 22r.5 (Derived from Example 21r.5 and Cap-51)		RT = 2.02 min (condition 2); LCMS: Anal. Calcd for $C_{46}H_{55}N_8O_6$ 815.42; found: 815.52 (M+H). HRMS: Calcd for $C_{46}H_{55}N_8O_6$ 815.4239; found: 813.4239 (M+H).
Example 22s (Derived from Example 21s and Cap-51)		RT = 2.1 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{52}FN_8O_6$ 783.39; found: 783.64 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{52}FN_8O_6$ 783.3988; found:

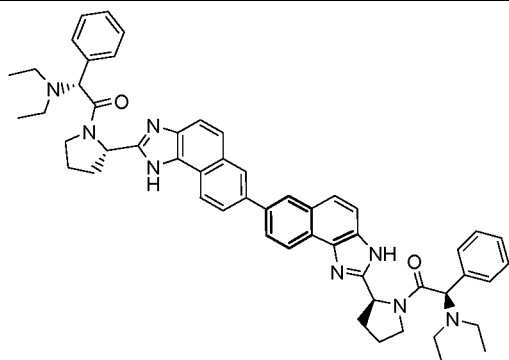
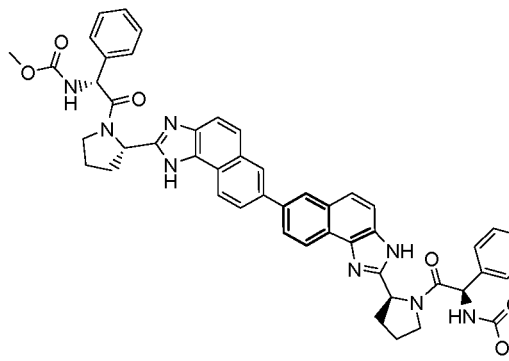
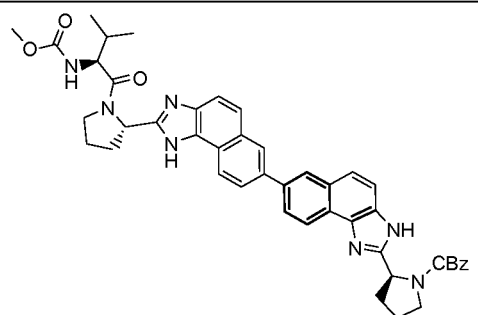
		783.3972 (M+H).
Example 22s.a (Derived from Example 21s and Cap-2)		RT = 1.8 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{60}FN_8O_2$ 847.47; found: 847.76 (M+H). HRMS: Anal. Calcd. for $C_{52}H_{60}FN_8O_2$ 847.4818; found: 847.4804 (M+H).
Example 22s.b (Derived from Example 21s and Cap-52)		RT = 1.8 minutes (condition 2); LCMS: Anal. Calcd. for $C_{38}H_{43}FN_8O_6$ 727.34; found: 727.70 (M+H). HRMS: Anal. Calcd. for $C_{38}H_{43}FN_8O_6$ 727.3362; found: 727.3378 (M+H).
Example 22s.c (Derived from Example 21s and Cap-86)		RT = 1.9 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{51}FN_8O_8$ 815.39; found: 815.73 (M+H).

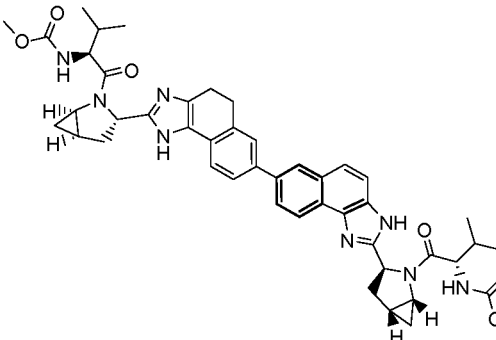
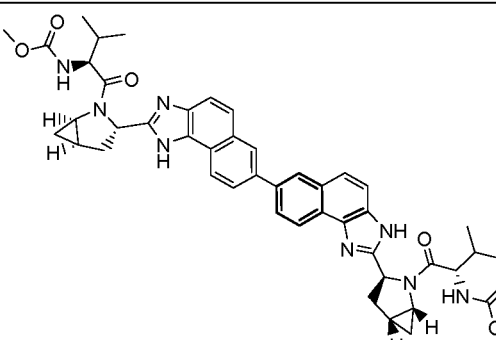
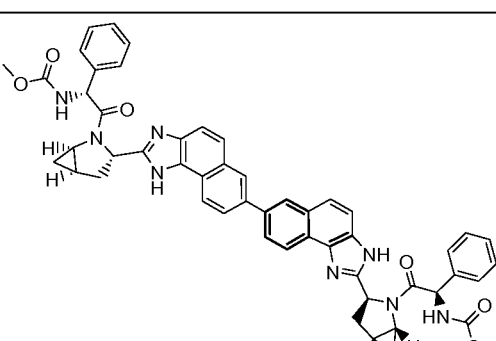
		HRMS: Anal. Calcd. for $C_{42}H_{51}FN_8O_8$ 815.3887; found: 815.3916 (M+H).
Example 22s.1 (Derived from Example 21s.1 and Cap-51)		RT = 2.00 min, (condition 2). HRMS: Calcd for $C_{44}H_{52}FN_8O_6$ 807.3988; found: 807.4008 (M+H).
Example 22s.1a (Derived from Example 21s.1 and Cap-2)		RT = 1.74 min, (condition 2). HRMS: Calcd for $C_{54}H_{60}FN_8O_2$ 871.4818; found: 871.4830 (M+H)..
Example 22s.1b (Derived from Example 21s.1 and Cap-4)		RT = 2.02 min (condition 2); LCMS: Anal. Calcd for $C_{50}H_{48}FN_8O_6$ 875.37; found: 875.53 (M+H).

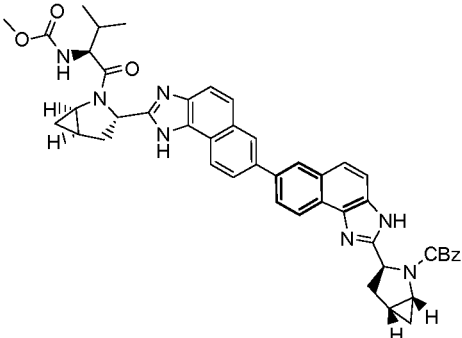
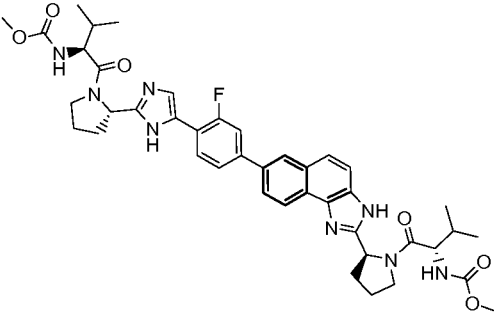
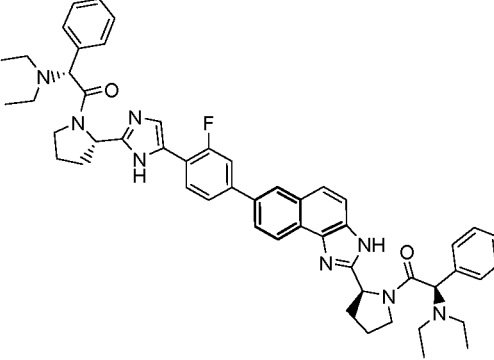
Example 22t (Derived from Example 21t and Cap-51)		RT = 2.0 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{51}F_2N_8O_6$ 801.39; found: 801.73 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{51}F_2N_8O_6$ 801.3900; found: 801.3874 (M+H).
Example 22t.a (Derived from Example 21t and Cap-2)		RT = 1.8 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{59}F_2N_8O_2$ 865.47; found: 865.86 (M+H). HRMS: Anal. Calcd. for $C_{52}H_{59}F_2N_8O_2$ 865.4729; found: 865.4706 (M+H).
Example 22t.1 (Derived from Example 21t.1 and Cap-51)		RT = 2.0 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{50}F_2N_8O_6$ 801.39; found: 801.45 (M+H). HRMS: Anal.

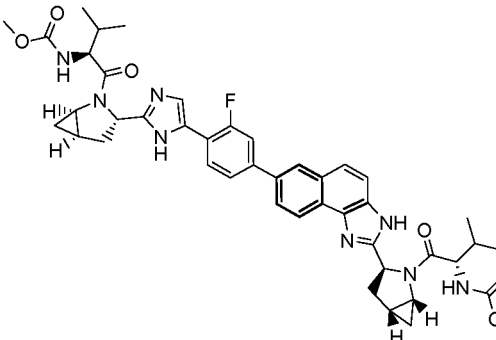
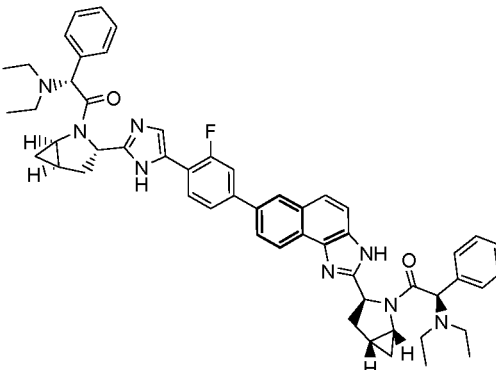
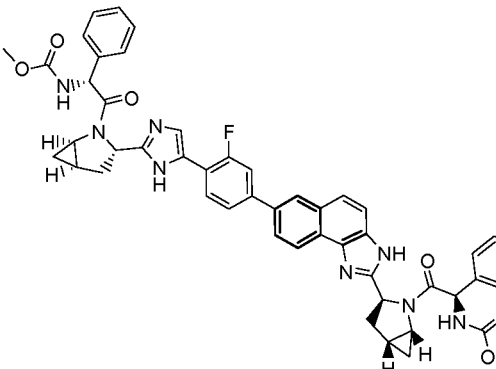
		Calcd. for $C_{42}H_{50}F_2N_8O_6$ 801.3894; found: 801.3923 (M+H).
Example 22t.1a (Derived from Example 21t.1 and Cap-2)		RT = 1.8 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{59}F_2N_8O_2$ 865.47; found: 865.54 (M+H). HRMS: Anal. Calcd. for $C_{52}H_{59}F_2N_8O_2$ 865.4724; found: 865.4735 (M+H).
Example 22u (Derived from Example 21u and Cap-51)		RT = 2.0 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{51}N_8O_6$ 763.39; found: 763.75 (M+H).
Example 22u.a (Derived from Example 21u and Cap-2)		RT = 1.8 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{59}N_8O_2$ 827.48; found: 827.75 (M+H). HRMS: Anal. Calcd. for

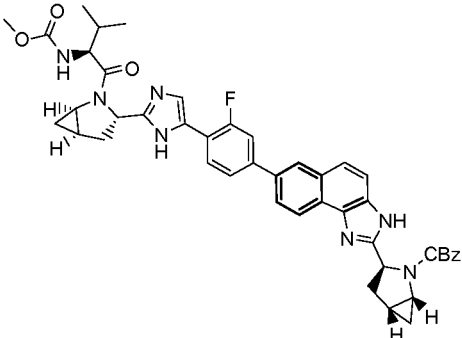
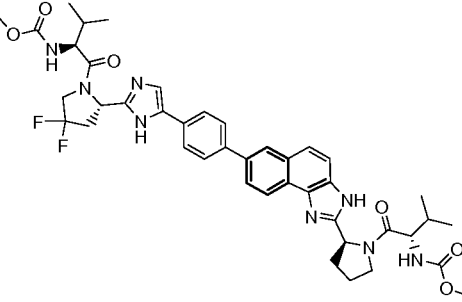
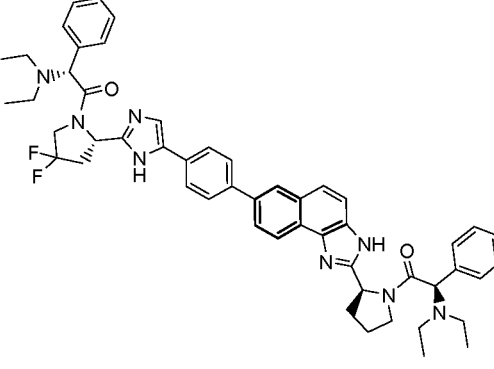
		$C_{52}H_{59}N_8O_2$ 827.4756; found: 827.4762 (M+H).
Example 22u.b (Derived from Example 21u and Cap-86)		RT = 1.9 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{51}N_8O_8$ 795.38; found: 795.72 (M+H).
Example 22u.1 (Derived from Example 21u.1 and Cap-51)		RT = 2.00 min, (condition 2), LCMS: Anal. Calcd for $C_{44}H_{51}N_8O_6$ 787.39; found: 787.39 (M+H). HRMS: Calcd for $C_{44}H_{51}N_8O_6$ 787.3926; found: 787.3944 (M+H).
Example 22u.2 (Derived from Example 21x and Cap-51)		RT = 2.0 minutes (condition 2); LRMS: Anal. Calcd. for $C_{44}H_{51}N_8O_6$ 787.39; found: 787.58 (M+H). HRMS: Anal. Calcd. for $C_{44}H_{51}N_8O_6$ 787.3926; found:

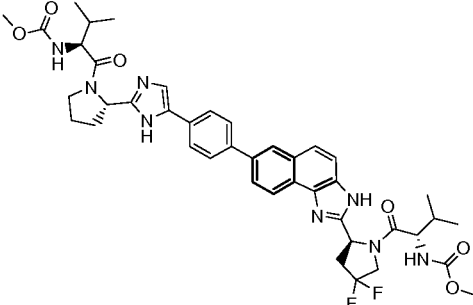
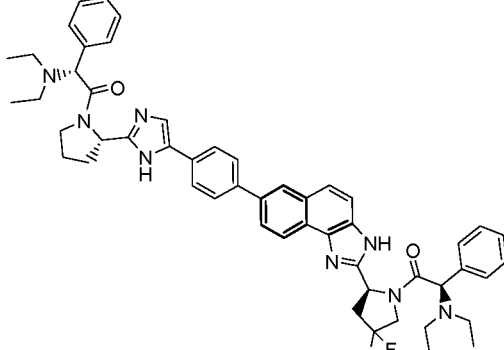
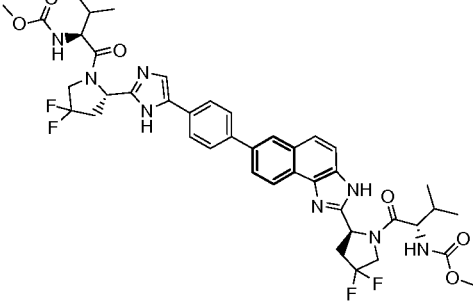
		787.3921 (M+H).
Example 22u.2a (Derived from Example 21x and Cap-2)		RT = 1.86 min, (condition 2), LCMS: Anal. Calcd for $C_{54}H_{59}N_8O_2$ 851.48; found: 851.44 (M+H). HRMS: Calcd for $C_{54}H_{59}N_8O_2$ 851.4755; found: 851.4756 (M+H).
Example 22u.2b (Derived from Example 21x and Cap-4)		RT = 2.14 min, (condition 2), LCMS: Anal. Calcd for $C_{50}H_{47}N_8O_6$ 855.36; found: 855.58 (M+H). HRMS: Calcd for $C_{50}H_{47}N_8O_6$ 855.3613; found: 855.3611 (M+H).
Example 22u.3 (Derived from Example 21u.3 and Cap-51)		RT = 2.18 min, (condition 2), LCMS: Anal. Calcd for $C_{45}H_{46}N_7O_5$ 764.36; found: 764.57 (M+H).

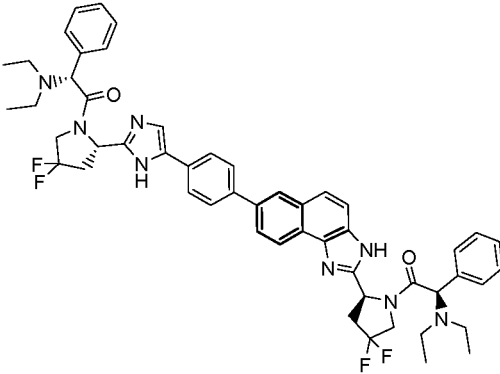
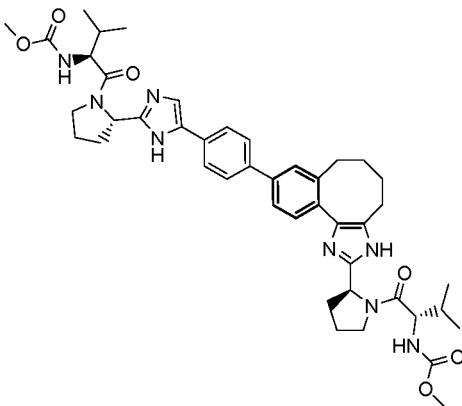
Example 22u.4 (Derived from Example 21u.4 and Cap-51)		RT = 2.08 min (condition 2); LCMS: Anal. Calcd for $C_{46}H_{53}N_8O_6$ 813.41; found: 813.35 (M+H). HRMS: Calcd for $C_{46}H_{53}N_8O_6$ 813.4083; found: 813.4087 (M+H).
Example 22u.5 (Derived from Example 21u.5 and Cap-51)		RT = 2.14 min, (condition 2), LCMS: Anal. Calcd for $C_{46}H_{51}N_8O_6$ 811.39; found: 811.39 (M+H). HRMS: Calcd for $C_{46}H_{51}N_8O_6$ 811.3926; found: 811.3945 (M+H).
Example 22u.5a (Derived from Example 21u.5 and Cap-4)		RT = 2.02 min (condition 2); LCMS: Anal. Calcd for $C_{52}H_{47}N_8O_6$ 879.36; found: 879.53 (M+H).

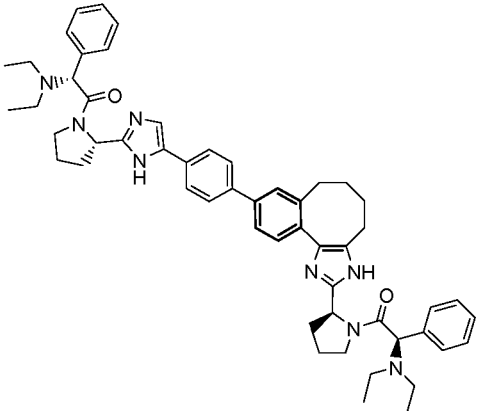
Example 22u.6 (Derived from Example 21u.6 and Cap-51)		RT = 2.02 min; (condition 2); LCMS: Anal. Calcd for $C_{47}H_{46}N_7O_5$ 788.41; found: 788.36 (M+H).
Example 22v (Derived from Example 21v and Cap-51)		RT = 2.1 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{50}FN_8O_6$ 781.38; found: 781.85 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{50}FN_8O_6$ 781.3832; found: 781.3850 (M+H).
Example 22v.a (Derived from Example 21v and Cap-2)		RT = 1.7 minutes (condition 2). HRMS: Anal. Calcd. for $C_{52}H_{58}FN_8O_2$ 845.4661; found: 845.4655 (M+H).

Example 22v.1 (Derived from Example 21v.1 and Cap-51)		RT = 2.05 min, (condition 2), Calcd for $C_{44}H_{50}FN_8O_6$ 805.38; found: 805.35 (M+H). HRMS: Calcd for $C_{44}H_{50}FN_8O_6$ 805.3832; found: 805.3850 (M+H).
Example 22v.1a (Derived from Example 21v.1 and Cap-2)		RT = 1.38 min, (condition 2). HRMS: Calcd for $C_{54}H_{58}FN_8O_2$ 869.4678 found: 869.4661 (M+H).
Example 22v.1b (Derived from Example 21v.1 and Cap-4)		RT = 1.94 min (condition 2); Anal. Calcd for $C_{50}H_{47}FN_8O_6$ 873.35; found: 873.33 (M+H).

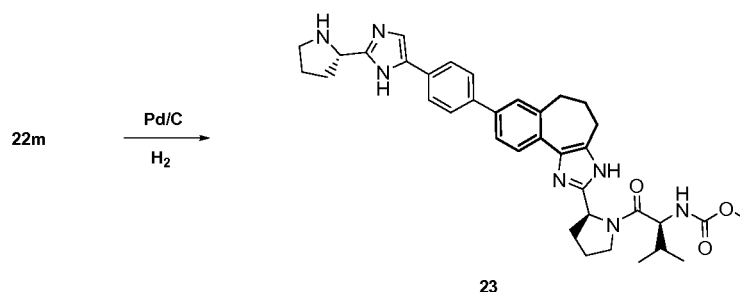
Example 22v.1c (Derived from Example 21v.2 and Cap-51)		RT = 1.88 minutes (condition 2); LCMS: Anal. Calcd. for $C_{45}H_{45}FN_7O_5$ 782.35; found: 782.22 (M+H).
Example 22w (Derived from Example 21w and Cap-51)		RT = 2.1 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{49}F_2N_8O_6$ 799.37; found: 799.81 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{49}F_2N_8O_6$ 799.3738; found: 799.3759 (M+H).
Example 22w.a (Derived from Example 21w and Cap-2)		RT = 1.7 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{57}F_2N_8O_2$ 863.47; found: 863.64 (M+H). HRMS: Anal. Calcd. for $C_{52}H_{57}F_2N_8O_2$ 863.4567; found: 863.4561 (M+H).

Example 22w.1 (Derived from Example 21w.1 and Cap-51)		RT = 2.1 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{49}F_2N_8O_6$ 799.37; found: 799.41 (M+H). HRMS: Anal. Calcd. for $C_{42}H_{49}F_2N_8O_6$ 799.3738; found: 799.3761 (M+H).
Example 22w.1a (Derived from Example 21w.1 and Cap-2)		RT = 2.0 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{57}F_2N_8O_2$ 863.46; found: 863.50 (M+H). HRMS: Anal. Calcd. for $C_{52}H_{57}F_2N_8O_2$ 863.4567; found: 863.4575 (M+H).
Example 22w.2 (Derived from Example 21w.2 and Cap-51)		RT = 2.1 minutes (condition 2); LCMS: Anal. Calcd. for $C_{42}H_{47}F_4N_8O_6$ 835.36; found: 835.61 (M+H). HRMS: Anal.

		Calcd. for $C_{42}H_{47}F_4N_8O_6$ 835.3549; found: 835.3547 (M+H).
Example 22w.2a (Derived from Example 21w.2 and Cap-2)		RT = 2.0 minutes (condition 2); LCMS: Anal. Calcd. for $C_{52}H_{55}F_4N_8O_2$ 899.44; found: 899.66 (M+H). HRMS: Anal. Calcd. for $C_{52}H_{55}F_4N_8O_2$ 899.4379; found: 899.4375 (M+H).
Example 22x.1 (Derived from Example 21x.1 and Cap-51)		RT = 2.1 minutes (condition 2); LRMS: Anal. Calcd. for $C_{44}H_{57}N_8O_6$ 793.43; found: 793.48 (M+H). HRMS: Anal. Calcd. for $C_{44}H_{57}N_8O_6$ 793.4396; found: 793.4396 (M+H).

Example 22x.1a (Derived from Example 21x.1 and Cap-2)		RT = 1.8 minutes (condition 2); LRMS: Anal. Calcd. for C₅₄H₆₅N₈O₂ 857.52; found: 857.61 (M+H). HRMS: Anal. Calcd. for C₅₄H₆₅N₈O₂ 857.5225; found: 857.5219 (M+H).
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Synthetic route 15 (Unsymmetrical Cap Analogs)

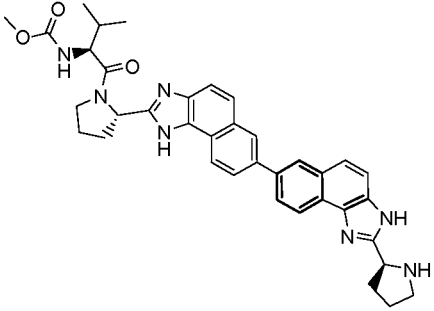
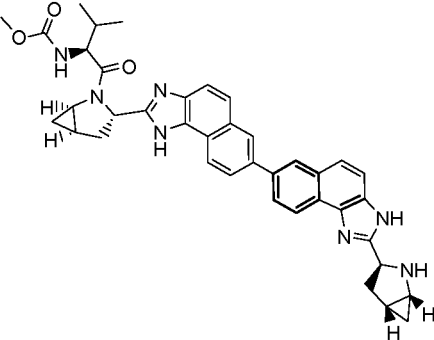
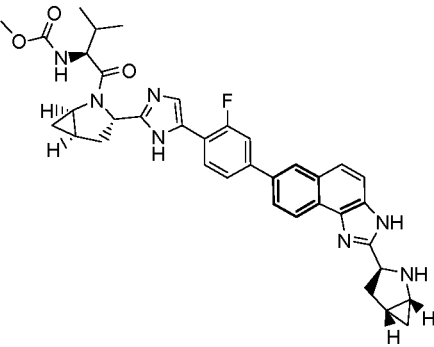


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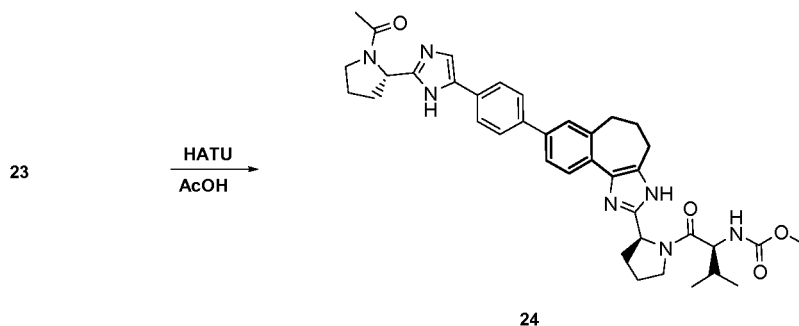
A solution of Example 22m, (149 mg, 0.197 mmol) and K₂CO₃ (27 mg) in CH₃OH (5 mL) and water (0.3 mL) was flushed with nitrogen and 10% palladium/carbon (30 mg) added. The reaction was flushed with hydrogen and stirred 6 h, filtered through diatomaceous earth (Celite[®]), and the filtrate concentrated and dried under high vacuum to give Example 23, 122 mg (100%) RT = 1.5 minutes (condition 1). ¹H NMR (500 MHz, DMSO-d₆) δ 8.05 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 2H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.50-7.40 (m, 3H), 7.28 (d, *J* = 8.6 Hz, 1H), 5.04 (br. s, 1H), 4.18 (t, *J* = 7.0 Hz, 1H), 4.09 (t, *J* = 8.2 Hz, 1H), 3.82 (br. s, 2H), 3.55 (s, 3H), 3.01-2.85 (m, 6H), 2.16-1.71 (m, 10H), 0.9-0.87 (m, 7H).

LRMS: Anal. Calcd. for C₃₆H₄₃N₇O₃ 622.35; found: 622.44 (M+H).

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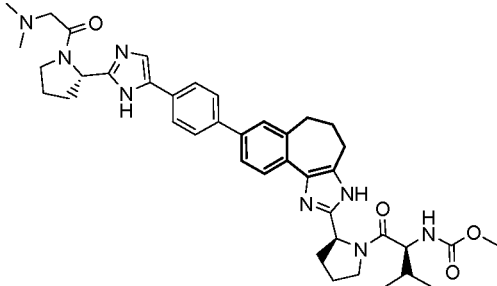
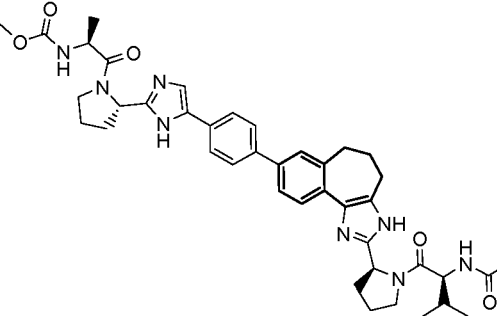
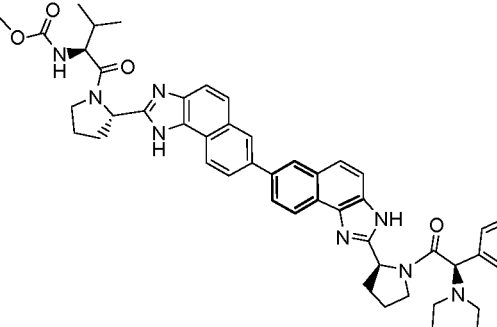
Example 23.1 (Derived from Example 22u.3)		RT = 1.90 minutes (condition 2), LCMS: Calcd for $C_{37}H_{40}N_7O_3$ 630.32; found: 630.41 (M+H).
Example 23.2 (Derived from Example 22u.6)		RT = 1.75 minutes (condition 2), LCMS: Calcd for $C_{39}H_{40}N_7O_3$ 654.32; found: 654.35 (M+H).
Example 23.3 (Derived from Example 22v.1c)		RT = 1.57 minutes (condition 2), LCMS: Calcd for $C_{37}H_{39}FN_7O_3$ 648.31; found: 648.21 (M+H).

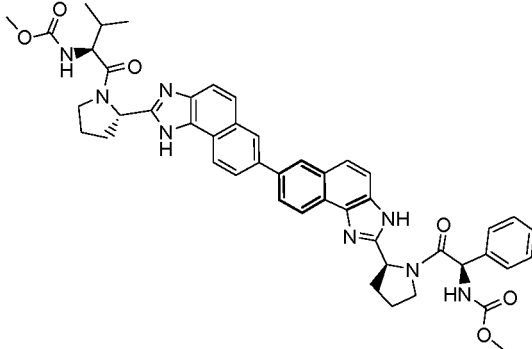
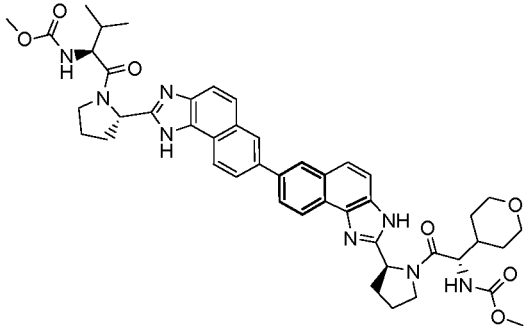
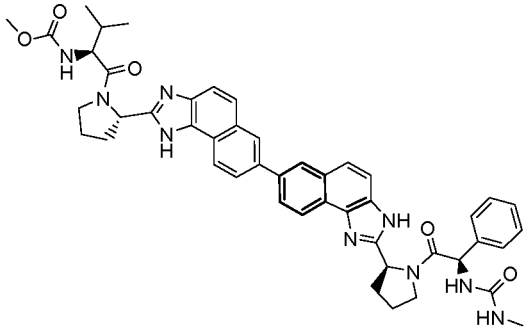
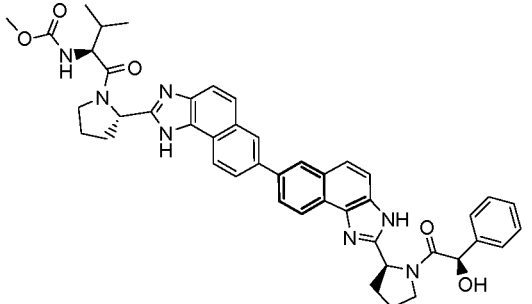
Synthetic route 16 (Unsymmetrical Cap Analogs)

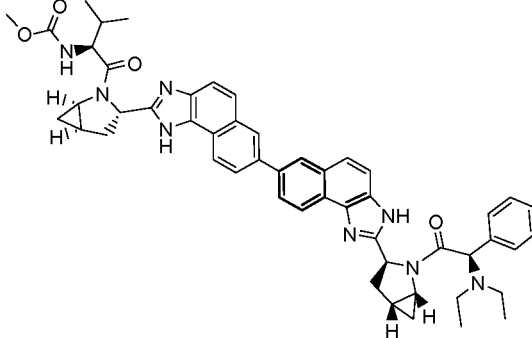
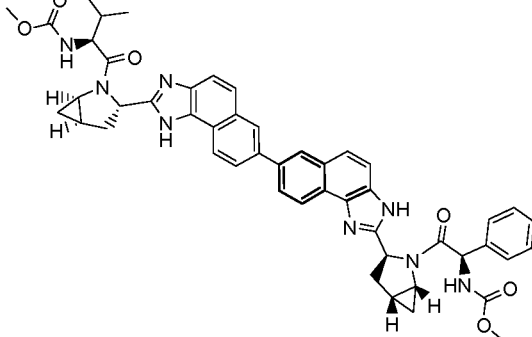
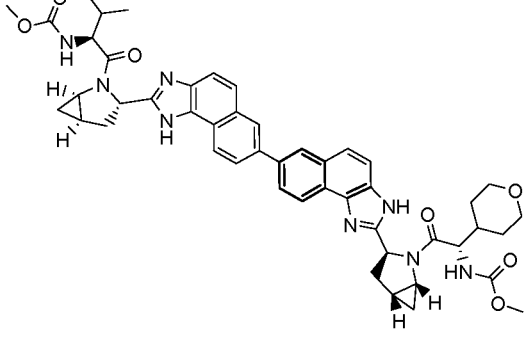
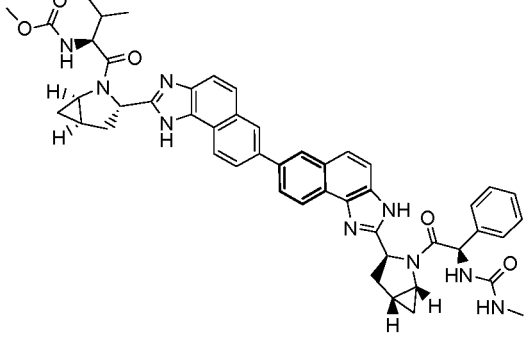


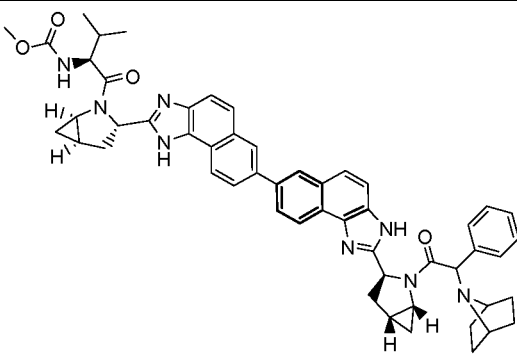
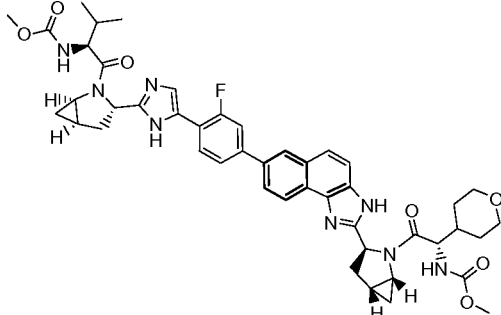
Capping was performed on Example 23 as described in synthetic route 14 to prepare
 5 Example 22. Except only 1 equivalent of HATU and 4 equivalents Hunig's base

were used to prepare Example 24: RT = 1.5 minutes (condition 1); LCMS: Anal. Calcd. for $C_{38}H_{45}N_7O_4$ 664.36; found: 664.48 (M+H).

Example 24.a (Derived from Example 23 and N,N-dimethyl glycine)		RT = 1.4 minutes (condition 1); LCMS: Anal. Calcd. for $C_{40}H_{50}N_8O_4$ 707.40; found: 707.53 (M+H).
Example 24.b (Derived from Example 23 and Cap-52)		RT = 1.5 minutes (condition 1); LCMS: Anal. Calcd. for $C_{41}H_{50}N_8O_6$ 751.39; found: 751.33 (M+H).
Example 24.1 (Derived from Example 23.1 and Cap-2)		RT = 1.95 min, (condition 2), LCMS: Calcd for $C_{49}H_{55}N_8O_4$ 819.43; found: 819.65 (M+H).

Example 24.1a (Derived from Example 23.1 and Cap-4)		RT = 2.10 (condition 2), LCMS: Calcd for $C_{47}H_{49}N_8O_8$ 821.38; found: 821.61 (M+H).
Example 24.1b (Derived from Example 23.1 and Cap-170)		RT = 1.98 min (condition 2), LCMS: Calcd for $C_{46}H_{53}N_8O_7$ 829.40; found: 829.61 (M+H).
Example 24.1c (Derived from Example 23.1 and Cap-45a)		RT = 2.14 min (condition 2), LCMS: Calcd for $C_{48}H_{52}N_9O_5$ 834.41; found: 834.60 (M+H).
Example 24.1d (Derived from Example 23.1 and R-Mandelic acid)		RT = 2.02 min, (condition 2), LCMS: Calcd for $C_{45}H_{46}N_7O_5$ 764.36; found: 764.57 (M+H).

Example 24.2 (Derived from Example 23.2 and Cap-2)		RT = 1.80 min; (condition 2); LCMS: Calcd for $C_{51}H_{55}N_8O_4$ 843.43; found: 843.48 (M+H).
Example 24.2a (Derived from Example 23.2 and Cap-4)		RT = 1.99 min; (condition 2); LCMS: Calcd for $C_{49}H_{49}N_8O_6$ 845.38; found: 845.32 (M+H).
Example 24.2b (Derived from Example 23.2 and Cap-170)		RT = 1.85 min (condition 2); LCMS: Calcd for $C_{48}H_{53}N_8O_7$ 853.40; found: 853.51 (M+H).
Example 24.2c (Derived from Example 23.2 and Cap-45a)		RT = 2.02 min, (condition 2), LCMS: Calcd for $C_{50}H_{52}N_9O_5$ 858.41; found: 858.36 (M+H).

Example 24.2d (Derived from Example 23.2 and Cap-77)		RT = 1.81 min; (condition 2); LCMS: Calcd for $C_{53}H_{55}N_8O_4$ 867.43; found: 867.47 (M+H).
Example 24.3 (Derived from Example 23.3 and Cap-170)		RT = 1.68 min; (condition 2); LCMS: Calcd for $C_{46}H_{52}FN_8O_7$ 847.40; found: 847.32 (M+H).

BIOLOGICAL ACTIVITY

An HCV Replicon assay was utilized in the present disclosure, and was prepared, conducted and validated as described in commonly owned

5 PCT/US2006/022197 and in O'Boyle et. al. *Antimicrob Agents Chemother.* **2005** Apr;49(4):1346-53.

HCV 1b-377-neo replicon cells were used to test the currently described compound series as well as cells resistant to compound A containing a Y2065H mutation in NS5A (described in application PCT/US2006/022197). The compounds

10 tested were determined to have more than 10-fold less inhibitory activity on cells containing the mutation than wild-type cells indicating a related mechanism of action between the two compound series. Thus, the compounds of the present disclosure can be effective to inhibit the function of the HCV NS5A protein and are understood to be as effective in combinations as previously described in application

15 PCT/US2006/022197 and commonly owned WO/O4014852. Further, the compounds of the present disclosure can be effective against the HCV 1b genotype.

It should also be understood that the compounds of the present disclosure can inhibit multiple genotypes of HCV. Table 2 shows the EC₅₀ values of representative compounds of the present disclosure against the HCV 1b genotype. In one embodiment compounds of the present disclosure are active against the 1a, 1b, 2a, 2b, 3a, 4a, and 5a genotypes. EC₅₀ ranges against HCV 1b are as follows: A = >100 nM; B = 1-99 nM; C = 101-999 pM; and D = 1-100 pM.

The compounds of the present disclosure may inhibit HCV by mechanisms in addition to or other than NS5A inhibition. In one embodiment the compounds of the present disclosure inhibit HCV replicon and in another embodiment the compounds of the present disclosure inhibit NS5A.

Table 2

<i>Example</i>	<i>Activity or Range</i>
22	5 pM
22.1	D
22.2	D
22.3	D
22a.1	D
22a.2	D
22a.3	10 pM
22a.4	D
22b	D
22b.1	D
22b.2	D
22b.3	D
22c	D
22c.1	D
22c.3	D
22d	D
22e	3 pM
22f	D
22g	1 pM

22g.1	D
22g.2	20 pM
22g.3	D
22h	D
22h.1	D
22i	130 pM
22j	14 nM
22j.1	B
22k	D
22k.1	D
22m	D
22n	D
22n.1	D
22o	C
22p	160 pM
22q	D
22q.1	D
22r	D
22r.a	D
22r.b	D
22r.1	D
22r.2	D
22r.2a	D
22r.2b	D
22r.3	3 pM
22r.4	D
22r.5	D
22s	D
22s.a	D
22s.c	20 pM
22s.1	D
22s.1a	D

22s.1b	D
22t	1 pM
22t.a	D
22t.1	D
22t.1a	D
22u	D
22u.a	10 pM
22u.b	D
22u.1	D
22u.2	D
22u.2a	D
22u.2b	20 pM
22u.4	D
22u.5	D
22u.5a	D
22v	D
22v.a	C
22v.1	D
22v.1a	D
22v.1b	D
22w	D
22w.a	120 pM
22w.1	D
22w.1a	D
22w.2	D
22w.2a	D
22x.1	D
22x.1a	D
24	320 pM
24.a	D
24.b	D
24.1	D

24.1a	D
24.1b	D
24.1c	D
24.1d	D
24.2	D
24.2a	D
24.2b	D
24.2c	D
24.2d	D
24.3	

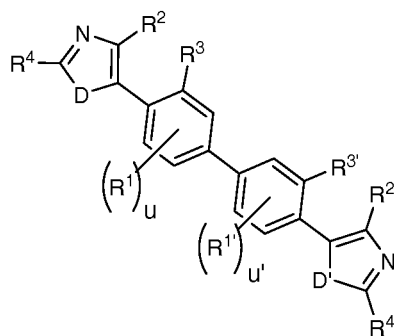
It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore
5 desired that the examples be considered in all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

The compounds of the present disclosure may inhibit HCV by mechanisms in
10 addition to or other than NS5A inhibition. In one embodiment the compounds of the present disclosure inhibit HCV replicon and in another embodiment the compounds of the present disclosure inhibit NS5A. Compounds of the present disclosure may inhibit multiple genotypes of HCV.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein

u and u' are independently 0, 1, 2, or 3;

- D and D' are each independently selected from NR⁵, O, and S; wherein each R⁵ is independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, hydroxy, (NR^aR^b)carbonyl, and trialkylsilylalkoxyalkyl;

- each R¹ and R^{1'} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

R² is selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl; and

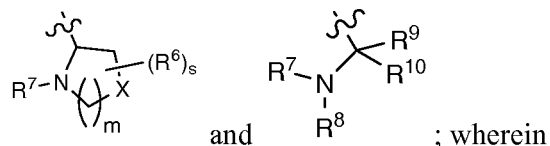
- R³ is selected from hydrogen, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, -NR^aR^b, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl; or

- R² and R³, together with the carbon atoms to which they are attached, form a five- to eight-membered aromatic or non-aromatic ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the five- to eight-membered ring is optionally substituted with one, two, or three substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylsulfonyl, aryl, arylalkyl, arylsulfonyl, carboxy, formyl, halo, haloalkoxy,

haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b) alkyl, (NR^aR^b) carbonyl, oxo, and spirocycle;

$R^{2'}$ and $R^{3'}$, together with the carbon atoms to which they are attached, form a five- to eight-membered aromatic or non-aromatic ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the five- to eight-membered ring is optionally substituted with one, two, or three substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylsulfonyl, aryl, arylalkyl, arylsulfonyl, carboxy, formyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b) alkyl, (NR^aR^b) carbonyl, oxo, and spirocycle;

R^4 and $R^{4'}$ are each independently selected from



each m is independently 0, 1, or 2;

each s is independently 0, 1, 2, 3, or 4;

each X is independently selected from O, S, S(O), SO₂, CH₂, CHR⁶, and C(R⁶)₂; provided that when n is 0, X is selected from CH₂, CHR⁶, and C(R⁶)₂;

each R^6 is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^aR^b$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

each R^7 is independently selected from hydrogen and R¹¹-C(O)-, and R¹¹-C(S)-;

R^8 is selected from hydrogen and alkyl;

R^9 and R^{10} are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and (NR^aR^b) alkyl; or,

R^9 and R^{10} , together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from NR^z, O, and S; wherein R^z is selected from hydrogen and alkyl; and each R^{11} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy,

arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclioxyalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d) alkenyl, (NR^cR^d) alkyl, and (NR^cR^d) carbonyl.

5

2. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein D and D' are each NR^5 .

3. A compound of claim 2, or a pharmaceutically acceptable salt thereof,
10 wherein each R^5 is independently selected from hydrogen and hydroxy.

4. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein u and u' are each 0.

15 5. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from hydrogen and haloalkyl.

6. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from hydrogen and halo.

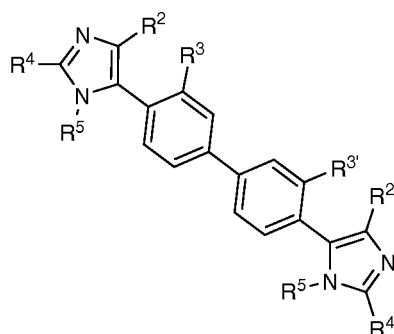
20

7. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 , together with the carbon atoms to which they are attached, form a six- or seven-membered carbocyclic ring.

25 8. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein $R^{2'}$ and $R^{3'}$, together with the carbon atoms to which they are attached, form a six- to eight-membered ring optionally containing one heteroatom selected from oxygen, nitrogen, and sulfur; wherein the ring is optionally substituted with one or two alkyl groups.

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9. A compound of Formula (II)



(II),

or a pharmaceutically acceptable salt thereof, wherein

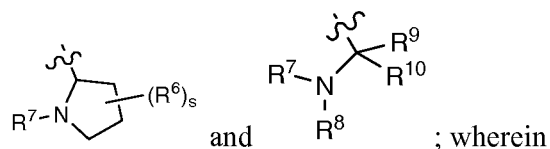
R^2 is selected from hydrogen and haloalkyl; and

5 R^3 is selected from hydrogen and halo; or

R^2 and R^3 , together with the carbon atoms to which they are attached, form a five- or six-membered aromatic or non-aromatic ring carbocyclic ring;

$R^{2'}$ and $R^{3'}$, together with the carbon atoms to which they are attached, form a six- to eight-membered aromatic or non-aromatic ring optionally containing one
 10 heteroatom selected from oxygen, nitrogen, and sulfur; wherein the ring is optionally substituted with one or two alkyl groups;

$R^{4'}$ and $R^{4'}$ are each independently selected from



each s is 0 or 2;

15 each R^6 is independently selected from alkyl and halo, wherein the alkyl forms a fused three-membered ring with an adjacent carbon atom;

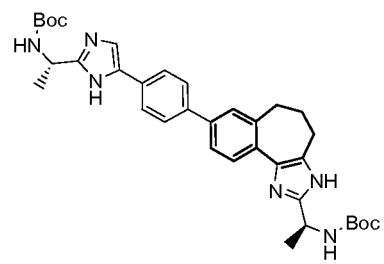
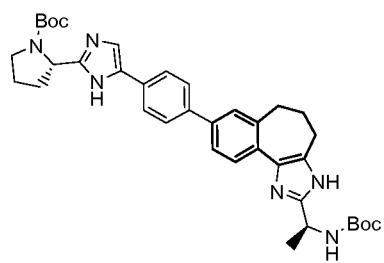
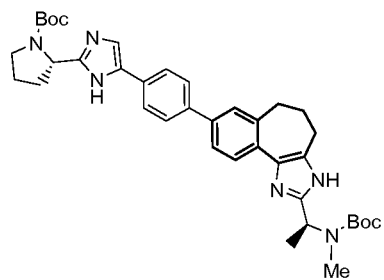
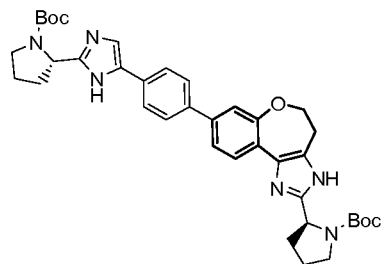
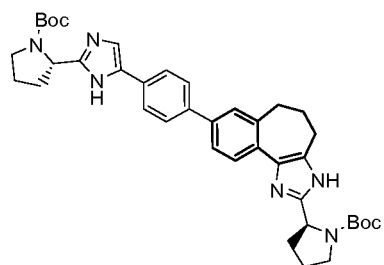
each R^7 is independently selected from hydrogen and $R^{11}-C(O)-$;

R^8 is selected from hydrogen and alkyl;

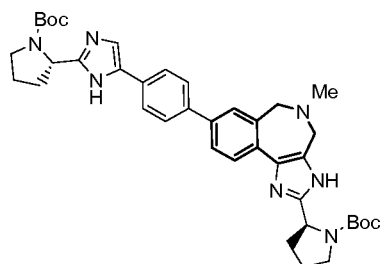
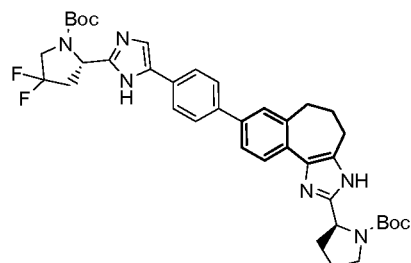
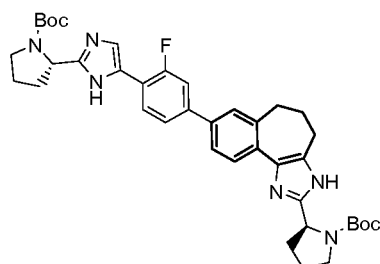
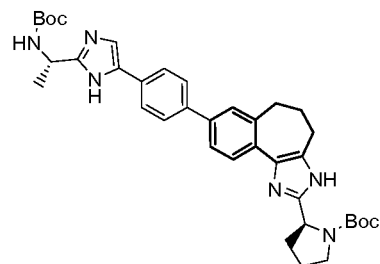
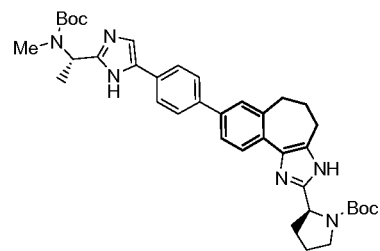
R^9 and R^{10} are each independently selected from hydrogen and alkyl; and

20 each R^{11} is independently selected from alkyl, arylalkoxy, arylalkyl, and $(NR^cR^d)alkyl$.

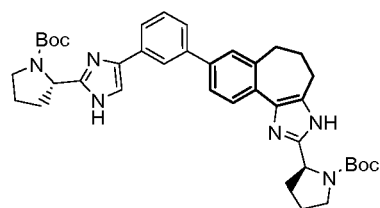
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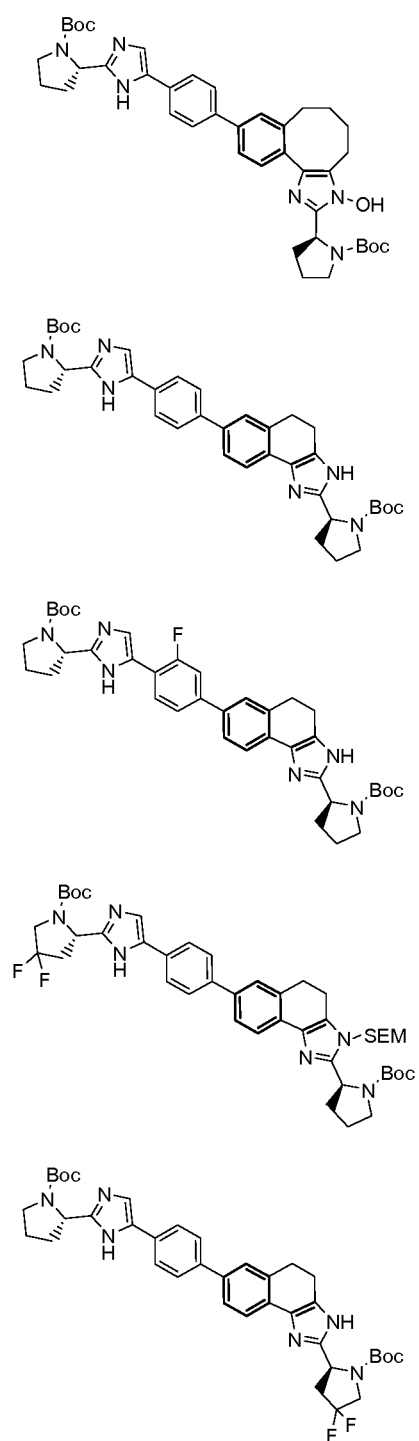
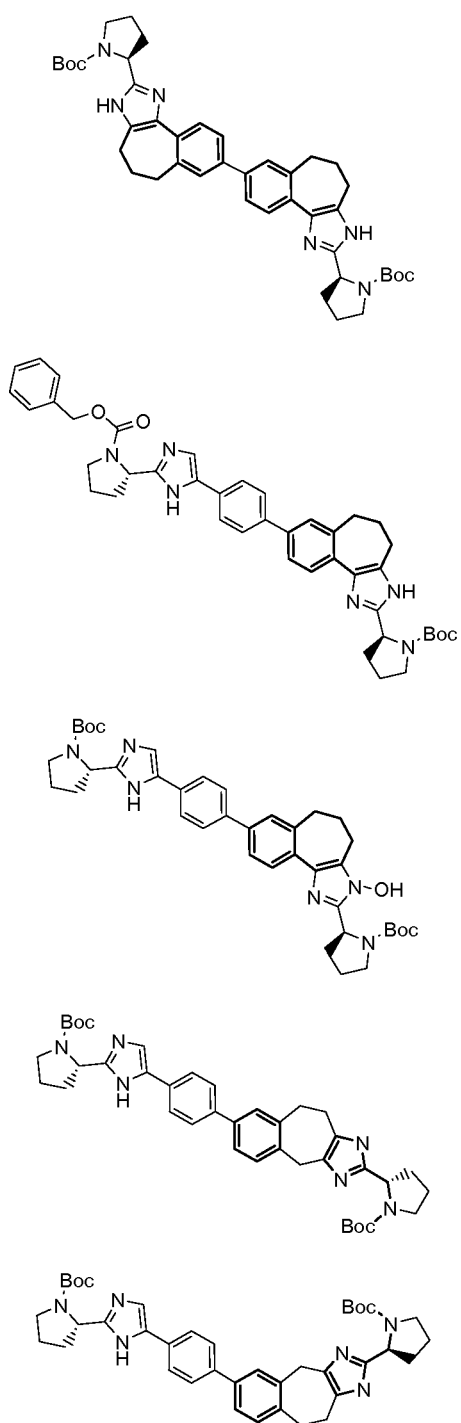


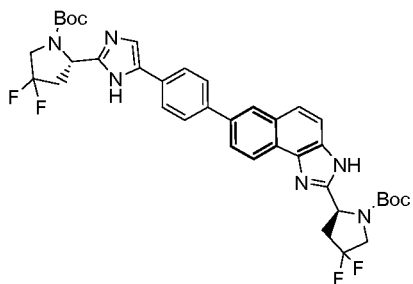
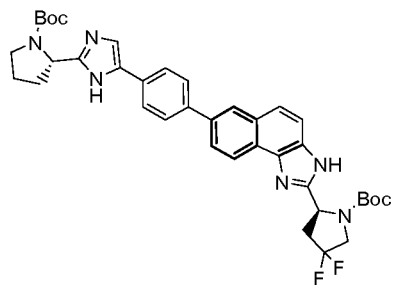
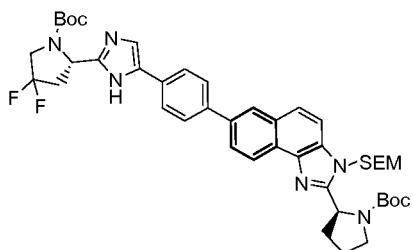
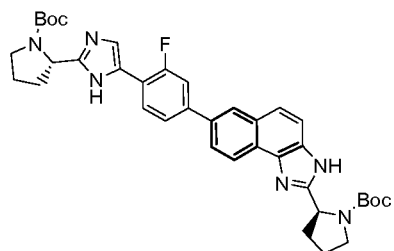
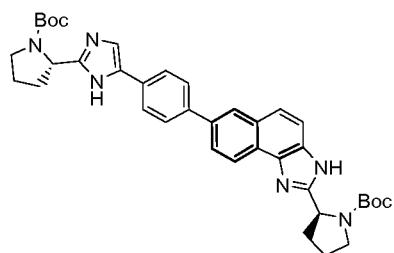
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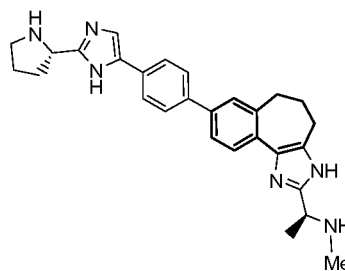
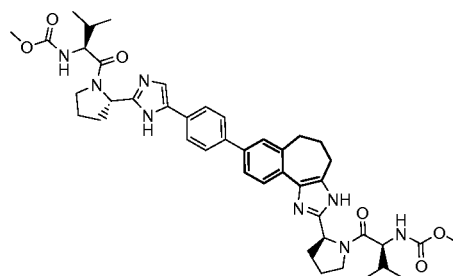
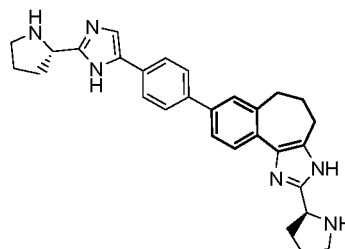
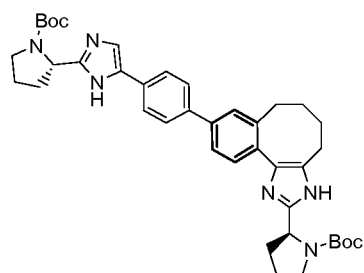
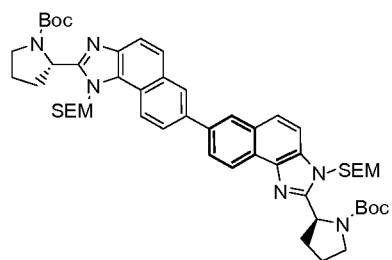
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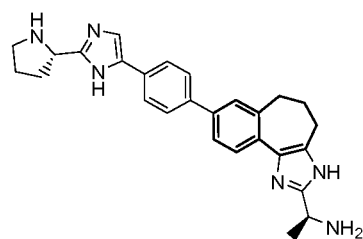


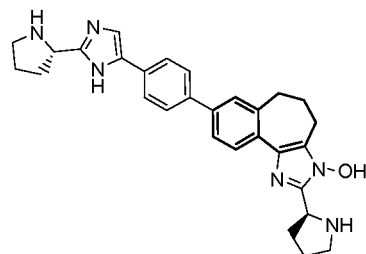
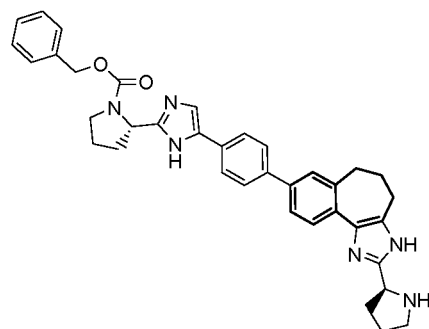
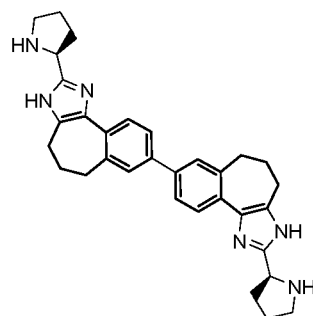
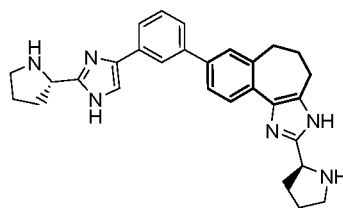
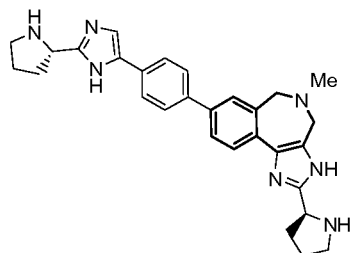
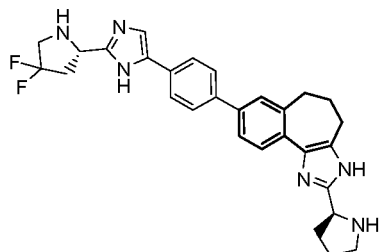
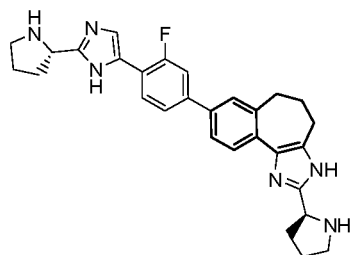
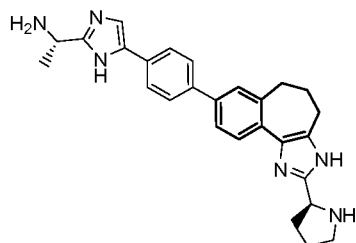
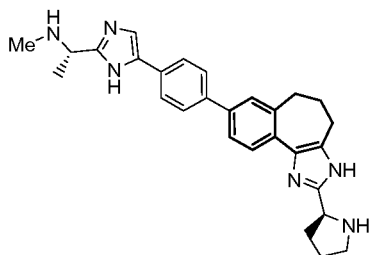
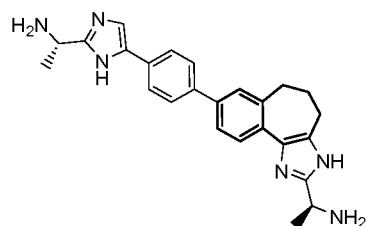


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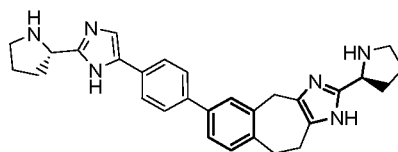
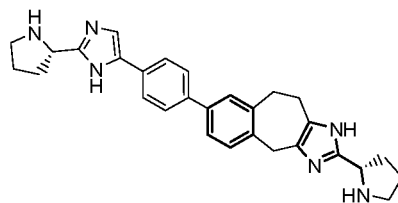


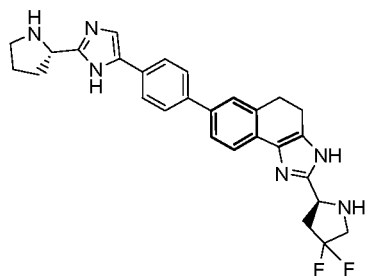
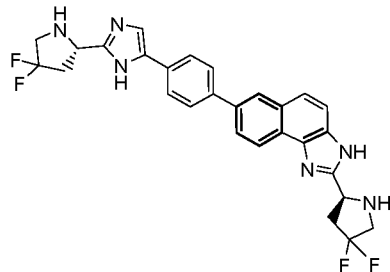
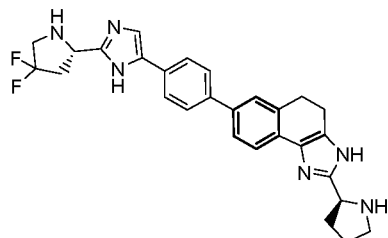
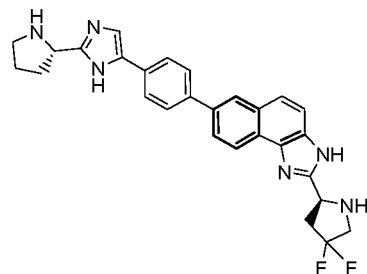
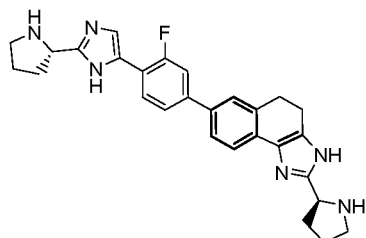
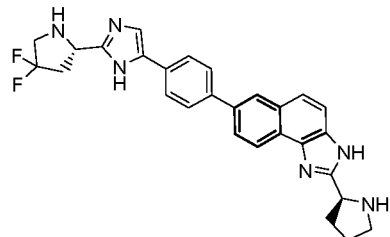
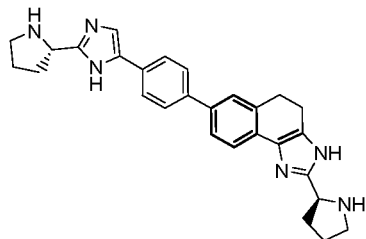
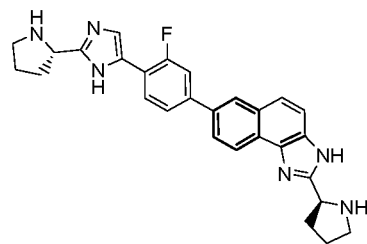
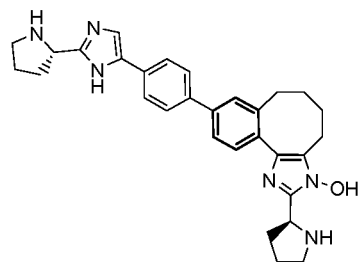
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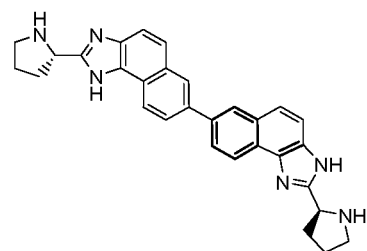


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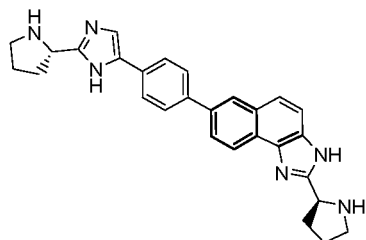


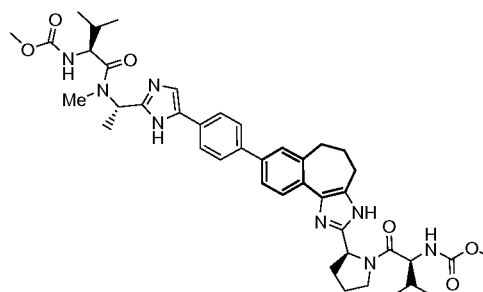
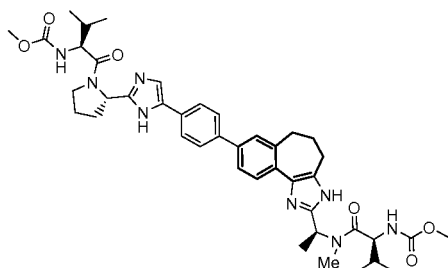
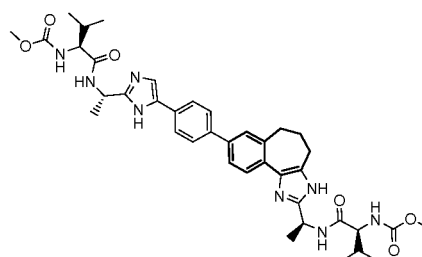
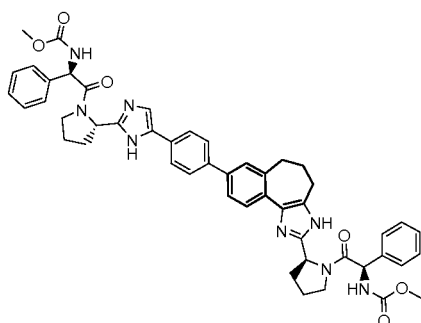
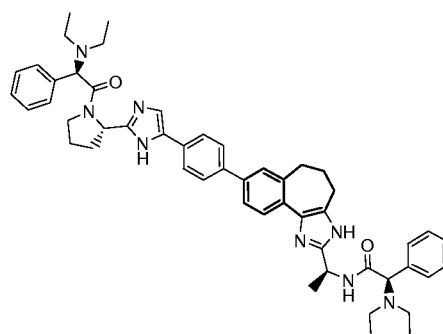
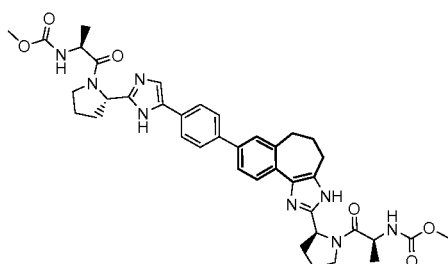
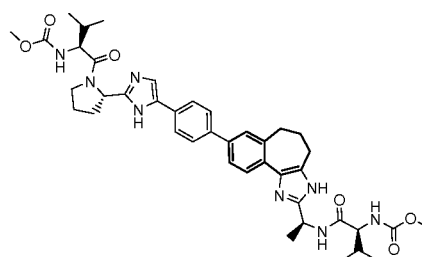
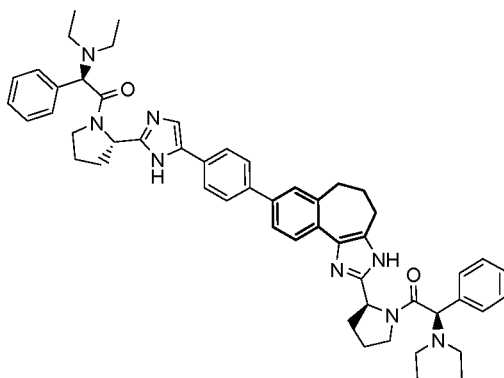
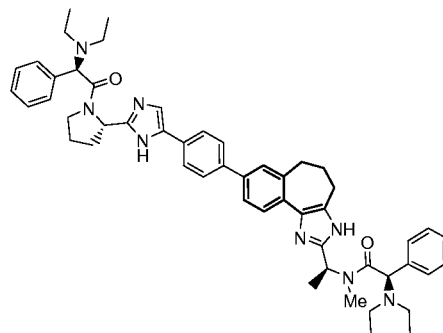
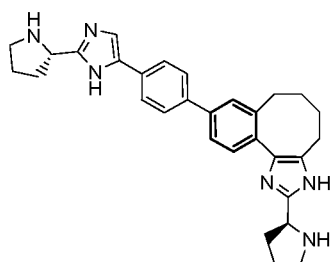


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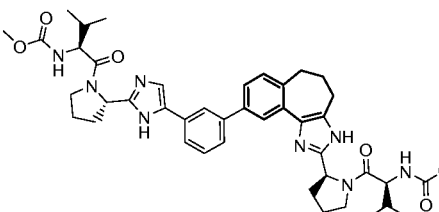
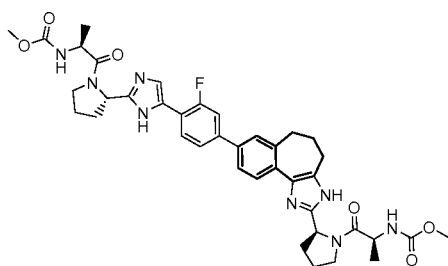
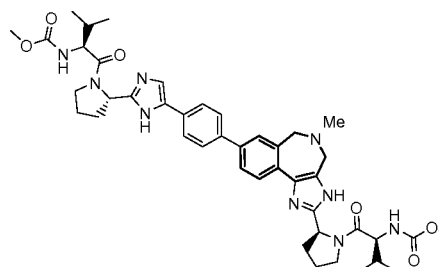
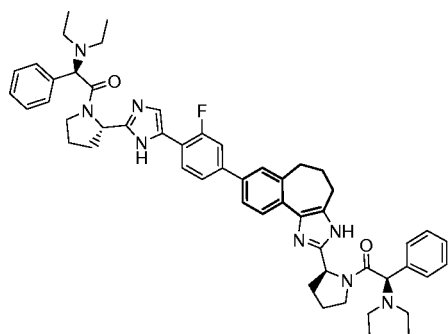
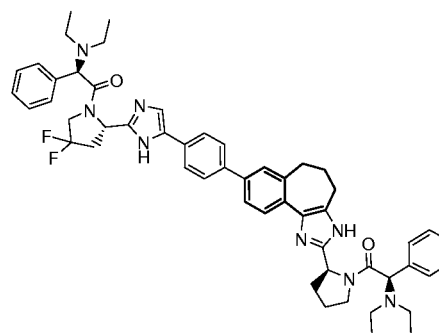
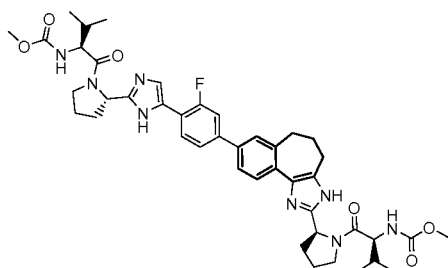
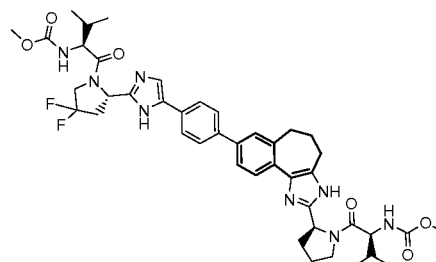
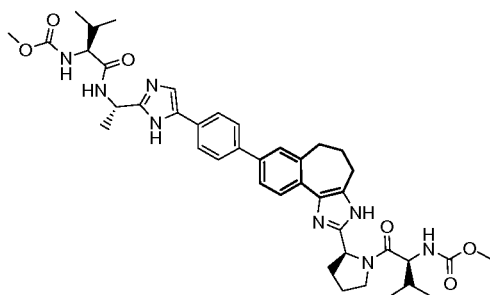
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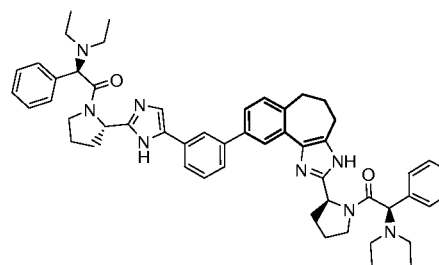
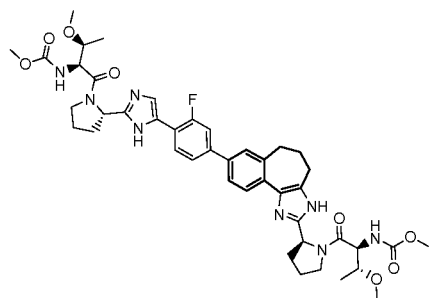
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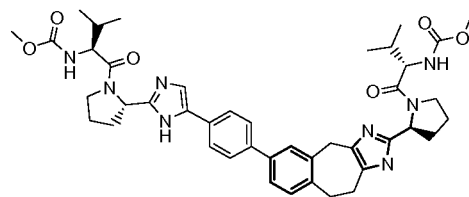
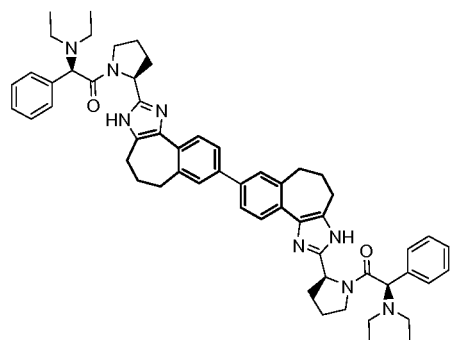
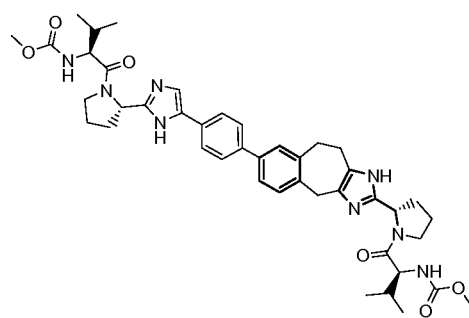
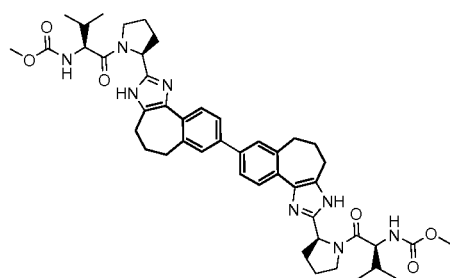
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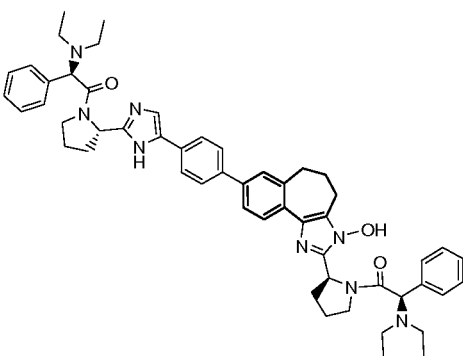
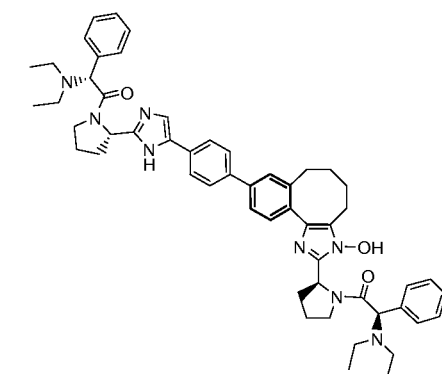
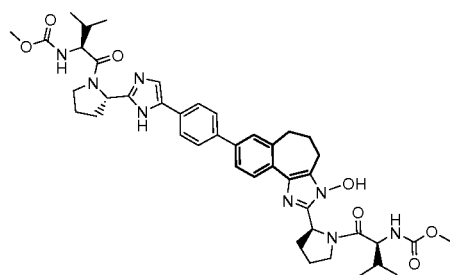
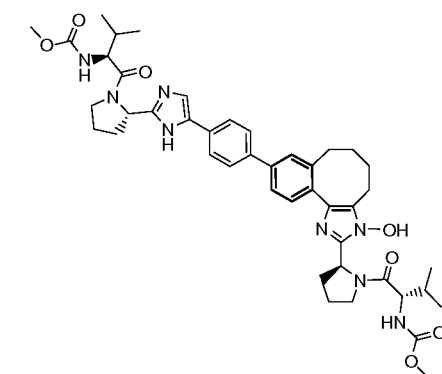
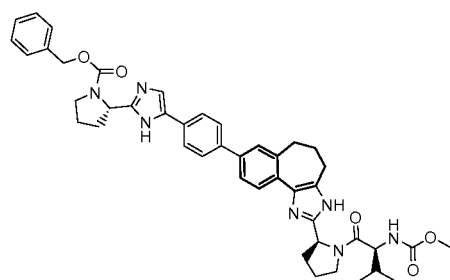
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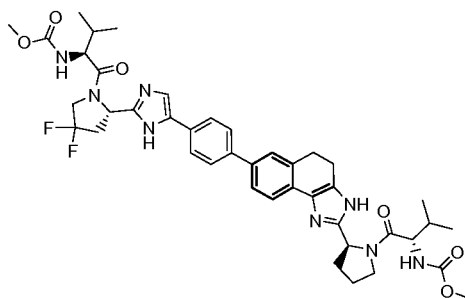
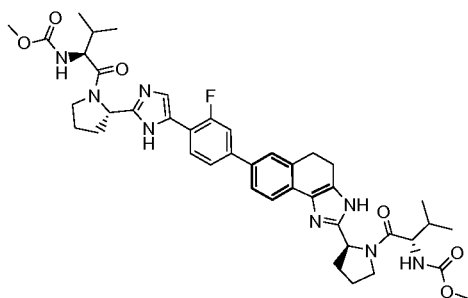
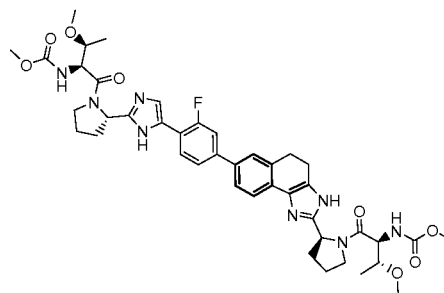
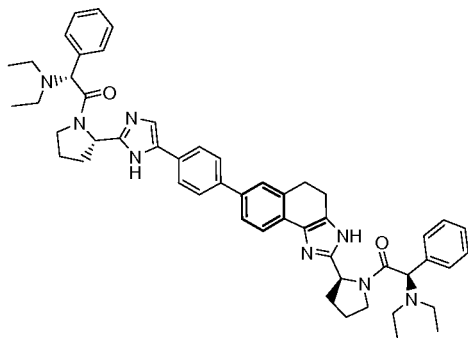
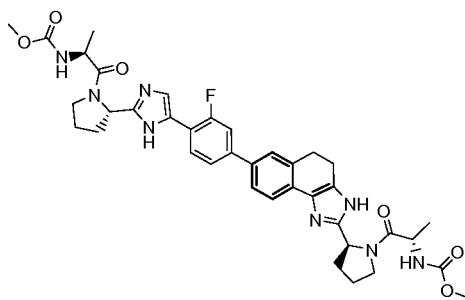
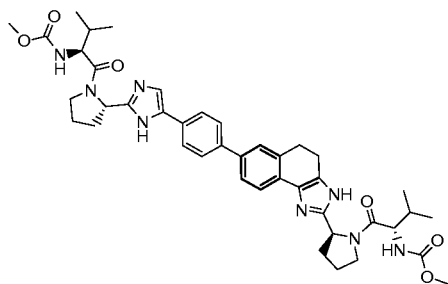
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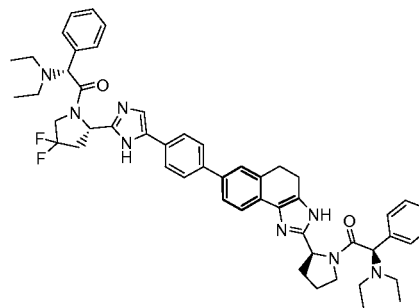
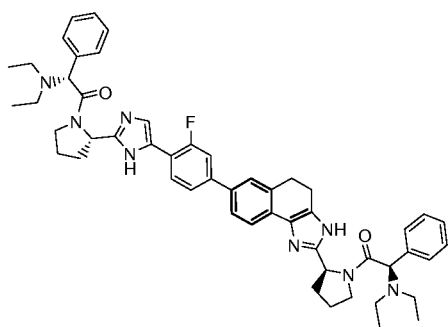
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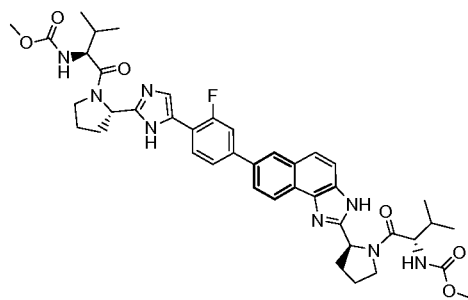
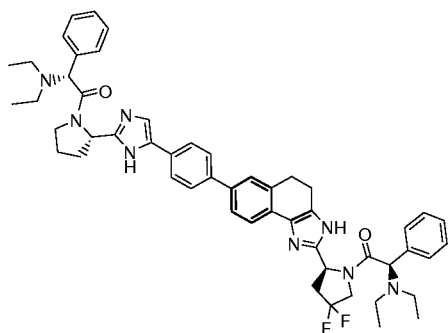
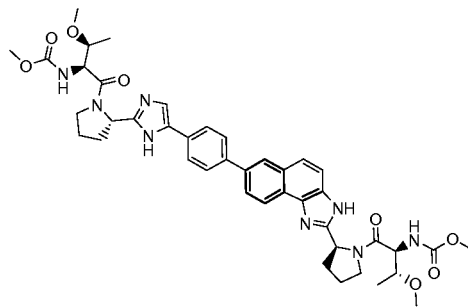
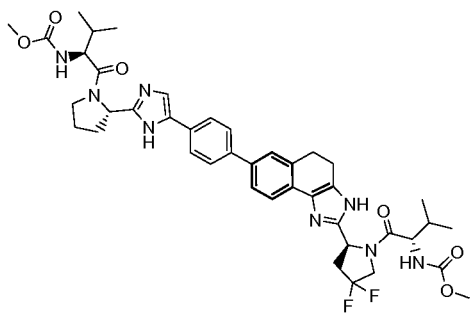




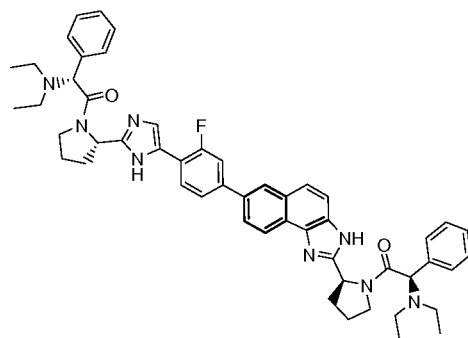
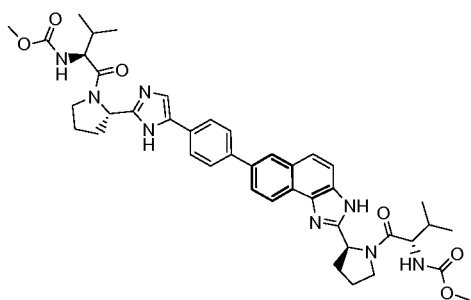
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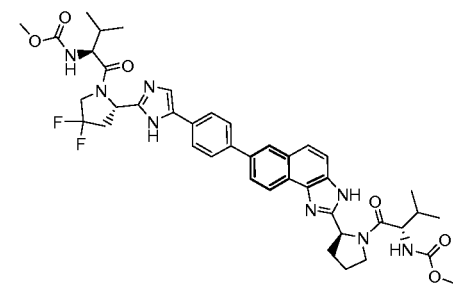
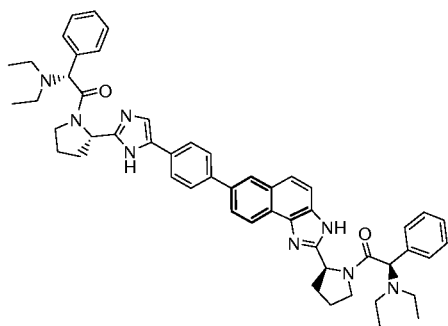


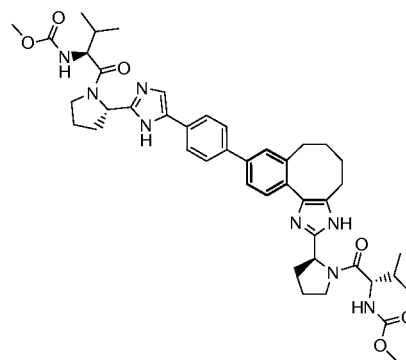
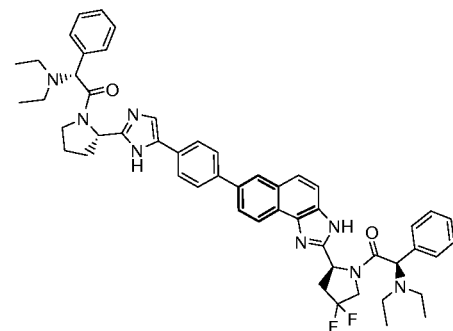
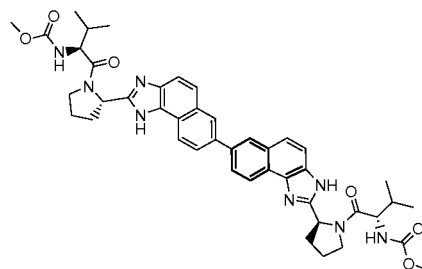
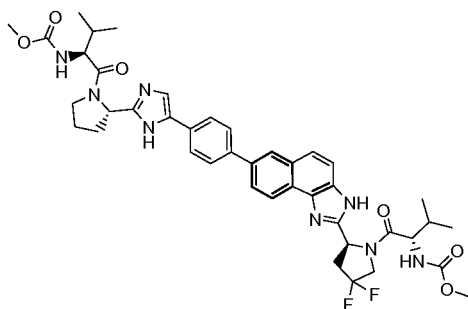
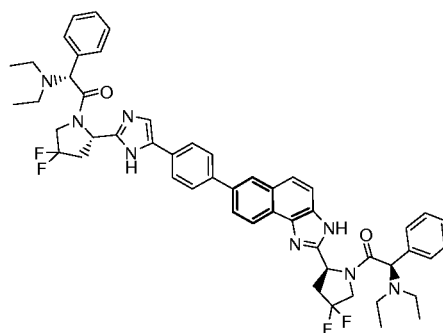
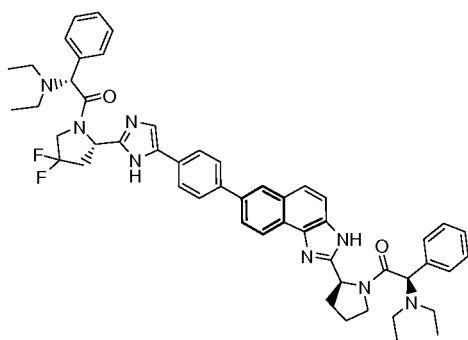


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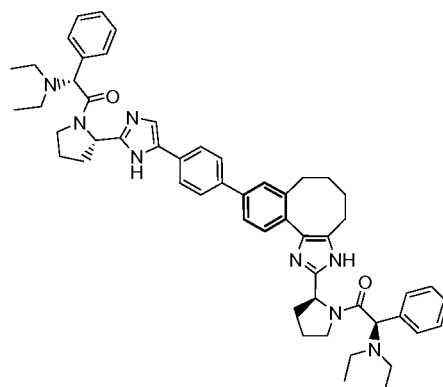
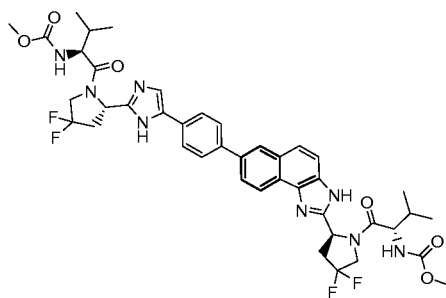


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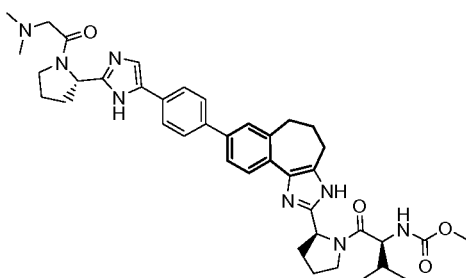
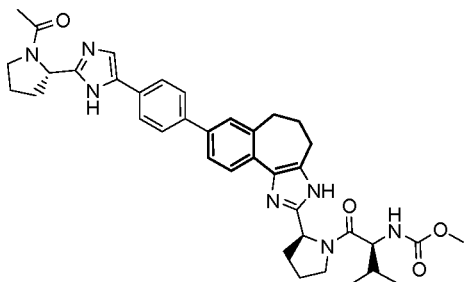
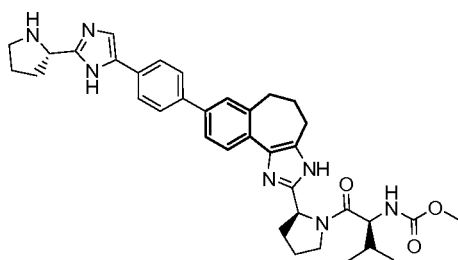




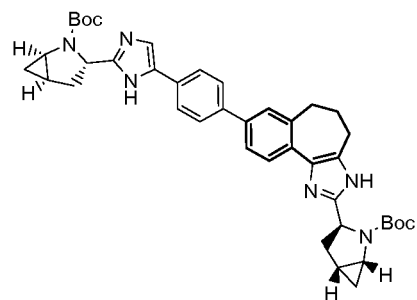
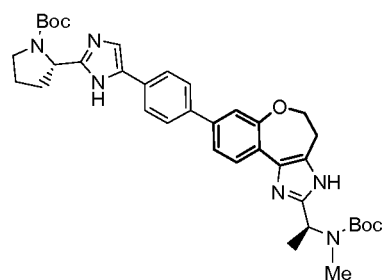
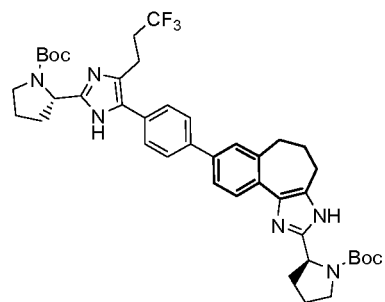
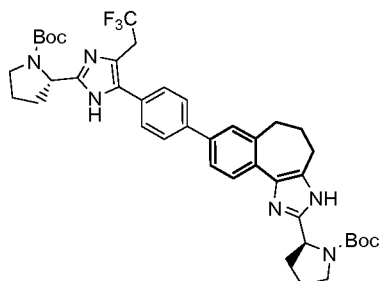
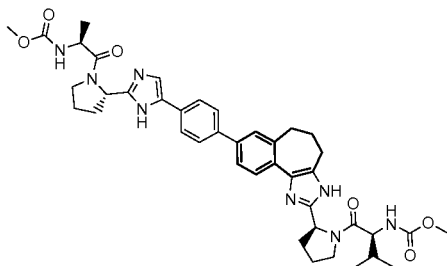
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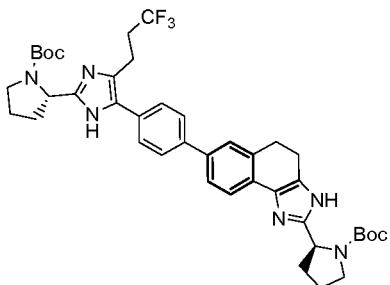
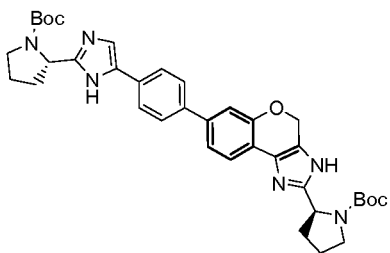
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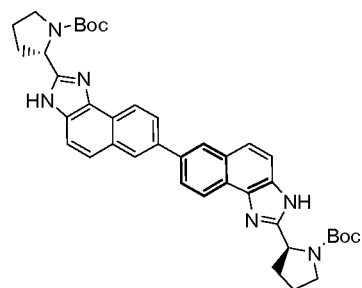
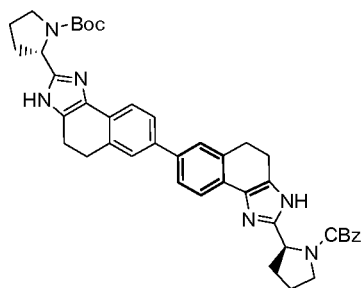
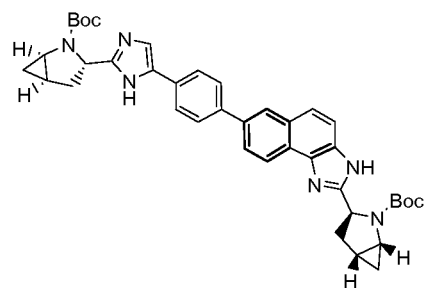
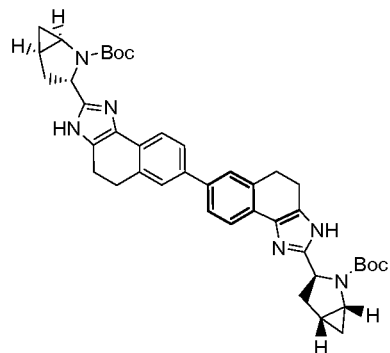
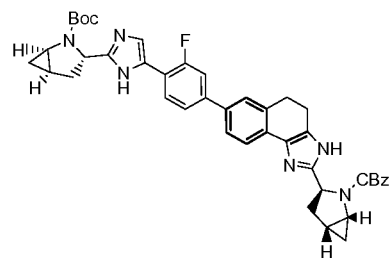
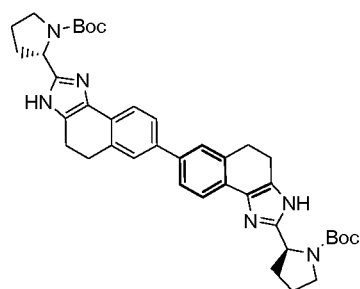
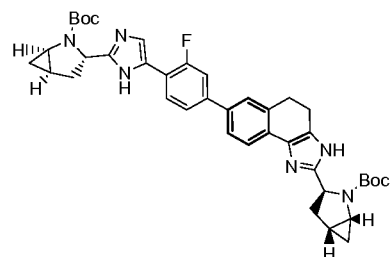
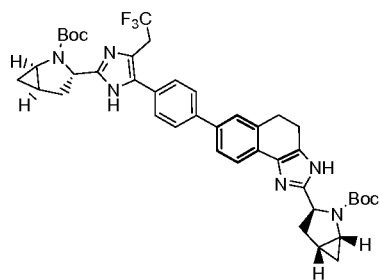
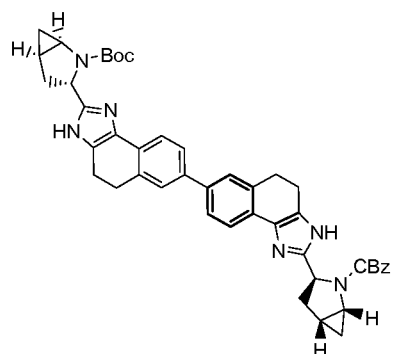
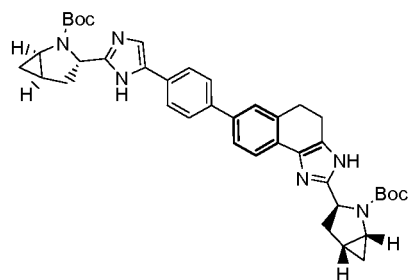


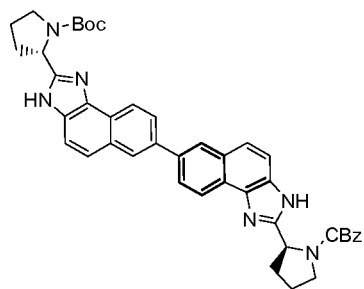
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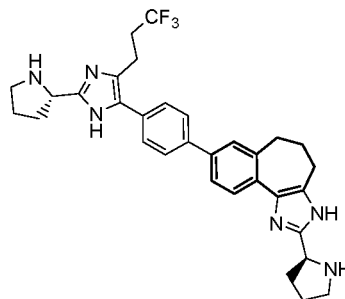
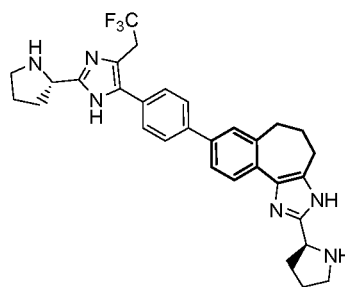
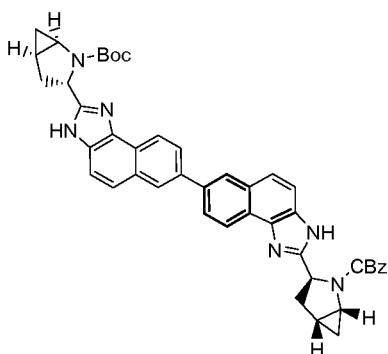
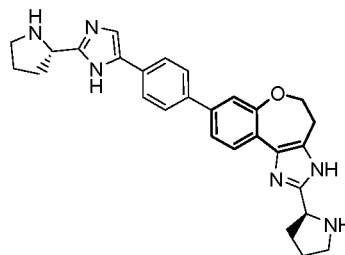
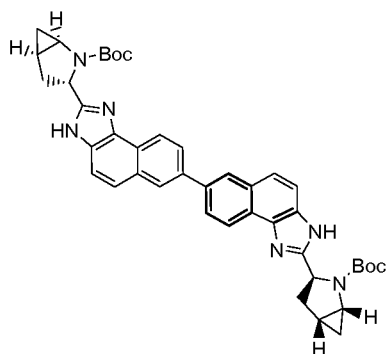
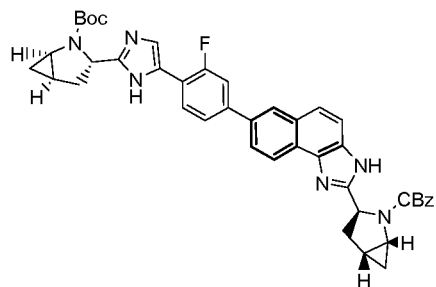
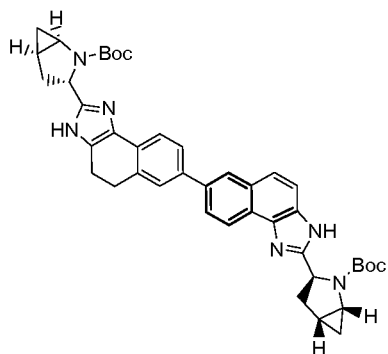
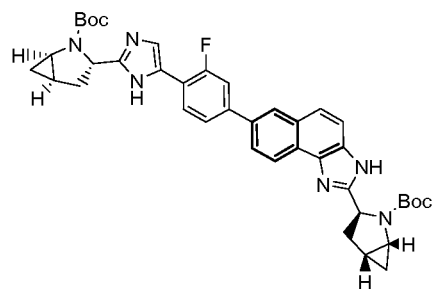
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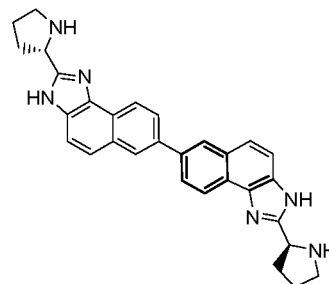
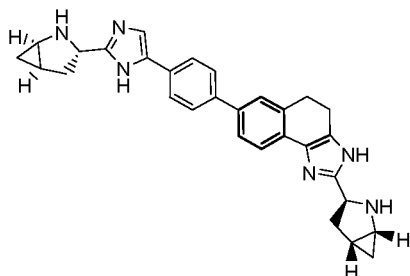
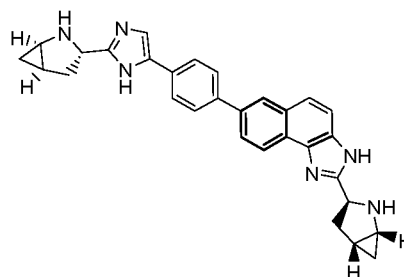
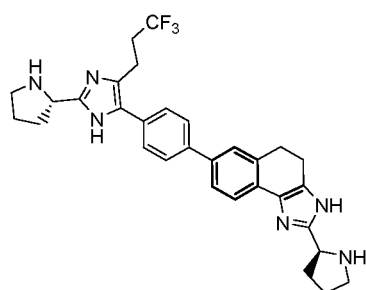
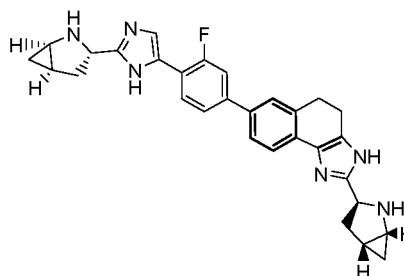
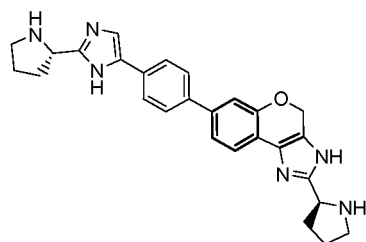
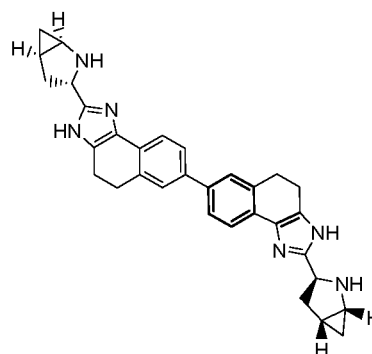
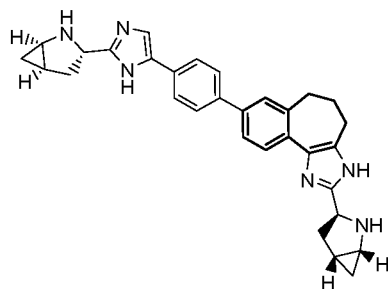
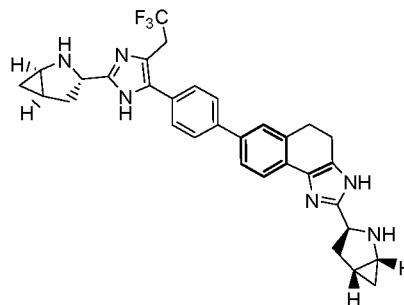
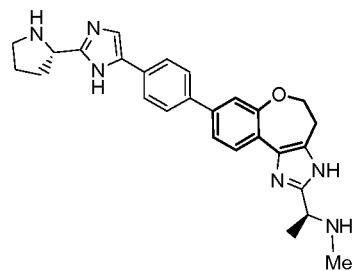




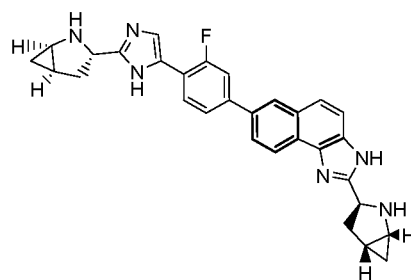
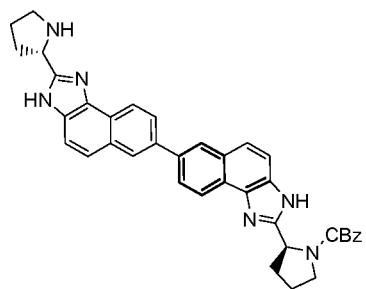


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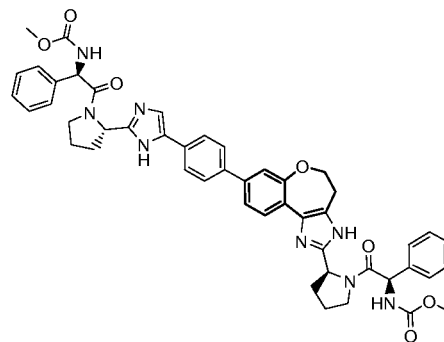
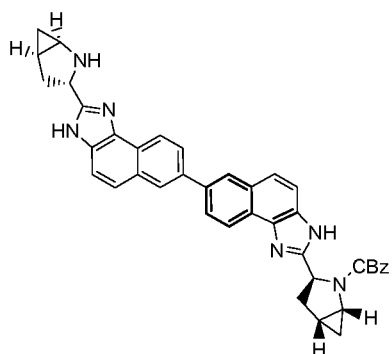
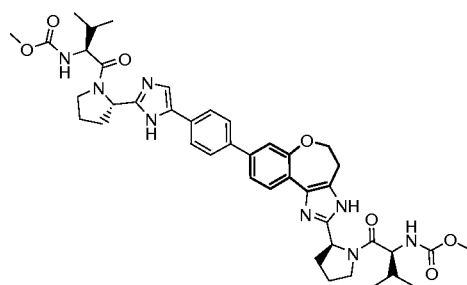
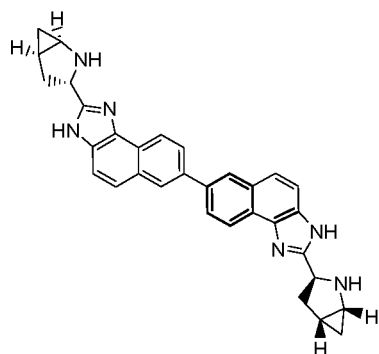
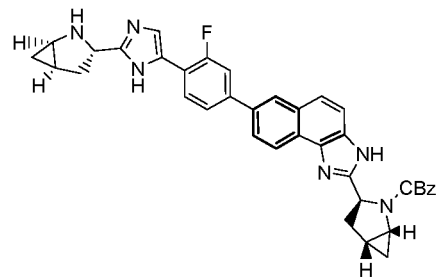
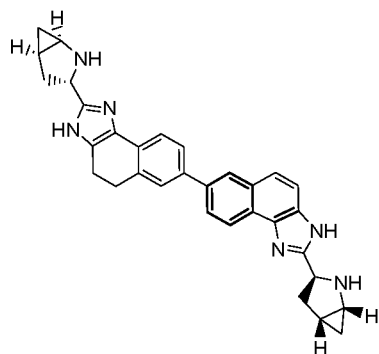




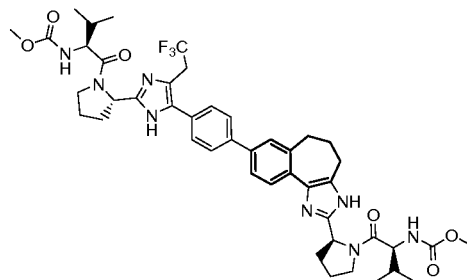
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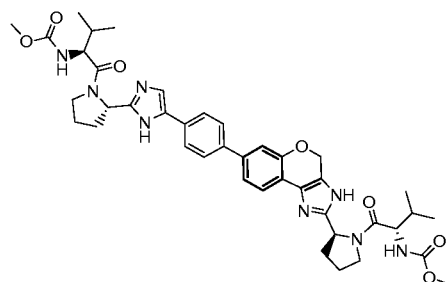
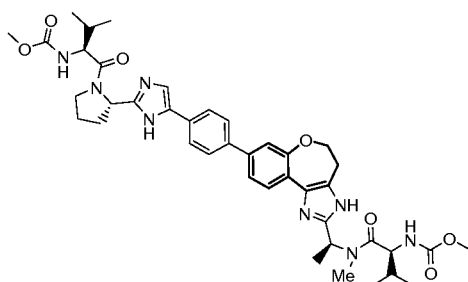
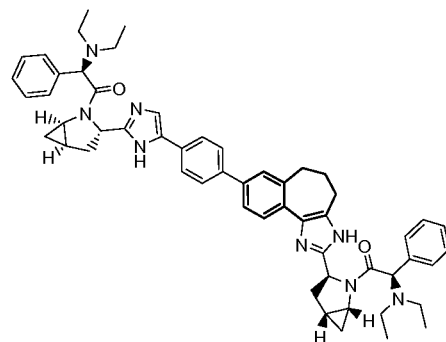
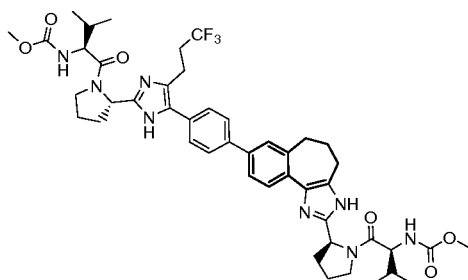
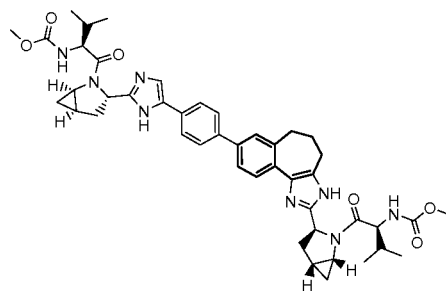
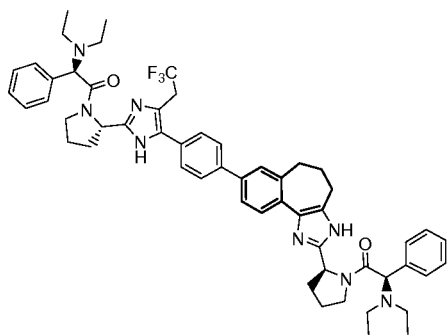


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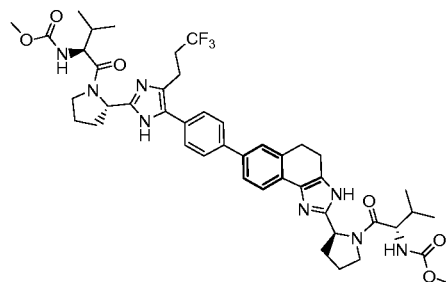
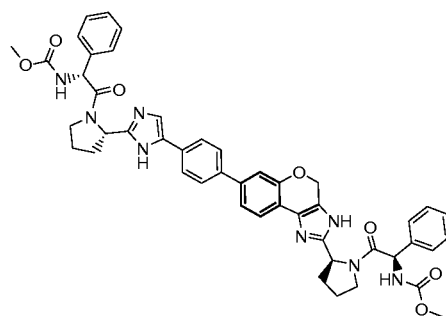
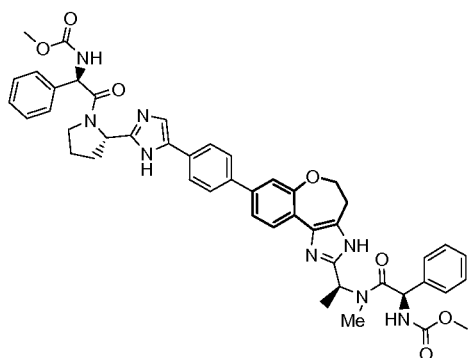
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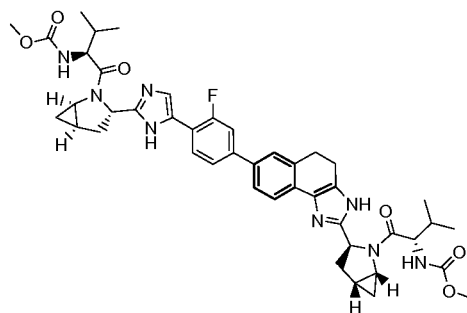
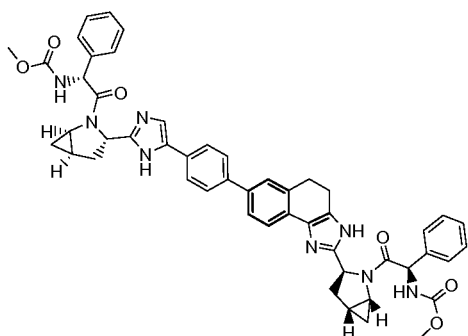
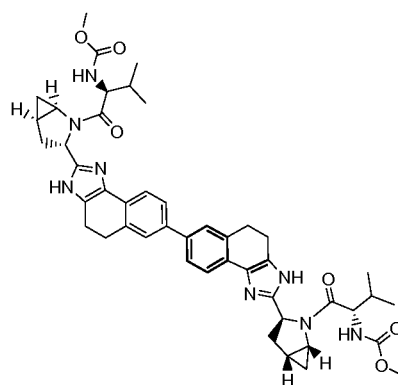
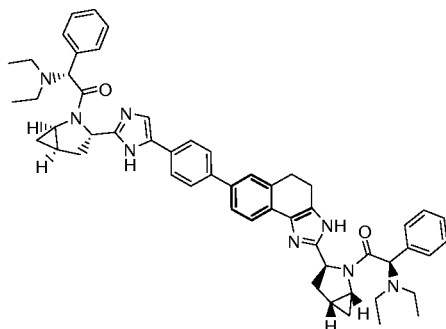
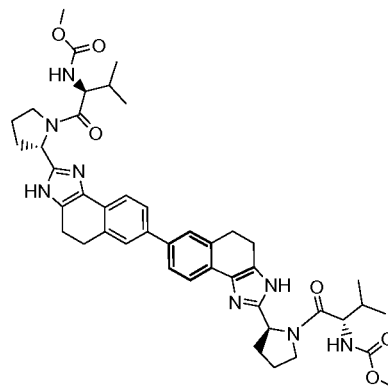
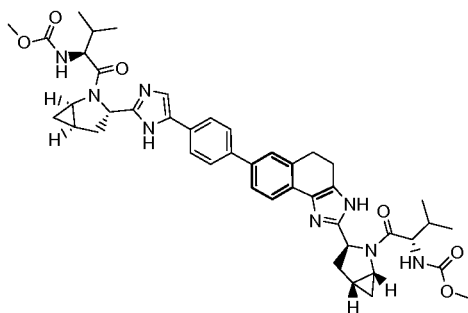




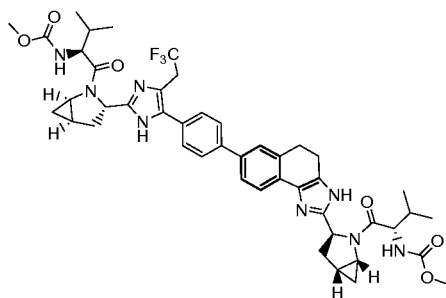
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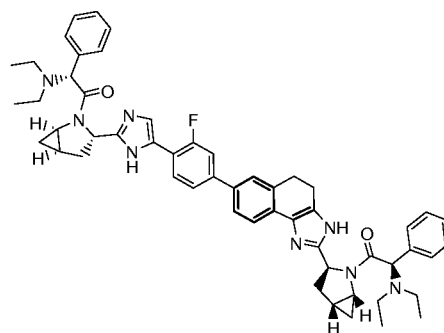


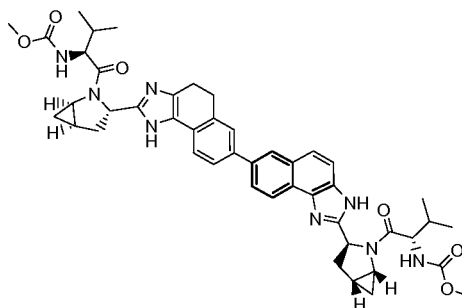
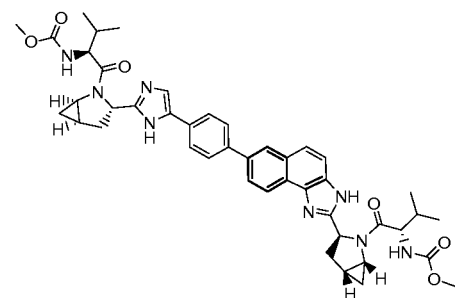
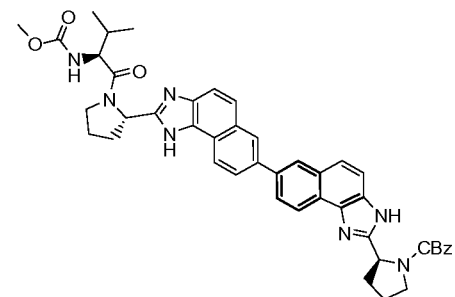
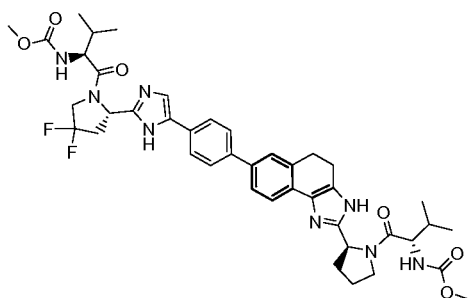
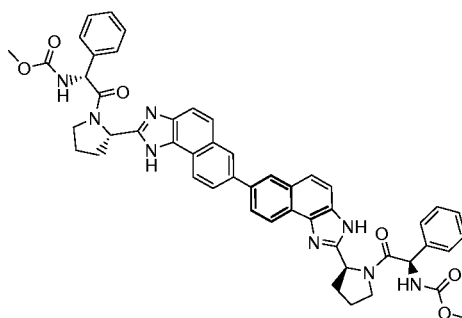
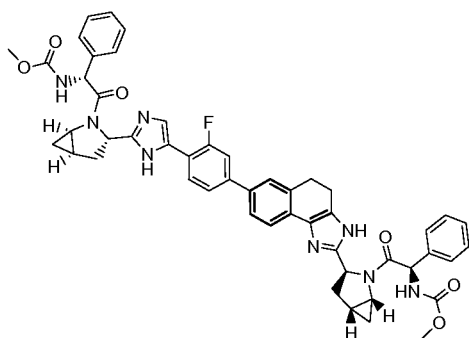


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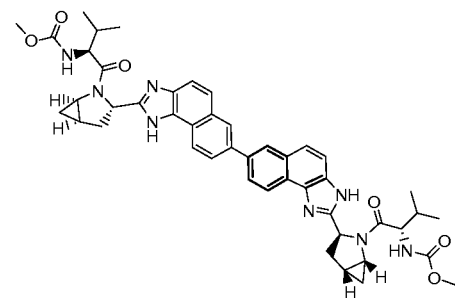
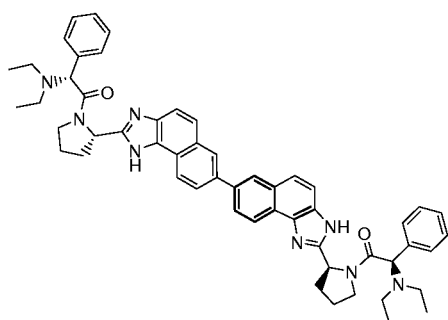
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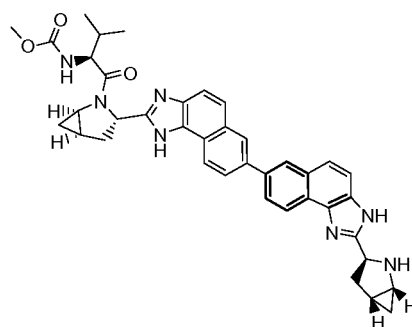
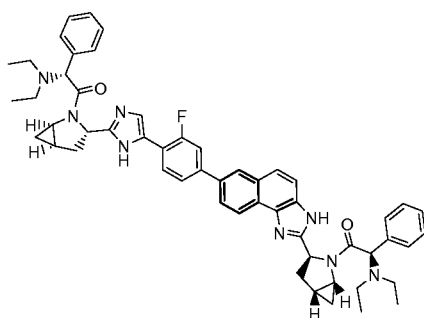
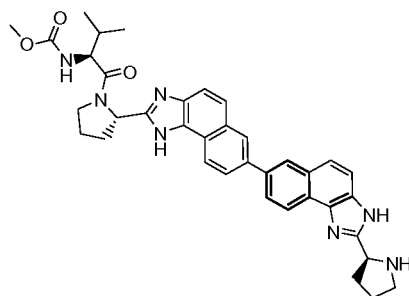
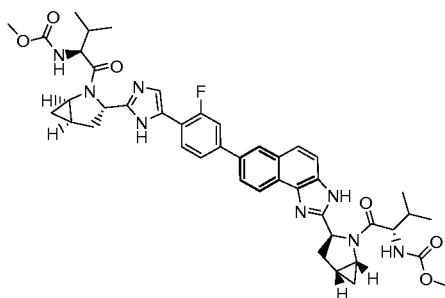
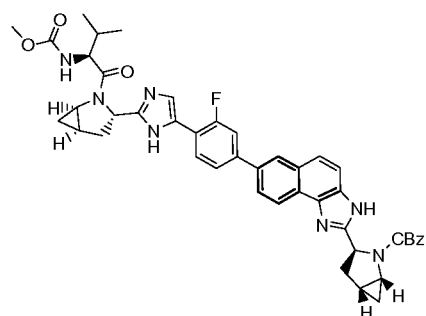
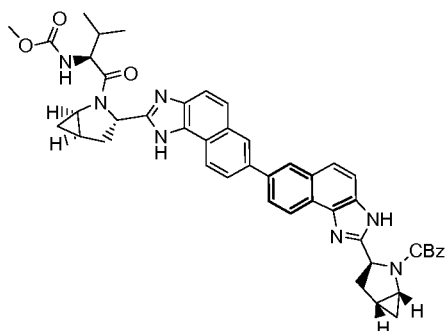
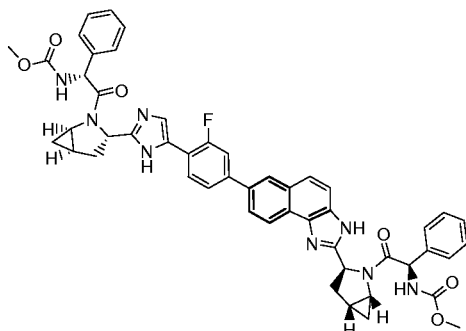
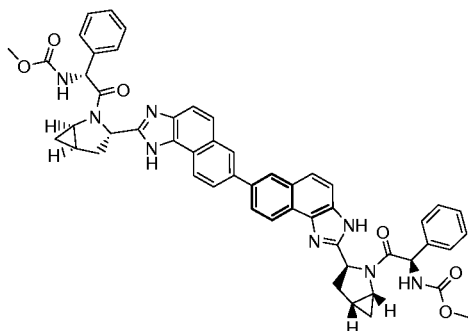


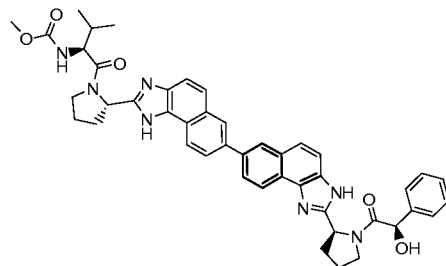
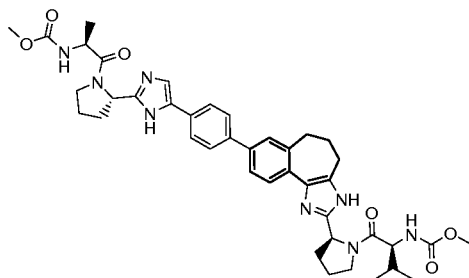
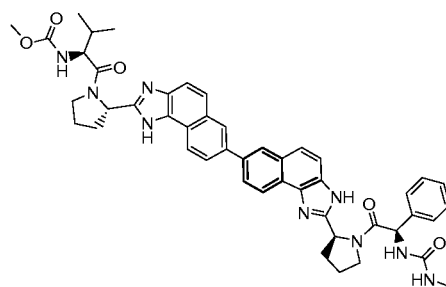
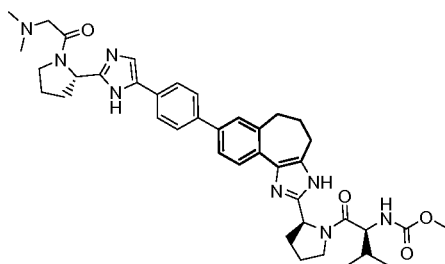
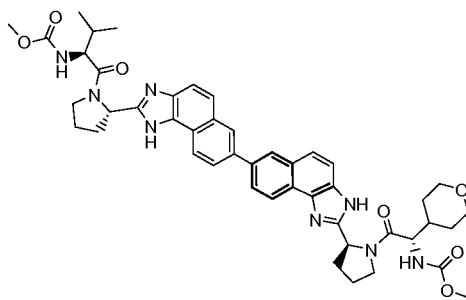
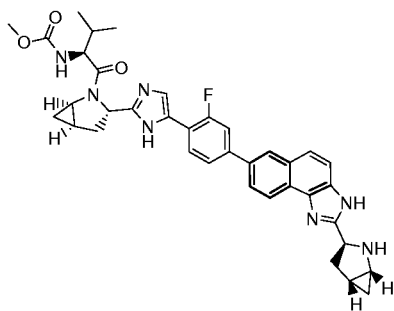


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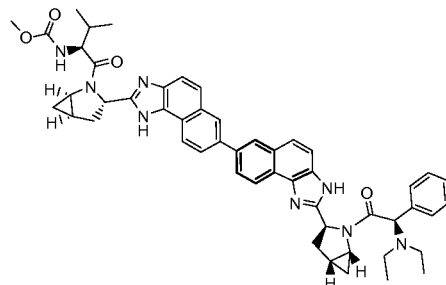
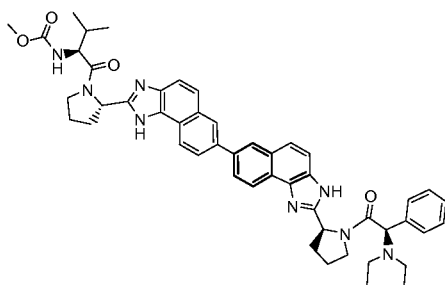
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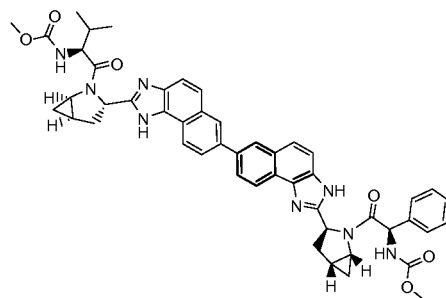
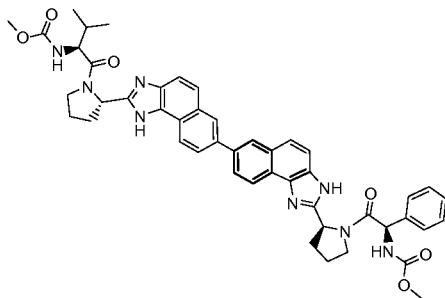


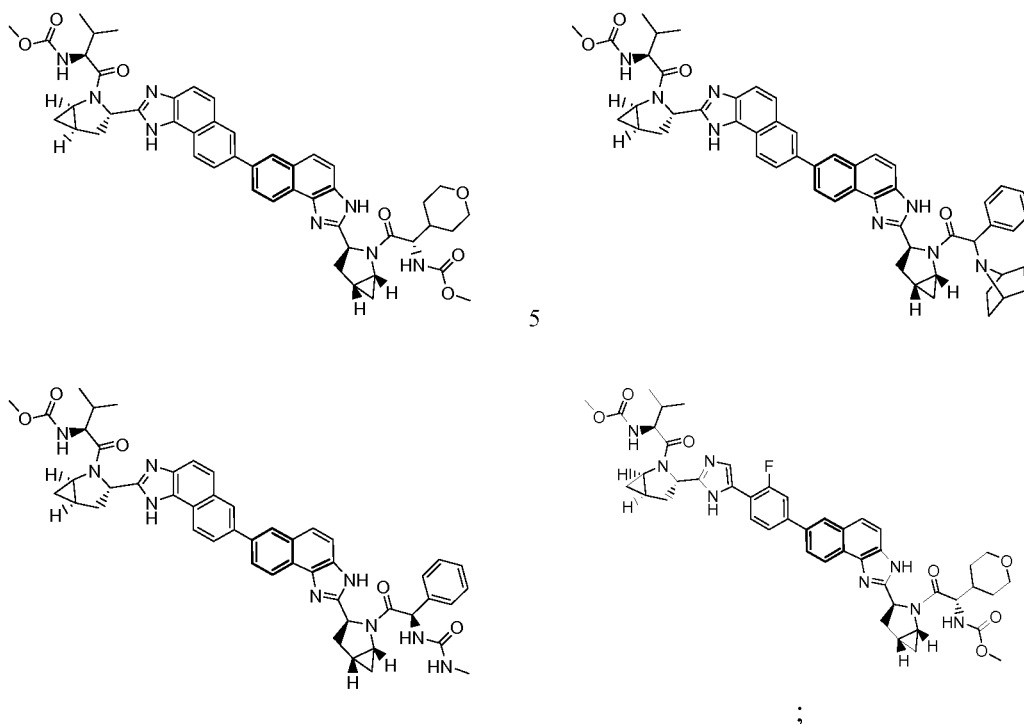


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and

10 or a pharmaceutically acceptable salt thereof.

11. A composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

15 12. The composition of claim 11 further comprising one or two additional compounds having anti-HCV activity.

13. The composition of claim 12 wherein at least one of the additional compounds is an interferon or a ribavirin.

20

14. The composition of claim 13 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

25 15. The composition of claim 14 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound

that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

5 16. The composition of claim 15 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

10

17. A method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

15 18. The method of claim 17 further comprising administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of claim 1, or a pharmaceutically acceptable salt thereof.

19. The method of claim 18 wherein at least one of the additional compounds is
20 an interferon or a ribavirin.

20. The method of claim 19 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

25

21. The method of claim 18 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor,
30 amantadine, and rimantadine.

22. The method of claim 18 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV

serine protease, HCV polymerase, HCV helicase, HCV NS4B portein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.