CONFORMATIONALLY RESTRICTED BIPHENYL DERIVATIVES FOR USE AS HEPATITIS C VIRUS INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 61/028,266 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.

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-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, there is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection.

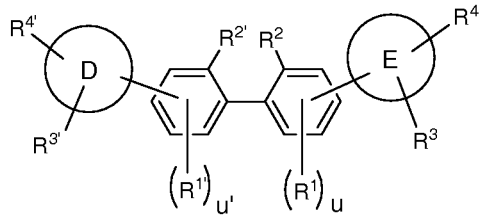
HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain 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 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 E are each five-membered aromatic rings containing one, two, or three

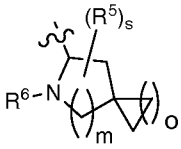
heteroatoms independently selected from nitrogen, oxygen, and sulfur;

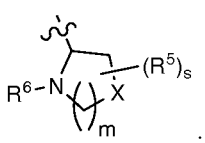
each R^1 and $R^{1'}$ is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

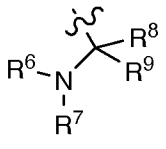
R^2 and $R^{2'}$, together with the carbon atoms to which they are attached, form a five- to eight-membered unsaturated ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the five- to eight-membered unsaturated ring is optionally substituted 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^3 and $R^{3'}$ are each independently selected from hydrogen, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, heterocyclylalkyl, hydroxyalkyl, (NR^aR^b)carbonyl, and trialkylsilylalkoxyalkyl;

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



;


; and


; wherein

each m is independently 0, 1, or 2;

each o is independently 1, 2, or 3;

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

each X is independently selected from O, S, S(O), SO_2, CH_2, CHR^5, and $C(R^5)_2$; provided that when n is 0, X is selected from CH_2, CHR^5, and $C(R^5)_2$;

each R^5 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^6 is independently selected from hydrogen and R^{10}-C(O)-, and R^{10}-C(S)-;

R^7 is selected from hydrogen and alkyl;

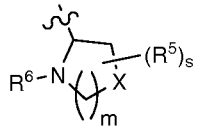
R^8 and R^9 are each independently selected from hydrogen, alkenyl,

alkoxyalkyl, alkyl, haloalkyl, and (NR^aR^b)alkyl; or,

R^8 and R^9, 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

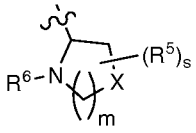
each R^{10} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, 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 compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^4 and $R^{4'}$ are each



In a second embodiment of the first aspect each m is 1. In a third embodiment of the first aspect each X is CH_2.

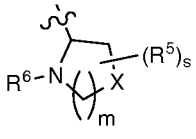
In a third embodiment of the first aspect aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^4 and $R^{4'}$ are each



; and

wherein s is 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^4 and $R^{4'}$ are each



; and

wherein each R^6 is R^{10}-C(O)-. In a fifth embodiment of the first aspect each R^{10} is

independently selected from arylalkyl, (cycloalkyl)alkyl, and (NR^cR^d)alkyl.

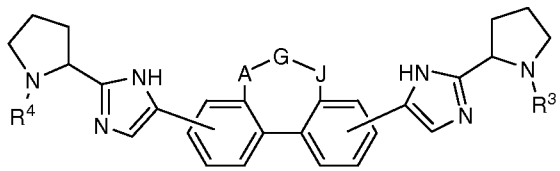
In a sixth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein u and u' are each 0.

In a seventh embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein wherein R^3 and $R^{3'}$ are each hydrogen.

In an eight embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^2 and $R^{2'}$, together with the atoms to which they are attached, form a five-membered ring optionally containing an oxygen or nitrogen atom, wherein said ring is optionally substituted with one or two 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, and oxo.

In a ninth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^2 and $R^{2'}$, together with the atoms to which they are attached, form a seven-membered ring containing a heteroatom selected from oxygen and nitrogen, wherein said 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, and oxo.

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



(II);

or a pharmaceutically acceptable salt thereof, wherein

A is absent or $CR^{11}R^{12}$;

G is selected from $CR^{11}R^{12}$, O, and NR^{13};

J is absent or $CR^{11}R^{12}$;

R^3 and R^4 are each independently selected from hydrogen and R^{10}-C(O)-;

each R^{10} is independently selected arylalkyl, (cycloalkyl)alkyl, and (NR^cR^d)alkyl;

each R^{11} and R^{12} are independently selected from hydrogen, alkyl, and -NR^aR^b; or

R^{11} and R^{12} together form an oxo group; or

R^{11} and R^{12}, together with the carbon atom to which they are attached, form a three- to eight-membered spirocycle; and

each R^{13} is independently selected from hydrogen, alkoxyalkyl, alkyl, and arylsulfonyl.

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 further comprises one or two additional compounds having anti-HCV activity. In a second embodiment of the third aspect at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment of the third aspect the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a fourth embodiment of the third aspect 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, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

In a fifth embodiment of the third aspect 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 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 thereof. In a first embodiment of the fouth 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 the pharmaceutically acceptable salt thereof. In a second embodiment of the fourth aspect at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment of the fourth aspect the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau. IMPDH for the treatment of an HCV infection.

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 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 the 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, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate 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 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 the pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds iseffective 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. In some instances it may be necessary to remove a hydrogen atom in order accommodate a substitutent at any given location.

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.

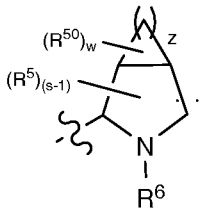
The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxy groups.

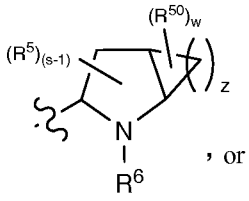
The term "alkoxyalkylcarbonyl," as used herein, refers to an alkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

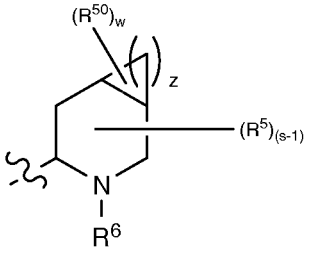
The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

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

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^5, and R^5 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:



,


, or


;

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.

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

The term "alkylene," as used herein, refers to a divalent group derived from a straight or branched chain saturated hydrocarbon containing from one to six carbon atoms.

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-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 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 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 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 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 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 $-NR^cR^d$, wherein the heterocyclyl is further optionally substitued 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 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.

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 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 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.

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 futher optionally substituted with one, two, or three substituents 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 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.

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.

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.

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 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-tyl, and 2-azabicyclo[2.2.2]oc-3-tyl. 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, indolinyl, indolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrrolopyridinyl, pyrrolyl, thiazolyl, thienyl, thiomorpholinyl, 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-tyl, and 2-azabicyclo[2.2.2]oc-3-tyl. 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 substitued with

one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstitued 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, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, -C(NCN)OR', and -C(NCN)NR^xR^y, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl 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 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, alkylsulfanyl, arylalkoxyalkylcarbonyl, carboxy, heterocyclyl, heterocyclylcarbonyl, hydroxy, and (NR^eR^f)carbonyl; wherein the heterocyclyl 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 attached to the parent molecular moiety through a carbonyl group.

The term "$-NR^eR^f$," as used herein, refers to two groups, R^e and R^f, which are attached to the parent molecular moiety through a nitrogen atom. R^e and R^f are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, (NR^xR^y)alkyl, and (NR^xR^y)carbonyl.

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

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, 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.

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 "spirocyclyl," as used herein, refers to an alkylene diradical, each end of which is attached to the same carbon atom of the parent molecular moiety forming a bicyclic moiety.

The term "sulfonyl," as used herein, refers to -SO_2-.

The term "trialkylsilyl," as used herein, refers to -SiR_3, wherein R is alkyl. 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.

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 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, diydrochloride, 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-phenylproprionate, 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, 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.

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

When the compositions of this disclosure comprise a combination of a

compound of the present disclosure and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent are usually present at dosage levels of between about 10 to 150%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

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

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

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 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. 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 aliginate, 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 phopholipids, such as cholesterol, stearylamine, or phophatidylcholines.

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 polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palitoyl 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, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, 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 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.

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 course powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, *i.e.*, by rapid inhalation through the nasal passage from a container of the powder

held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or nasal drops, include aqueous or oil solutions of the active ingredient.

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

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
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 Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceuticals 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

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
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

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Levovirin	Antiviral	ribavirin	ICN Pharmaceuticals, Costa Mesa, CA
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

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Civacir	Immunosuppressant	HCV IgG immunosuppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albuferon - α	Interferon	albumin IFN-α2b	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-β1a	Serono, Geneva, Switzerland
Roferon A	Interferon	IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Intron A	Interferon	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
Intron A and Zadaxin	Interferon	IFN-α2b/α1-thymosin	RegeneRx Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Rebetron	Interferon	IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
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-αn1	GlaxoSmithKline plc, Uxbridge, UK
Omniferon	Interferon	natural IFN-α	Viragen Inc., Plantation, FL
Pegasys	Interferon	PEGylated IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ceplene	Interferon	PEGylated IFN-α2a/ immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys and Ribavirin	Interferon	PEGylated IFN-α2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
PEG-Intron	Interferon	PEGylated IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	Interferon	PEGylated IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
IP-501	Liver protection	antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
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: HATU for O-(7-

azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; NH_4OAc for ammonium acetate; Boc or BOC for tert-butoxycarbonyl; NBS for N-bromosuccinimide; TFA for trifluoroacetic acid; MeOH for methanol; DMSO for dimethylsulfoxide; THF for tetrahydrofuran; RT for room temperature or retention time (context will dictate); t_R for retention time; DMAP for 4-dimethylaminopyridine; EDCI for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DEA for diethylamine; DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene; t-Bu_3P for tri-*tert*-butylphosphine; HMDS for hexamethyldisilazide; DMF for N,N-dimethylformamide; EtOAc or EtOAC for ethyl acetate; Me_2S for dimethylsulfide; Et_3N or TEA for triethylamine; LiHMDS for lithium hexamethyldisilazide; DIBAL for diisobutyl aluminum hydride; TBDMSCl for tert-butyldimethylsilyl chloride; iPrOH for isopropyl alcohol; Cb z for carbobenzyloxy; iPr_2EtN or DIPEA or DIEA for diisopropylethylamine; BnBr for benzyl bromide; KOAc for potassium acetate; CAN for ceric ammonium nitrate; SEM-Cl for (trimethylsilyl)ethoxymethyl chloride; Me_2NH for dimethylamine; TMS for trimethylsilyl; OAc for acetate; PPh_3 for triphenylphosphine; MeI for methyl iodide; MeCN for acetonitrile; n-BuLi for n-butyllithium; and TBDMSOTf for *tert*-butyldimethylsilyl triflate.

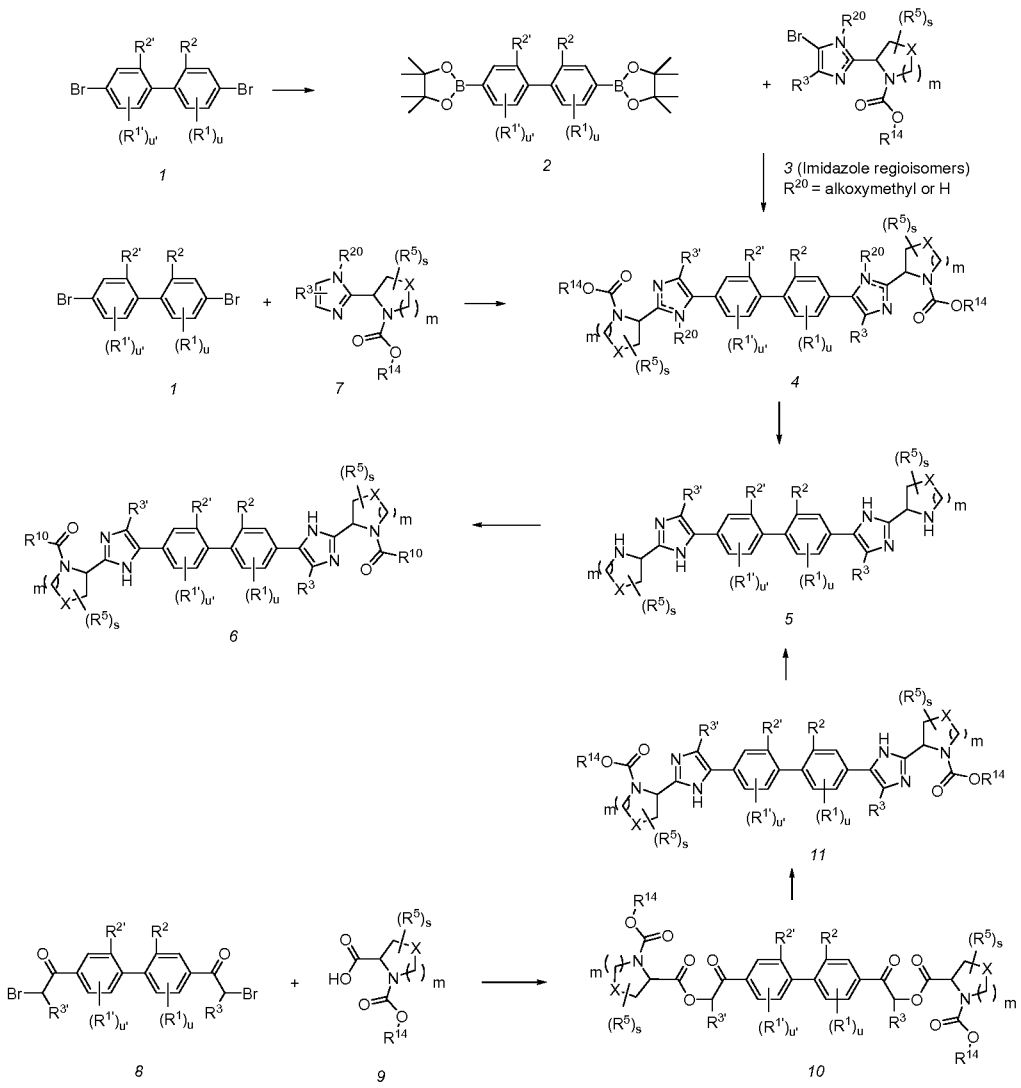
The compounds and processes of the present disclosure will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the present disclosure may be prepared. Starting materials can be obtained from commercial sources or prepared by well-established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

Scheme 1:

Dibromide *1* could be elaborated to boronate ester *2* and then coupled with bromoimidazole *3* using standard Suzuki-Miayura coupling conditions (*Journal of*

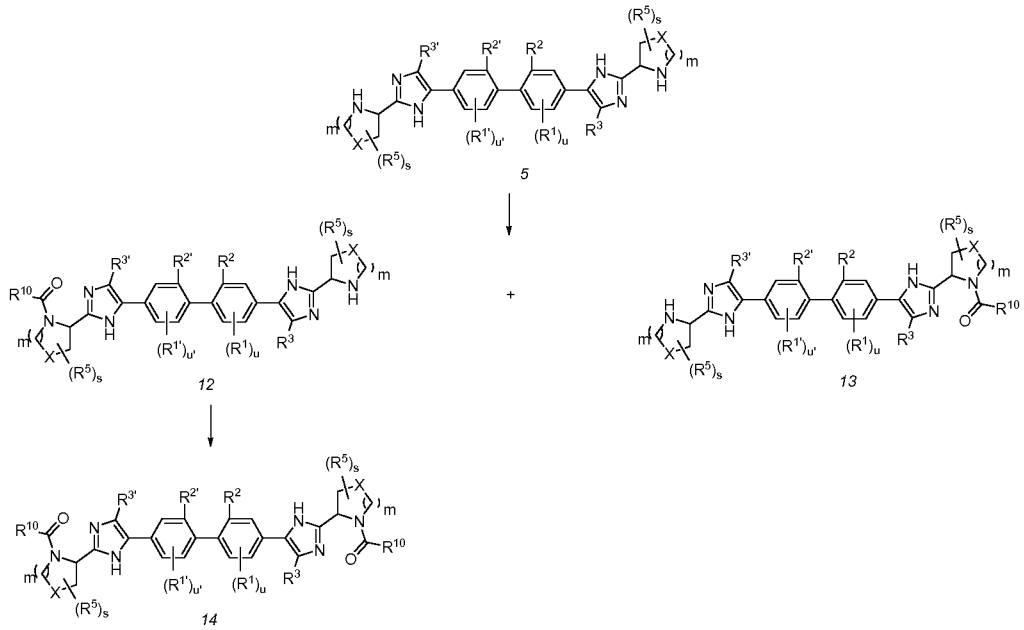
Organic Chemistry 1995, *60*, 7508; *Angew Chem. Int. Ed. Engl* 2001, 40, 4544, or variation thereof). It should be noted that the boronic acid analog of *2* may be used in place of the ester, and that imidazole *3* could be employed as a mixture of regioisomers, regarding the position of R^{20}, and is inconsequential to the final outcome of the synthetic route. Deprotection of the pyrrolidine group of *4*, in the case where R^{14} = t-butyl, could be accomplished by treatment with strong acid such as HCl or trifluoroacetic acid. Acylation of *5* can be accomplished under standard acylation conditions. A coupling reagent such as HATU in combination with an amine base such as Hunig's base can be used in this regard. Alternatively, *5* may be reacted with an isocyanate or a carbamoyl chloride to provide compounds of formula *6* where R^{10} is an amine. Pyrrolidine *5* can also be reacted with chloroformates to afford *6* where R^{10} is an alcohol.

Intermediates *4* could also be prepared through an alternative route. The coupling of bromide *1* with imidazole *7* under palladium assisted electophilic aromatic substitution condition could afford *4* (*Org. Let.* 2003, 5, 4835). Alkylation of keto-bromide *8* with appropriately substituted acid *9* could afford ketoester *10*, which could be cyclized into imidazole *11* by reacting with NH_4OAc in solvents such as toluene, under thermal or microwave heating conditions. Conversion of *11* to *5* is accomplished in analogous fashion to the methods used to prepare *5* from *4*.



Scheme 2:

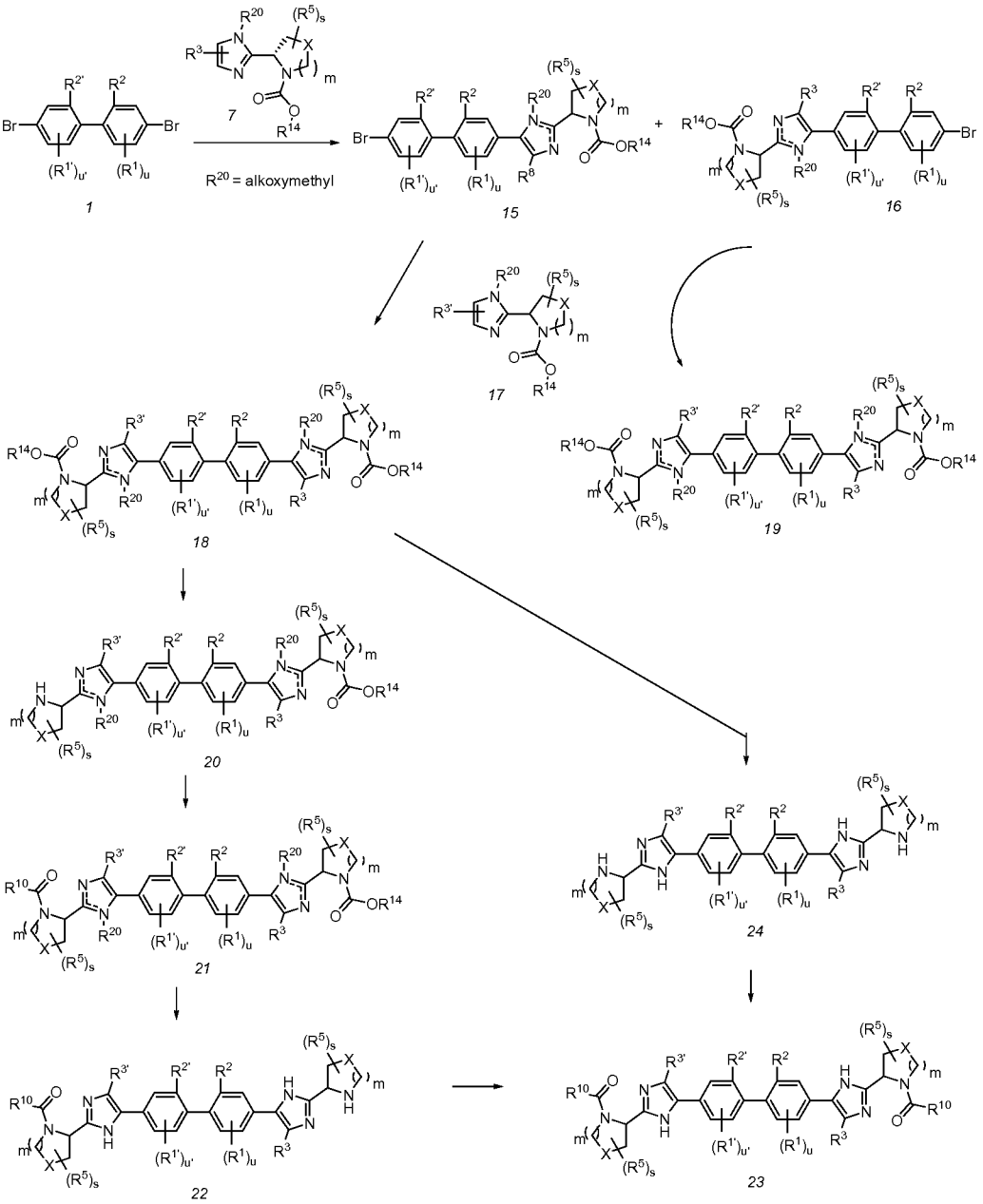
Pyrrolidine *5* can be converted to a separable mixture of amides *12* and *13*, using standard amide coupling conditions such as HATU with an amine base, such as Hunig's base. By employing the same coupling conditions, either of the mono-derivitized products (*12* or *13*) could be converted to *14*, where the R^{10} groups on the two pyrrolidine moieties could be different or the same. In the event where the two R^{10} groups of *14* are the same, it will be identical with *6*.



Scheme 3:

Compounds such as *18* (or its regioisomer *19*) could be synthesized from dibromide *1* by integrating the two imidazopyrrolidines *7* and *17* in a sequential manner via a palladium assisted electrophilic aromatic substitution reaction. It is apparent to one of ordinary skill in the art that monocoupled products *15* and *16* might need to be separated before proceeding to the second coupling step. Mono-deprotection of the pyrrolidine moiety of *18* may be accomplished when the two R^{14} groups are different. When one R^{14} = benzyl, and the other R^{14} = t-butyl treatment with hydrogenolytic conditions produces *20*. For example, Pd/C catalyst in the presence of hydrogen gas and a base such as potassium carbonate can be used. Acylation of *20* can be accomplished under standard acylation conditions. A coupling reagent such as HATU in combination with an amine base such as Hunig's base can be used in this regard. Alternatively, *20* may be reacted with an isocyanate, carbamoyl chloride or a chloroformate to provide compounds of formula *21* where R^{10} is an amine or an alcohol. Further deprotection of *21* can be accomplished by treatment with strong acid such as HCl or trifluoroacetic acid. Standard conditions analogous to those used to convert *20* to *21*can be used to prepare *23* from *22*. In another embodiment where each R^{14} = t-Bu, direct conversion of *18* to *24* can be accomplished by treatment with strong acid such as HCl or trifluoroacetic acid. Conversion of *24* to *23* is accomplished in analogous fashion to the methods used to

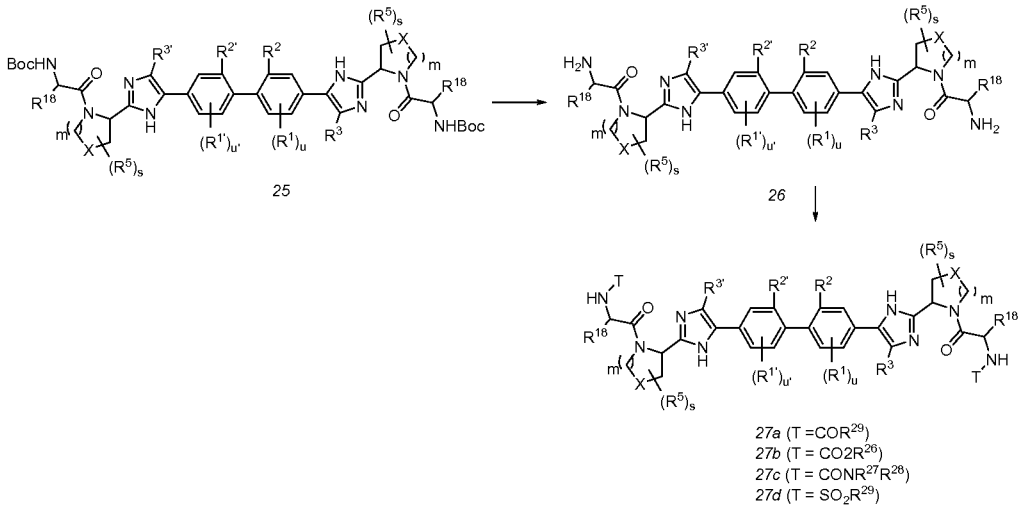
prepare *23* from *22*. In this instance, however, the caps in *23* will be identical. It is apparent to one of ordinary skill in the art that compound *19* could also be elaborated under similar route as the one described for *18* to prepare the corresponding regioisomeric final products.



Scheme 4:

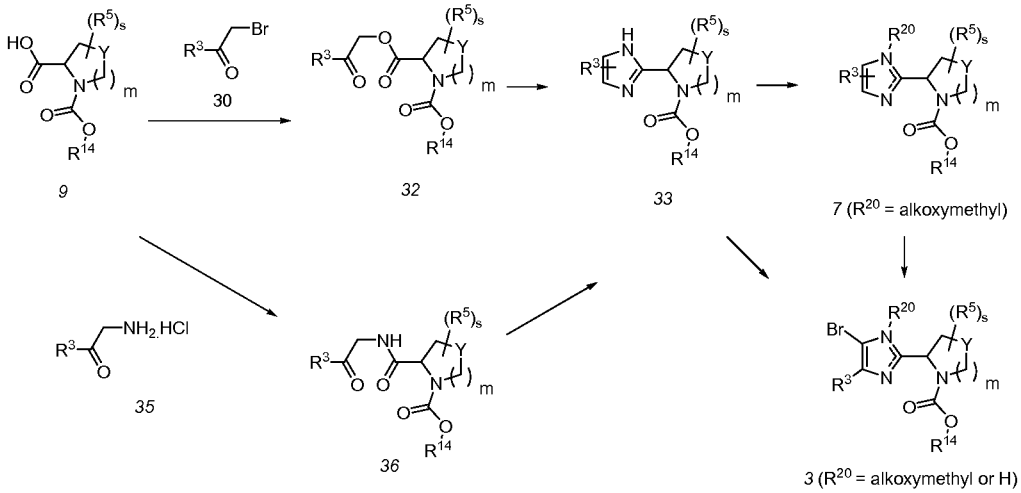
Compound *25* (*25* = *6* (Scheme 1) wherein each R^{10} is -CH(NHBoc)R^{18}) can be converted to *26 via* treatment with strong acid such as HCl or trifluoroacetic acid.

Amine *26* could be acylated under coupling conditions such as HATU/Hunig's base to afford amide *27a*. Treatment of amine *26* with appropriate chloroformate, isocyanate or carbamoyl chloride, or sulfonyl chloride affords compounds *27b*, *27c* or *27d* respectively.



Scheme 5:

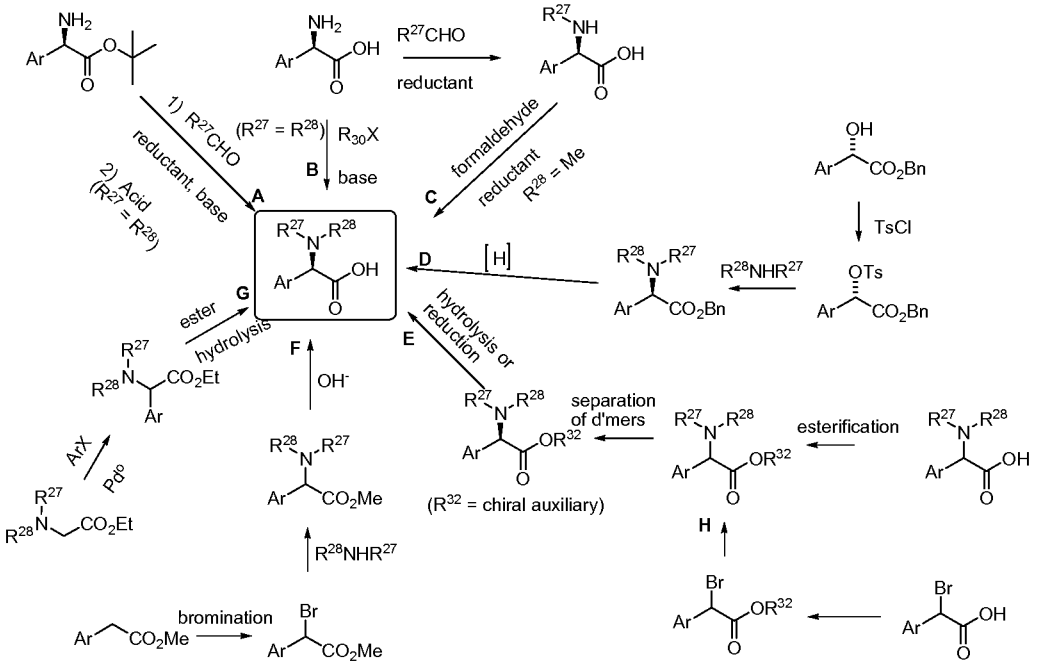
The starting materials required for the synthetic sequences depicted in Schemes 1-4 could be prepared according to the following procedures. Key intermediate *33* is prepared from keto-amide *36* or keto-ester *32 via* heating with ammonium acetate under thermal or microwave conditions. Keto-amide *36* can be prepared from *35 via* condensation with an appropriate cyclic or acyclic amino acid under standard amide formation conditions. Bromide *30* can be converted to *32* by reacting with an appropriate cyclic or acyclic N-protected amino acid in the presence of base such as Hunig's base. Bromination of *33* (or its alkoxy methyl protected derivative *7*) with a source of bromonium ion, such as bromine or NBS, results in the formation of *3*. A special case of imidazole *33* (where R^3 = H) can be prepared from appropriately substituted N-protected amino acids by reacting with glyoxal in a methanolic solution of ammonium hydroxide.



Scheme 6:

Substituted phenylglycine derivatives can be prepared by a number of methods exemplified below. Phenylglycine t-butyl ester can be reductively alkylated (pathyway 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 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

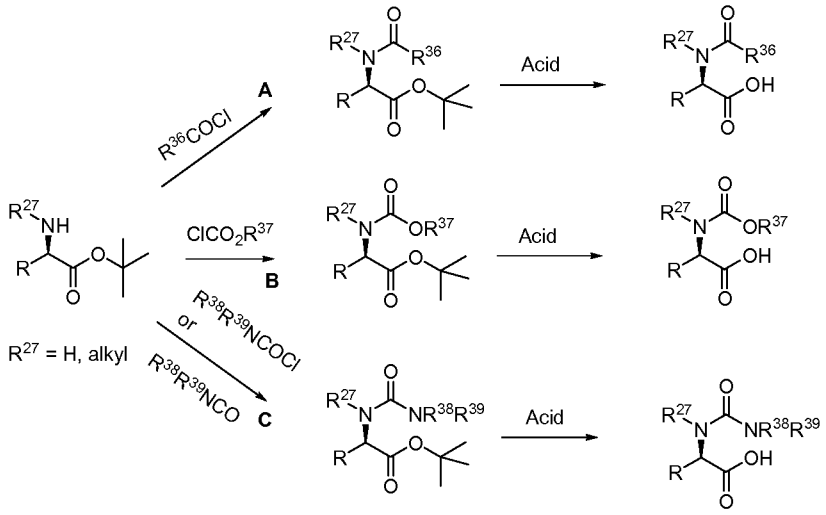
prior to amine addition. Alternatively, an ester of an arylacetic acid can be brominated with a source of bromonium ion such as bromine, N-bromosuccinimide, or CBr_4. The resultant benzylic bromide can be displaced with a variety of mono- or di-substituted amines in the presence of a tertiary amine base 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 using for example chiral column. It is apparent to one of ordinary skill in the art the approaches described for the synthesis of aromatic glycine derivatives is equally applicable to the synthesis glycine derivatives containing non-aromatic group at C-2.



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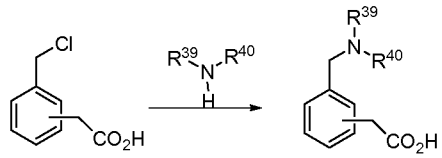
Scheme 7:

In another embodiment of the present disclosure, acylated glycine derivatives may be prepared as illustrated below. Glycine 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 glycine 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 (i.e., treatment of the t-butyl ester with strong base such as HCl or trifluoroacetic acid).



Scheme 8

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



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:

Condition 1

Column = Phenomenex-Luna 3.0X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 2

Column = Phenomenex-Luna 4.6X50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 5 mL/min
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 3

Column = HPLC XTERRA C18 3.0 x 50mm S7
Start %B = 0
Final %B = 100
Gradient time = 3 min

Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition M1

Column: Luna 4.6X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow rate = 4 mL/min
Solvent A: = 95% H_20: 5% CH_3CN, 10 mm Ammonium acetate
Solvent B: = 5% H_2O : 95% CH_3CN; 10 mm Ammonium acetate

Synthesis of common caps

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
Flow Rate = 5 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Cond.-MS-W2

Column = XTERRA 3.0 X 50 mm S7

Start %B	= 0
Final %B	= 100
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%H_2O
Solvent B	= 0.1% TFA in 90% methanol/10% H_2O

Cond.-MS-W5

Column	= XTERRA 3.0 X 50 mm S7
Start %B	= 0
Final %B	= 30
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_2O
Solvent B	= 0.1% TFA in 90% methanol/10% H_2O

Cond.-D1

Column	= XTERRA C18 3.0 X 50 mm S7
Start %B	= 0
Final %B	= 100
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%H_2O
Solvent B	= 0.1% TFA in 90% methanol/10% H_2O

Cond.-D2

Column	= Phenomenex-Luna 4.6 X 50 mm S10

Start %B = 0
Final %B = 100
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%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Cond.-M3
Column = XTERRA C18 3.0 X 50 mm S7
Start %B = 0
Final %B = 40
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_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

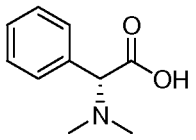
Condition I
Column = Phenomenex-Luna 3.0 X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition II
Column = Phenomenex-Luna 4.6 X 50 mm S10

Start %B = 0
Final %B = 100
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_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition III
Column = XTERRA C18 3.0 x 50mm S7
Start %B = 0
Final %B = 100
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%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

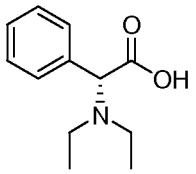
Cap-1



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 H_2 (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 H_2O; λ=589 nm]. ^1H NMR (DMSO-d_6, δ=2.5 ppm, 500 MHz): δ 7.43-7.34 (m, 5H), 4.14 (s, 1H), 2.43 (s, 6H);

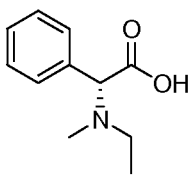
LC (Cond. I): RT=0.25; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.10; found 180.17; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.1025; found 180.1017.

Cap-2



$NaBH_3CN$ (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: $[\alpha]^{25}$ -102.21° (c=0.357, H_2O); crop-2: $[\alpha]^{25}$ -99.7° (c=0.357, H_2O). LC (Cond. I): RT=0.43 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{18}NO_2$: 208.13; found 208.26.

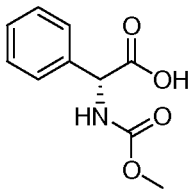
Cap-3



Acetaldehyde (5.0 mL, 89.1 mmol) and a suspension of 10% Pd/C (720 mg) in methanol/H_2O (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 H_2 for 17 hours. An additional acetaldehyde (10 mL, 178.2 mmol) was added and stirring continued under H_2 atmosphere for 24 hours [Note: the supply of H_2 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). ^{1}H 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 $[M+H]^+$ $C_{10}H_{14}NO_2$: 180.10; found 180.18.

A suspension of 10% Pd/C (536 mg) in methanol/H_2O (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 H_2 for ~72 hours, where the H_2 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). ^{1}H 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.

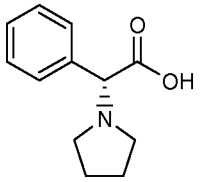
Cap-4



$ClCO_2Me$ (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.

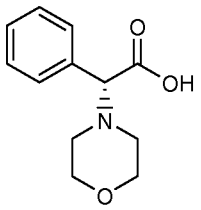
TFA (16 mL) was added dropwise to a cooled (ice/water) CH_2Cl_2 (160 mL) solution of the above product over 7 minutes, and the cooling bath was removed and the reaction mixture was stirred for 20 hours. Since the deprotection was still not complete, an additional TFA (1.0 mL) was added and stirring continued 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, δ=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 $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.08; found 210.17; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.0766; found 210.0756.

Cap-5



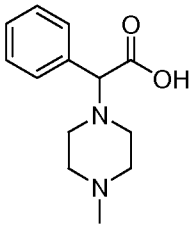
A mixture of (R)- 2-phenylglycine (1.0 g, 6.62 mmol), 1,4-dibromobutane (1.57 g, 7.27 mmol) and Na_2CO_3 (2.10 g, 19.8 mmol) in ethanol (40 mL) was heated at 100 °C for 21 hours. The reaction mixture was cooled to ambient temperature and filtered, and the filtrate was concentrated *in vacuo*. The residue 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). ^{1}H NMR (DMSO-d_6, δ=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 $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; found 206.25.

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. ^{1}H NMR (DMSO-d_6, δ=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); >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

A CH_2Cl_2 (200 mL) solution of p-toluenesulfonyl chloride (8.65 g, 45.4 mmol) was added dropwise to a cooled (-5 °C) CH_2Cl_2 (200 mL) solution of (S)-

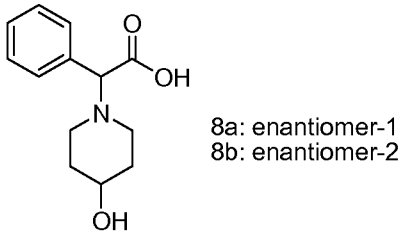
benzyl 2-hydroxy-2-phenylacetate (10.0 g, 41.3 mmol), triethylamine (5.75 mL, 41.3 mmol) and 4-dimethylaminopyridine (0.504 g, 4.13 mmol), while maintaining the temperature between -5 °C and 0 °C. The reaction was stirred at 0 °C for 9 hours, and then stored in a freezer (-25 °C) for 14 hours. It was 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 integrity of the product was not checked and that product was used for the next step without further purification. ^{1}H NMR (DMSO-d_6, δ=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.

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 °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 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 μm) 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 retrieved as viscous oil. ^{1}H 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 $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325.19; found 325.20.

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 (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. ^{1}H NMR (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); >90% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.14; found 235.15; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 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 SN_2 displacement step (i.e., 4-hydroxypiperidine for Cap-8 and (S)-3-fluoropyrrolidine for Cap-9) and modified conditions for the separation of the respective stereoisomeric intermedites, as described below.

Cap-8

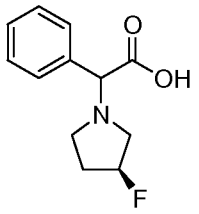


8a: enantiomer-1
8b: enantiomer-2

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 μm) 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: ^{1}H 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 $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.13; found 236.07; HRMS: Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.1287; found 236.1283.

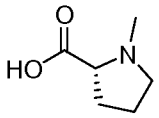
Cap-9



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 μm) 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 °C. The HPLC elute for the respective stereiosmers 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 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 H_2O/methanol/TFA solvent): ^1H NMR (DMSO-d_6, 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 $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14; Cap-9b (diastereomer-2): ^1H NMR (DMSO-d_6, 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 $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14.

Cap-10



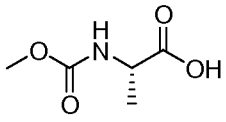
To a solution of D-proline (2.0 g, 17 mmol) and formaldehyde (2.0 mL of 37% wt. in H_2O) in methanol (15 mL) was added a suspension of 10% Pd/C (500 mg) in methanol (5 mL). The mixture was stirred under a balloon of hydrogen for 23 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo* to provide Cap-10 as an off-white solid (2.15 g). ^{1}H NMR (DMSO-d_6, 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 $[M+H]^+$ $C_6H_{12}NO_2$: 130.09; found 129.96.

Cap-11



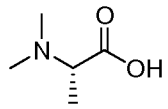
A mixture of (2S,4R)-4-fluoropyrrolidine-2-carboxylic acid (0.50 g, 3.8 mmol), formaldehyde (0.5 mL of 37% wt. in H_2O), 12 N HCl (0.25 mL) and 10% Pd/C (50 mg) in methanol (20 mL) was stirred under a balloon of hydrogen for 19 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) 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). ^{1}H NMR (DMSO-d_6, 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 $[M+H]^+$ $C_6H_{11}FNO_2$: 148.08; found 148.06.

Cap-12 (same as cap 52)



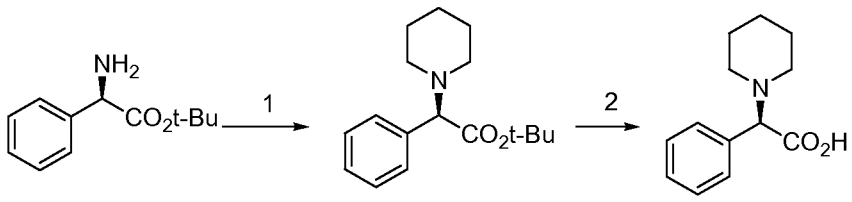
L-Alanine (2.0 g, 22.5 mmol) was dissolved in 10% aqueous sodium carbonate solution (50 mL), and a THF (50 mL) solution of methyl chloroformate (4.0 mL) was added to it. The reaction mixture was stirred under ambient conditions for 4.5 hours and concentrated *in vacuo*. The resulting white solid was 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 (Na_2SO_4), 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 (H_2O/methanol/TFA) to provide 150 mg of Cap-12 as a colorless oil . ^{1}H NMR (DMSO-d_6, 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).

Cap-13



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. ^{1}H NMR (DMSO-d_6, δ=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).

Cap-14



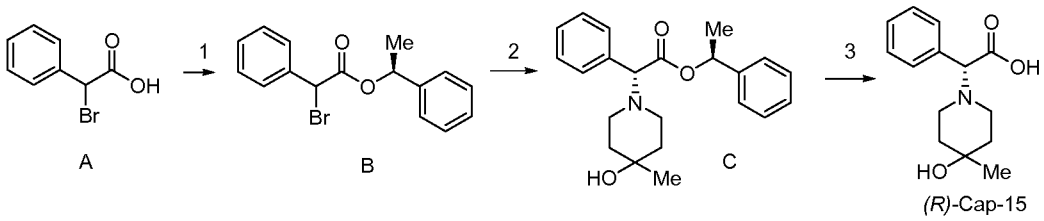
Cap-14

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 $C_{17}H_{25}NO_2$: 275; found: 276 $(M+H)^+$.

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 $C_{13}H_{17}NO_2$: 219; found: 220 $(M+H)^+$.

Cap-15



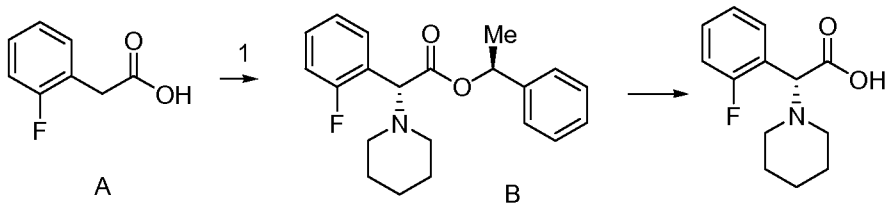
Step 1: (S)-1-Phenylethyl 2-bromo-2-phenylacetate: To a mixture of α-bromophenylacetic acid (10.75 g, 0.050 mol), (S)-(-)-1-phenylethanol (7.94 g, 0.065 mol) and DMAP (0.61 g, 5.0 mmol) in dry dichloromethane (100 mL) was added solid EDCI (12.46 g, 0.065 mol) all at once. The resulting solution was stirred 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. ^{1}H 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 °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: ^{1}H 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 $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$. (S,S)-isomer: ^{1}H 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 $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$.

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; CH_3CN-H_2O-0.1% TFA) to give the title compound (as TFA salt) as a pale bluish solid (0,128 g, 98%). LCMS: Anal. Calcd. for $C_{14}H_{19}NO_3$: 249; found: 250 $(M+H)^+$.

Cap-16



A B *(R)*-Cap-16

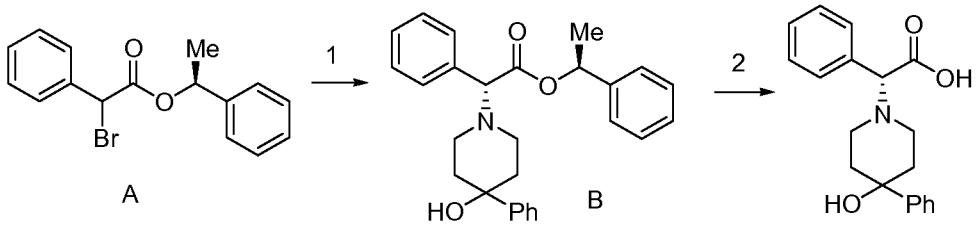
Step 1: (S)-1-Phenylethyl 2-(2-fluorophenyl)acetate: A mixture of 2-fluorophenylacetic acid (5.45 g, 35.4 mmol), (S)-1-phenylethanol (5.62 g, 46.0 mmol), EDCI (8.82 g, 46.0 mmol) and DMAP (0.561 g, 4.60 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 12 hours. The solvent was then concentrated 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 (H_2O, brine), dried (Na_2SO_4), 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%). ^{1}H NMR (400 MHz, CD_3OD) 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 CBr_4 (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. NH_4Cl and 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*. 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, CD_3OD) 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 $C_{21}H_{24}FNO_2$: 341; found: 342 $(M+H)^+$.

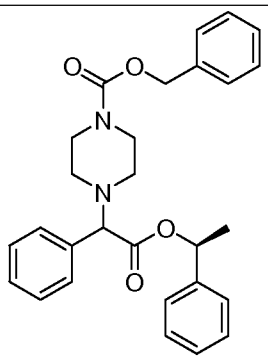
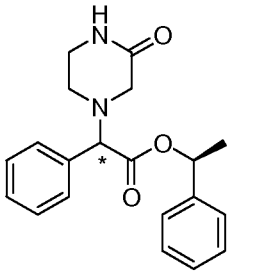
Step 3: (R)-2-(2-fluorophenyl)-2-(piperidin-1-yl)acetic acid: A mixture of (R)-((S)-1-phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate (0.737 g, 2.16 mmol) and 20% $Pd(OH)_2/C$ (0.070 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 2 hours. 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 $C_{13}H_{16}FNO_2$: 237; found: 238 $(M+H)^+$.

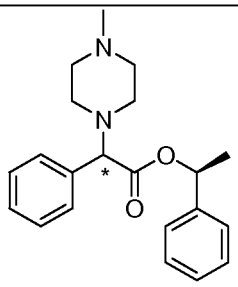
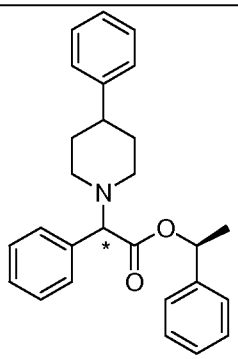
Cap-17



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 °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 $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$; (S,S)-isomer: H^1NMR (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 $(M+H)^+$.

The following esters were prepared in similar fashion:

Intermediate-17a		Diastereomer 1: ^{1}H NMR (500 MHz, DMSO-d_6) 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: ^{1}H NMR (500 MHz, DMSO-d_6) 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 $(M+H)^+$.
Intermediate -17b		Diasteromer 1: RT=11.76 minutes (Cond'n II); LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.16 Found: 339.39 $(M+H)^+$; Diastereomer 2:

		RT=10.05 minutes (Cond'n II); LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.16; Found: 339.39 $(M+H)^+$.
Intermediate -17c		Diastereomer 1: $T_{R=}$4.55 minutes (Cond'n I); LCMS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.20 Found: 339.45 $(M+H)^+$; Diastereomer 2: $T_{R=}$6.00 minutes (Cond'n I); LCMS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.20 Found: 339.45 $(M+H)^+$.
Intermediate -17d		Diastereomer 1: RT=7.19 minutes (Cond'n I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.22 Found: 400.48 $(M+H)^+$; Diastereomer 2: RT=9.76 minutes (Cond'n I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.22 Found: 400.48 $(M+H)^+$.

Chiral SFC Conditions for determining retention time

Condition I

Column: Chiralpak AD-H Column, 4.62x50 mm, 5μm

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

Injection: 1.0 mg/3mL methanol

Condition II

Column: Chiralcel OD-H Column, 4.62x50 mm, 5μm

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

Temp: 35 °C

Pressure: 150 bar

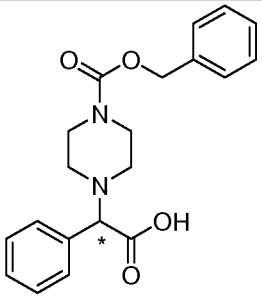
Flow rate: 2.0 mL/min.

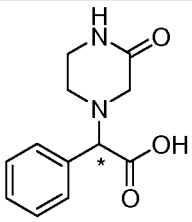
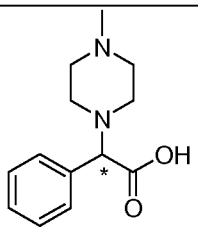
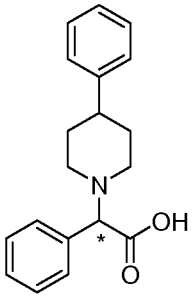
UV monitored @ 220 nm

Injection: 1.0 mg/mL methanol

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; CH_3CN-H_2O-0.1% TFA) to give the title compound (as TFA salt) as a white solid (0.230 g, 88%). LCMS: Anal. Calcd. for $C_{19}H_{21}NO_3$: 311.15; found: 312 $(M+H)^+$.

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

Cap-17a		RT=2.21 (Cond'n II); ^1H 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: $C_{20}H_{22}N_2O_4$

		354.16; Found: 355.38 $(M+H)^+$.
Cap-17b		RT=0.27 (Cond'n III); LCMS: Anal. Calcd. for: $C_{12}H_{14}N_2O_3$ 234.10; Found: 235.22 $(M+H)^+$.
Cap-17c		RT=0.48 (Cond'n II); LCMS: Anal. Calcd. for: $C_{13}H_{18}N_2O_2$ 234.14; Found: 235.31 $(M+H)^+$.
Cap-17d		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

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% H_2O – 0.1% TFA

Solvent B=90% methanol – 10% H_2O – 0.1% TFA

Condition II

Column: Waters-Sunfire 4.6 X 50 mm S5

Start % B=0

Fianl % B=100

Gradient Time=2 min

Flow Rate=4 mL/min

Wavelength=220

Solvent A=10% methanol – 90% H_2O – 0.1% TFA

Solvent B=90% methanol – 10% H_2O – 0.1% TFA

Condition III

Column: Phenomenex 10μ 3.0 X 50 mm

Start % B=0

Fianl % B=100

Gradient Time=2 min

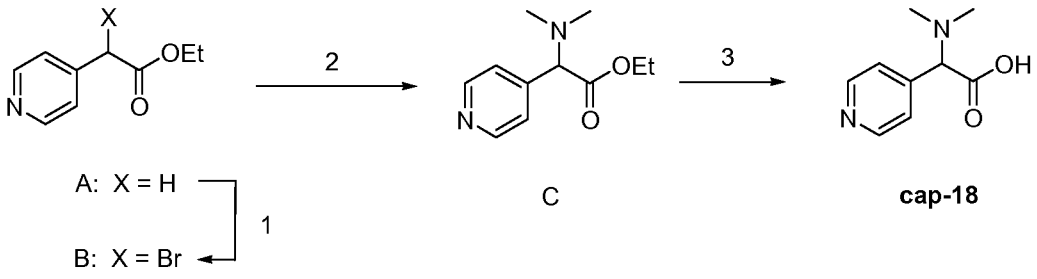
Flow Rate=4 mL/min

Wavelength=220

Solvent A=10% methanol – 90% H_2O – 0.1% TFA

Solvent B=90% methanol – 10% H_2O – 0.1% TFA

Cap-18



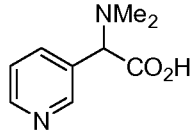
Step 1; (R,S)-Ethyl 2-(4-pyridyl)-2-bromoacetate: To a solution of ethyl 4-pyridylacetate (1.00 g, 6.05 mmol) in dry THF (150 mL) at 0 °C under argon was added DBU (0.99 mL, 6.66 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes and then it was cooled to -78 °C. To this mixture was added CBr_4 (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. NH_4Cl and the phases were separated. The organic phase was washed (brine), dried (Na_2SO_4), filtered, and

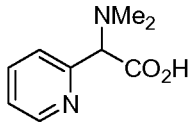
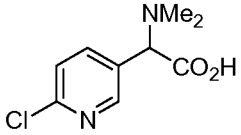
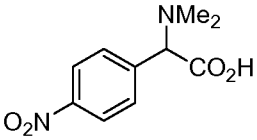
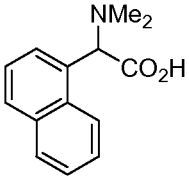
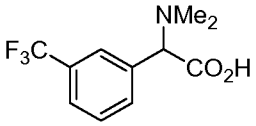
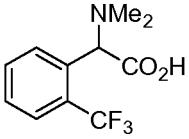
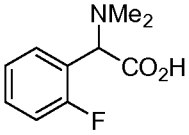
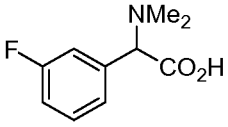
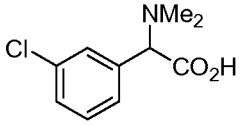
concentrated *in vacuo*. The resulting yellow oil was immediately purified by flash chromatography (SiO_2/ hexane-ethyl acetate, 1:1) to provide the title compound (1.40 g, 95%) as a somewhat unstable yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J*=4.6, 1.8 Hz, 2H), 7.45 (dd, *J*=4.6, 1.8 Hz, 2H), 5.24 (s, 1H), 4.21-4.29 (m, 2H), 1.28 (t, *J*=7.1 Hz, 3H). LCMS: Anal. Calcd. for $C_9H_{10}BrNO_2$: 242, 244; found: 243, 245 $(M+H)^+$.

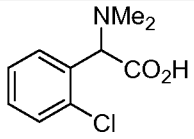
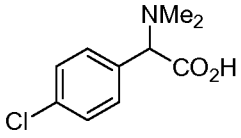
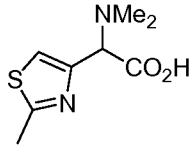
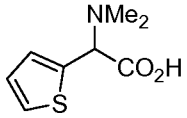
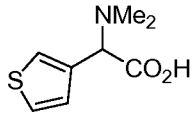
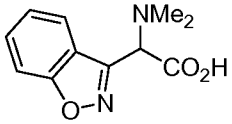
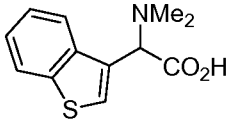
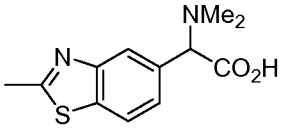
Step 2; (R,S)-Ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-bromoacetate (1.40 g, 8.48 mmol) in DMF (10 mL) at room temperature was added dimethylamine (2M in THF, 8.5 mL, 17.0 mmol). After completion of the reaction (as judged by thin layer chromatography) the volatiles were removed *in vacuo* and the residue was purified by flash chromatography (Biotage, 40+M SiO_2 column; 50%-100% ethyl acetate-hexane) to provide the title compound (0.539 g, 31%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) 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 $C_{11}H_{16}N_2O_2$: 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-H_2O (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. ^{1}H NMR (400 MHz, DMSO-d_6) 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).

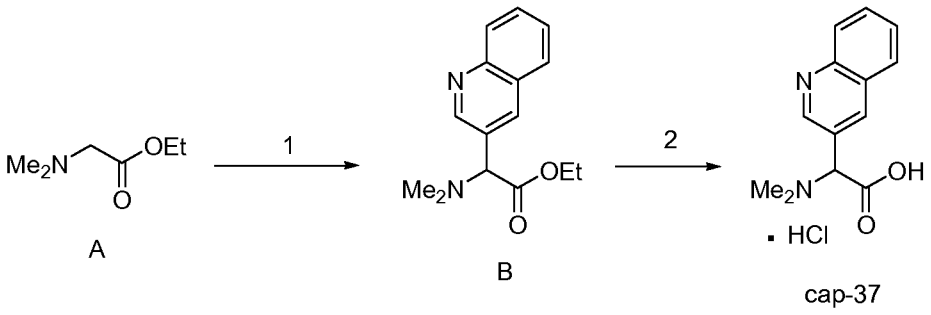
The following examples were prepared in similar fashion using the method described above;

Cap-19		LCMS: Anal. Calcd. for $C_9H_{12}N_2O_2$: 180; found: 181 $(M+H)^+$.

Cap-20		LCMS: no ionization. ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (d, *J*=4.3 Hz, 1H), 7.84 (app t, *J*=5.3 Hz, 1H), 7.61 (d, *J*=7.8 Hz, 1H), 7.37 (app t, *J*=5.3 Hz, 1H), 4.35 (s, 1H), 2.60 (s, 6H).
Cap-21		LCMS: Anal. Calcd. for $C_9H_{11}ClN_2O_2$: 214, 216; found: 215, 217 $(M+H)^+$.
Cap-22		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 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 $C_{11}H_{12}F_3NO_2$: 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 $C_{12}H_{13}NO_2S$: 235; found: 236 $(M+H)^+$.
Cap-36		LCMS: Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: 250; found: 251 $(M+H)^+$.

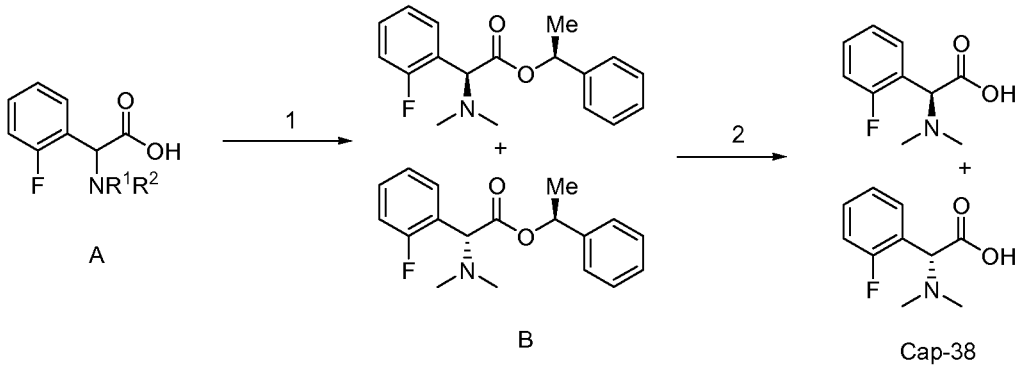
Cap-37



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), K_3PO_4 (1.90 g, 8.95 mmol), $Pd(t\text{-}Bu_3P)_2$ (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 H_2O. The mixture was 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 first by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-5 mM NH_4OAc) and then by flash chromatography (SiO_2/ hexane-ethyl acetate, 1:1) to provide the title compound (0.128 g, 17%) as an orange oil. ^1H NMR (400 MHz, $CDCl_3$) 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 $C_{15}H_{18}N_2O_2$: 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 $(M+H)^+$.

Cap-38



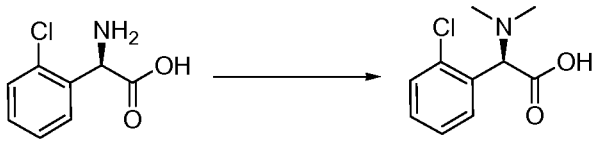
Step 1; (R)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate and (S)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate: To a

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: ^{1}H 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: ^{1}H 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 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 (H_2 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%). ^{1}H NMR (400 MHz, CD_3OD) 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.

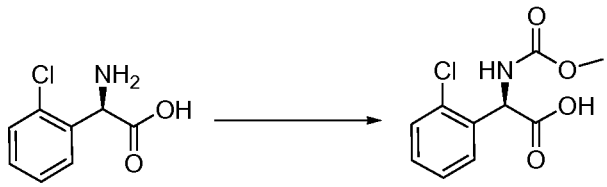
Cap-39



cap-39

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 (H_2 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; CH_3CN-H_2O-0.1% TFA) to give theTFA 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, CD_3OD) 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 $(M+H)^+$.

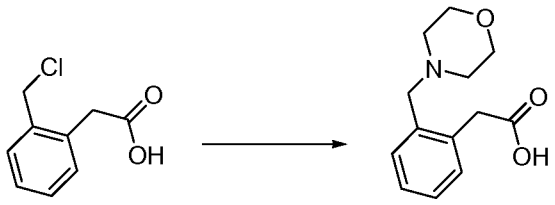
Cap-40



cap-40

To an ice-cold solution of (R)-(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 $C_{10}H_{10}ClNO_4$: 243; found: 244 $(M+H)^+$.

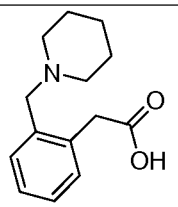
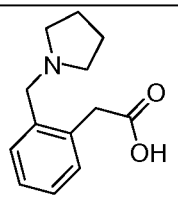
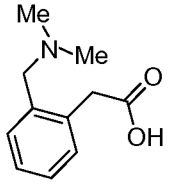
Cap-41

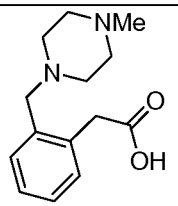


cap-41

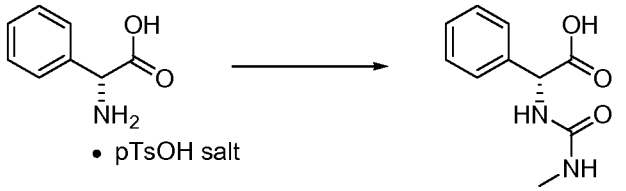
To a suspension of 2-(2-(chloromethyl)phenyl)acetic acid (2.00 g, 10.8 mmol) in THF (20 mL) was added morpholine (1.89 g, 21.7 mmol) and the solution was stirred at room temperature for 3 hours. The reaction mixture was then diluted with ethyl acetate and extracted with H_2O (2x). The aqueous phase was 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%). ^{1}H 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 $C_{13}H_{17}NO_3$: 235; found: 236 $(M+H)^+$.

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 $C_{14}H_{20}N_2O_2$: 248; found: 249 $(M+H)^+$.

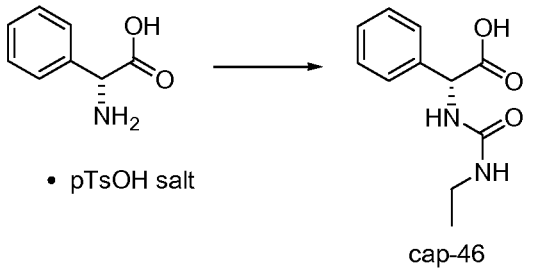
Cap-45a



Cap-45a

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 CH_2Cl_2 (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 H_2O (5 mL) and the resulting precipitate was filtered, washed with H_2O 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 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 $C_{10}H_{12}N_2O_3$ 208.08 found 209.121 $(M+H)^+$; 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.

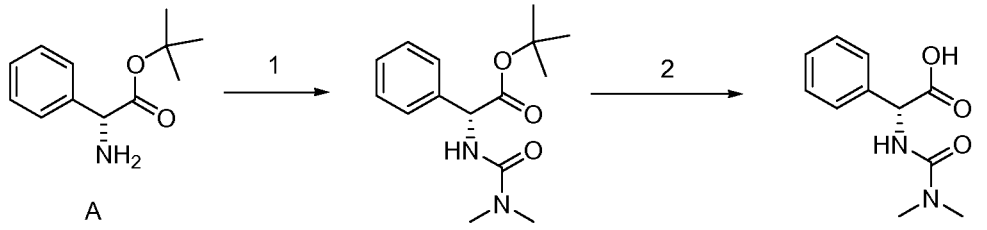
Cap-46



cap-46

The desired product was prepared according to the method described for Cap-45a. ^{1}H 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 $C_{11}H_{14}N_2O_3$ 222.10 found 223.15 $(M+H)^+$. 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.

Cap-47

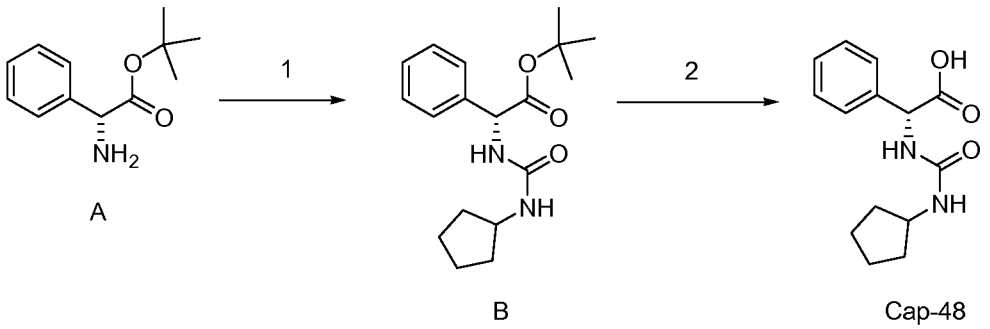


Step 1; (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate: To a stirred solution of (R)-tert–butyl-2-amino-2-phenylacetate (1.0 g, 4.10 mmol) and Hunig's base (1.79 mL, 10.25 mmol) in DMF (40 mL) was added dimethylcarbamoyl chloride (0.38 mL, 4.18 mmol) dropwise over 10 minutes. After stirring at 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 H_2O, 1N aq. HCl and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate was obtained as a white solid (0.86 g; 75%) and used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) 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 $C_{15}H_{22}N_2O_3$ 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% 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 CH_2Cl_2 (250 mL) was added TFA (15 mL) dropwise and the resulting solution was

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. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.82 (s, 6H) 5.22 (d, *J*=7.32 Hz, 1H) 6.58 (d, *J*=7.32 Hz, 1H) 7.28 (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 $C_{11}H_{14}N_2O_3$: 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% H_3PO_4, B=10% water, 90% methanol, 0.2% H_3PO_4, RT=0.75 min, 93% homogeneity index.

Cap-48



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 traken up in ethyl acetate. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), 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. ^{1}H NMR (500 MHz, CD_3Cl-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 $C_{18}H_{26}N_2O_3$ 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 CH_2Cl_2 (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%). ^{1}H NMR (500 MHz, DMSO-d_6) 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 $C_{14}H_{18}N_2O_3$: 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% H_3PO_4, B=10% water, 90% methanol, 0.2% H_3PO_4, RT=1.24 min, 100% homogeneity index.

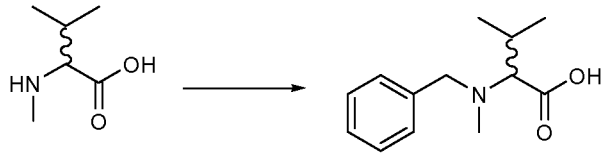
Cap-49



cap-49

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. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.75 (s, 3H) 4.04 (s, 2H) 4.34 (s, 2H) 7.29-7.68 (m, 5H). LCMS: Anal. Calcd. for: $C_{10}H_{13}NO_2$ 179.09; Found: 180.20 $(M+H)^+$.

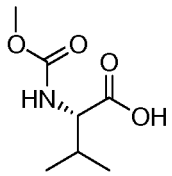
Cap-50



Cap-50

To a stirred solution of 3-methyl-2-(methylamino)butanoic acid (0.50 g, 3.81 mmol) in water (30 mL) was added K_2CO_3 (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. ^{1}H NMR (500 MHz, DMSO-d_6) 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: $C_{13}H_{19}NO_2$ 221.14; Found: 222.28 $(M+H)^+$.

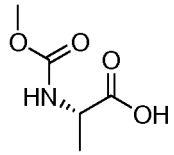
Cap-51



Na_2CO_3 (1.83g, 17.2 mmol) was added to NaOH (33 mL of 1M/H_2O, 33 mmol) solution of L-valine (3.9 g, 33.29 mmol) and the resulting solution was cooled 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 CH_2Cl_2 (50 mL, 3x). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to afford Cap-51 as a white solid (6 g). ^{1}H NMR for the dominant rotamer (DMSO-d_6, δ=2.5 ppm, 500

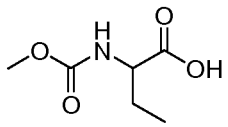
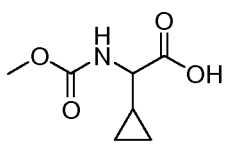
MHz): 12.54 (s, 1H), 7.33 (d, *J*=8.6, 1H), 3.84 (dd, *J*=8.4, 6.0, 1H), 3.54 (s, 3H), 2.03 (m, 1H), 0.87 (m, 6H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_7H_{14}NO_4$: 176.0923; found 176.0922.

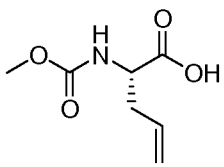
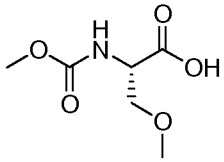
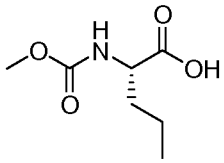
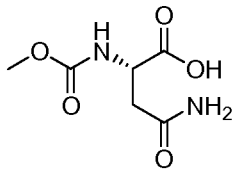
Cap-52 (Same as Cap-12)

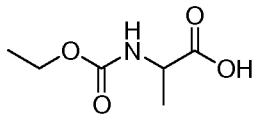
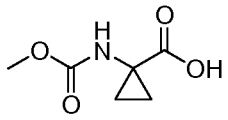
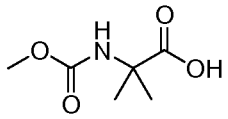
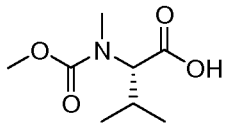
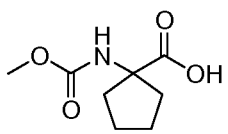


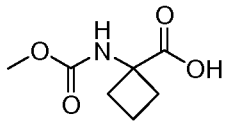
Cap-52 was synthesized from L-alanine according to the procedure described for the synthesis of Cap-51. For characterization purposes, a portion of the crude material was purified by a reverse phase HPLC (H_2O/methanol/TFA) to afford Cap-52 as a colorless viscous oil. ^1H NMR (DMSO-d_6, δ=2.5 ppm, 500 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).

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.

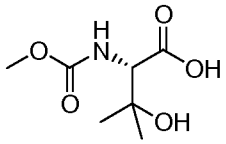
Cap	Structure	Data
Cap-53a: (R) *Cap-53b*: (S)		^1H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.51 (br s, 1H), 7.4 (d, *J* = 7.9, 0.9H), 7.06 (app s, 0.1H), 3.86-3.82 (m, 1H), 3.53 (s, 3H), 1.75-1.67 (m, 1H), 1.62-1.54 (m, 1H), 0.88 (d, *J* = 7.3, 3H). RT = 0.77 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.06; found 184.07. HRMS Calcd. for $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.0586; found 184.0592.
Cap-54a: (R) *Cap-54b*: (S)		^1H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.48 (s, 1H), 7.58 (d, *J* = 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 $[M+H]^+$ $C_7H_{12}NO_4$: 174.0766; found 174.0771
Cap-55		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.62 (s, 1H), 7.42 (d, *J* = 8.2, 0.9H), 7.07 (app s, 0.1H), 5.80-5.72 (m, 1H), 5.10 (d, *J* = 17.1, 1H), 5.04 (d, *J* = 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).
Cap-56		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.75 (s, 1H), 7.38 (d, *J* = 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, *J* = 7.7, 0.08H), 7.40 (d, *J* = 7.9, 0.76H), 7.19 (d, *J* = 8.2, 0.07H), 7.07 (d, *J* = 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, *J* = 7.4, 3H). LC (Cond. 2): RT = 1.39 LC/MS: Anal. Calcd. for $[M+H]^+$ $C_7H_{14}NO_4$: 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, *J* = 8.2, 1H), 6.92 (s, 1H), 4.33-4.29 (m, 1H), 3.54 (s, 3H), 2.54(dd, *J* = 15.5, 5.4, 1H), 2.43 (dd, *J* = 15.6, 8.0, 1H). RT = 0.16 min (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{11}N_2O_5$: 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, *J* = 7.3, 0.89H), 7.04 (br s, 0.11H), 4.00-3.95 (m, 3H), 1.24 (d, *J* = 7.3, 3H), 1.15 (t, *J* = 7.2, 3H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; found 162.0771.
Cap-60		The crude material was purified with a reverse phase HPLC (H_2O/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		^{1}H 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		^{1}H 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.] ^{1}H 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.] ^{1}H 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).

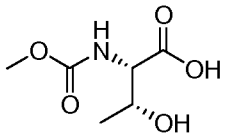
Cap-65



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 filterate was rotervaped to afford *Cap*-65 as a white semi-viscous foam (1.236 g). ^{1}H NMR (DMSO-d_6, δ = 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).

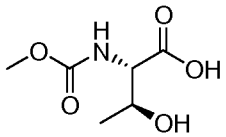
Cap-66 and -67 were prepared from appropriate commercially available starting materials by employing the procedure described for the synthesis of *Cap*-65.

Cap-66



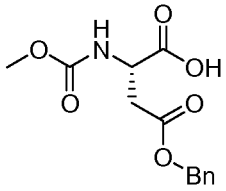
^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.58 (br s, 1H), 7.07 (d, *J* = 8.3, 0.13H), 6.81 (d, *J* = 8.8, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, *J* = 9.1, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, *J* = 6.2, 3H). [Note: only the dominant signals of NH were noted].

Cap-67



^{1}H NMR (DMSO-d_6, 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].

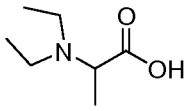
Cap-68



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 $NaHCO_3$ (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 (Na_2SO_4), 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). ^{1}H NMR (DMSO-d_6, 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 $[M+H]^+$ $C_{13}H_{16}NO_6$: 282.10; found 282.12.

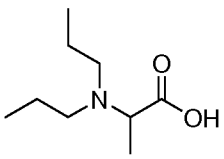
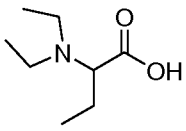
Cap-69a and -69b

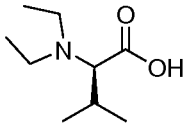
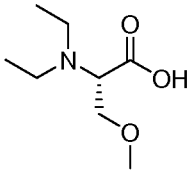
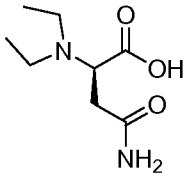
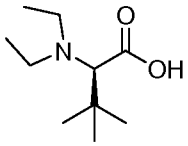


Cap-69a: (R)-enantiomer
Cap-69b: (S)-enantiomer

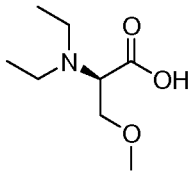
$NaCNBH_3$ (2.416 g, 36.5 mmol) was added in batches to a chilled (~15 °C) water (17 mL)/MeOH (10 mL) solution of alanine (1.338 g, 15.0 mmol). A few minutes later acetaldehyde (4.0 mL, 71.3 mmol) was added drop-wise over 4 min, the cooling bath was removed, and the reaction mixture was stirred at ambient 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 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 NH_4OH, prepared by mixing 18 ml of NH_4OH and 282 ml of water) to afford *Cap*-69 (2.0 g) as an off-white soft hygroscopic solid. ^1H NMR (DMSO-d_6, 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.

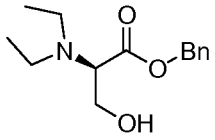
Cap-70a: (R) *Cap-70b*: (S)		^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 3.42 (q, J = 7.1, 1H), 2.68-2.60 (m, 4H), 1.53-1.44 (m, 4H), 1.19 (d, J = 7.3, 3H), 0.85 (t, J = 7.5, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; found 174.13.
Cap-71a: (R) *Cap-71b*: (S)		^1H NMR (DMSO-d_6, 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, *J* = 7.2, 6H), 0.91 (t, *J* = 7.3, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{18}NO_2$: 160.13; found 160.06.
Cap-72		^{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, *J* = 7.1, 6H), 0.91 (d, *J* = 6.5, 3H), 0.85 (d, *J* = 6.5, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; found 174.15.
Cap-73		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 9.5 (br s, 1H), 3.77 (dd, *J* = 10.8, 4.1,1H), 3.69-3.61 (m, 2H), 3.26 (s, 3H), 2.99-2.88 (m, 4H), 1.13 (t, *J* = 7.2, 6H).
Cap-74		^{1}H 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 $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; found 189.13.
Cap-74x		LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{22}NO_2$: 188.17; found 188.21

Cap-75



Cap-75, step a

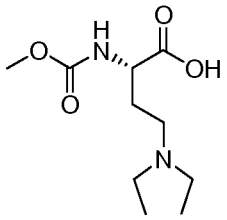


$NaBH_3CN$ (1.6 g, 25.5 mmol) was added to a cooled (ice/water bath) water (25 ml)/methanol (15 ml) solution of H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). Acetaldehyde (1.5 ml, 12.5 mmol) was added drop-wise over 5 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition 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 ($MeOH/H_2O$/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

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 μL, 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 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.

Cap-76

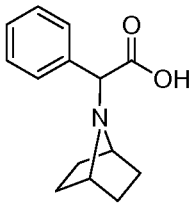


$NaCNBH_3$ (1.60 g, 24.2 mmol) was added in batches to a chilled (~15 °C) water/MeOH (12 mL each) solution of (*S*)-4-amino-2-(tert-butoxycarbonylamino) butanoic acid (2.17 g, 9.94 mmol). A few minutes later acetaldehyde (2.7 mL, 48.1 mmol) was added drop-wise over 2 min, the cooling bath was removed, 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 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 $[M+H]^+$ $C_{10}H_{21}N_2O_4$: 233.15; found 233.24.

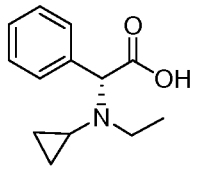
Cap-77a and -77b



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 SN_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 um) eluting with 90% CO_2-10% EtOH at 70 mL/min, and a temperature of 35 °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: ^{1}H 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.

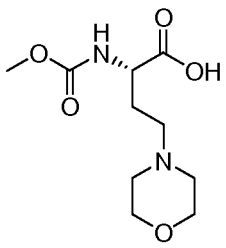
Cap-78



$NaCNBH_3$ (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 $NaCNBH_3$ (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 rotervaped. 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 (H_2O/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 D_2O 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.

Cap-79



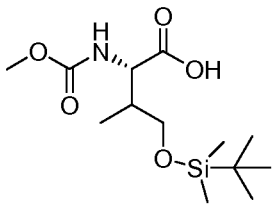
Ozone was bubbled through a cooled (-78 °C) CH_2Cl_2 (5.0 mL) solution *Cap*-55 (369 mg, 2.13 mmol) for about 50 min until the reaction mixture attained a tint of blue color. Me_2S (10 pipet drops) was added, and the reaction mixture was stirred for 35 min. The -78 °C bath was replaced with a -10 °C bath and stirring continued for an additional 30 min, and then the volatile component was removed *in vacuo* to afford a colorless viscous oil.

$NaBH_3CN$ (149 mg, 2.25 mmol) was added to a MeOH (5.0 mL) solution of 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 NH_3/MeOH elution) and a reverse

phase HPLC (H_2O/MeOH/TFA) to afford *Cap*-79 containing unknown amount of morpholine.

In order to consume the morpholine contaminant, the above material was dissolved in CH_2Cl_2 (1.5 mL) and treated with Et_3N (0.27 mL, 1.94 mmol) followed by acetic anhydride (0.10 mL, 1.06 mmol) and stirred at ambient condition for 18 hr. THF (1.0 mL) and H_2O (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 NH_3/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

$SOCl_2$ (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 $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (150 mL, 2x), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford (S)-1-benzyl 4-methyl 2-aminosuccinate as a colorless oil (9.706g). ^{1}H NMR (DMSO-d_6, 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 $[M+H]^+$ $C_{12}H_{16}NO_4$: 238.11; found 238.22.

$Pb(NO_3)_2$ (6.06 g, 18.3 mmol) was added over 1 min to a CH_2Cl_2 (80 mL) solution of (S)-1-benzyl 4-methyl 2-aminosuccinate (4.50 g, 19.0 mmol), 9-bromo-9-phenyl-9*H*-fluorene (6.44 g, 20.0 mmol) and Et_3N (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 $MgSO_4$ and filtered again, and the final filtrate was concentrated. The resulting crude material was submitted to a Biotage purification (350 g silica gel, CH_2Cl_2 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-d_6, 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 $[M+H]^+$ $C_{31}H_{28}NO_4$: 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 NH_4Cl solution (5 mL), most of the organic component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (100 mL) and water (40 mL). The organic layer was dried ($MgSO_4$), 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 dominant isomer was not determined at this juncture, and the mixture was submitted to the next step without separation. Partial ^1H NMR data (DMSO-d_6, δ = 2.5 ppm, 400 MHz): major diastereomer, δ 4.39 (d, J = 12.3, 1H of CH_2), 3.33 (s, 3H, overlapped with H_2O 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 CH_2), 3.76 (d, J = 10.9, NH), 3.64 (s, 3H), 0.77 (d, J = 7.0, 3H). LC (Cond. 1): RT = 2.19 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{30}NO_4$: 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 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 H_3PO_4/H_2O (250

mL) with stirring, and the mixture was extracted with ether (100 mL, 2x). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to chromatography (25% EtOAc/hexanes; gravity elution) to afford 1.1g of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate, contaminated with benzyl alcohol, as a colorless viscous oil and (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate containing the (2S,3R) stereoisomer as an impurity. The later sample was resubmitted to the same 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: ^{1}H NMR (DMSO-d_6, 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: ^{1}H NMR (DMSO-d_6, δ = 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.

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 µL 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-9*H*-fluoren-9-ylamino)butanoate (62.7 mg, 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; 10-15% EtOAc/hexanes) to afford (3S,4S)-4-methyl-3-(9-phenyl-9*H*-fluoren-9-ylamino)dihydrofuran-2(3*H*)-one as a colorless film of solid (28.1 mg). (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate was

elaborated similarly to (3S,4R)-4-methyl-3-(9-phenyl-9*H*-fluoren-9-ylamino)dihydrofuran-2(3*H*)-one. (3S,4S)-lactone isomer: ^{1}H NMR (DMSO-d_6, δ = 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: ^{1}H NMR (DMSO-d_6, δ = 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: ^{1}H NMR (DMSO-d_6, δ = 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: ^{1}H NMR (DMSO-d_6, δ = 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

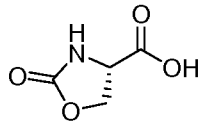
(d, J = 9.5, 1H), 3.41 (dd, J = 10, 6.2, 1H), 2.55 (dd, J = 9.5, 7.3, 1H), 1.74 (m, 1H), 0.77 (s, 9H), 0.61 (d, J = 7.1, 3H), -0.06 (s, 3H), -0.08 (s, 3H).

A balloon of hydrogen was attached to a mixture of (2S,3S)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9*H*-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/H_2O) 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: ^{1}H NMR (Methanol-d_4, 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 $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; found 248.44. (2S,3R)-amino acid isomer: ^{1}H NMR (Methanol-d_4, 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 $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; found 248.44.

Water (1 mL) and NaOH (0.18 mL of 1.0 M/H_2O, 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 Na_2CO_3 (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 CH_2Cl_2 (15 mL, 2x). The combined organic phase was dried ($MgSO_4$), 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: ^{1}H NMR (DMSO-d_6, 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 $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; found 328.46. *Cap*-80b: ^{1}H NMR ($CDCl_3$, 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.

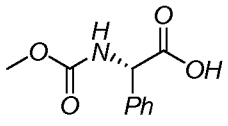
Cap-81



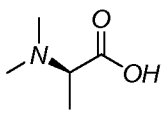
Prepared according to the protocol described by Falb et al. *Synthetic Communications* 1993, *23*, 2839.

Cap-82 to Cap-85

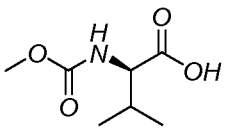
Cap-82 to *Cap*-85 were synthesized from appropriate starting materials according to the procedure described for *Cap*-51 or *Cap*-13. The samples exhibited similar spectral profiles as that of their enantiomers (i.e., *Cap*-4, *Cap*-13, *Cap*-51 and *Cap*-52, respectively).



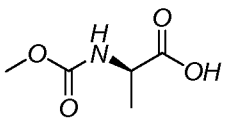
Cap-82



Cap-83

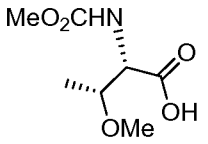


Cap-84



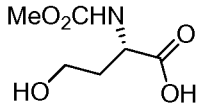
Cap-85

Cap-86



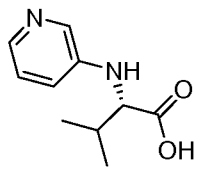
To a mixture of O-methyl-L-threonine (3.0 g, 22.55 mmol), NaOH (0.902 g, 22.55 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (1.74 mL, 22.55 mmol) dropwise at 0°C. The mixture was allowed to stir for 12 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2x250 mL) and 10% 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. ^{1}HNMR (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 $(M-H)^-$.

Cap-87



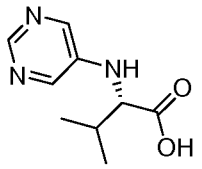
To a mixture of L-homoserine (2.0 g, 9.79 mmol), Na_2CO_3 (2.08 g, 19.59 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (0.76 mL, 9.79 mmol) dropwise at 0°C. The mixture was allowed to stir for 48 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2X250 mL) and the combined 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. ^{1}HNMR (400 MHz, $CDCl_3$) 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), 1.82 – 1.89 (m, 1H). LCMS: Anal. Calcd. for $C_7H_{13}NO_5$: 191; found: 192 $(M+H)^+$.

Cap-88



A mixture of L-valine (1.0 g, 8.54 mmol), 3-bromopyridine (1.8 mL, 18.7 mmol), K_2CO_3 (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 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 lyophyllized. The title compound was obtained as a foam (1.02 g, 62%). ^{1}HNMR (400 MHz, DMSO-d_6) 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 $C_{10}H_{14}N_2O_2$: 194; found: 195 $(M+H)^+$.

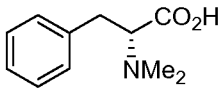
Cap-89



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 lyophyllized. The title compound was obtained as a foam (1.02 g, 62%). ^{1}HNMR (400 MHz, CD_3OD) showed the mixture to contain

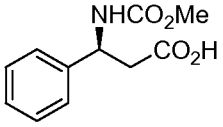
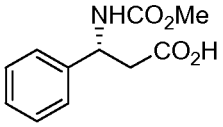
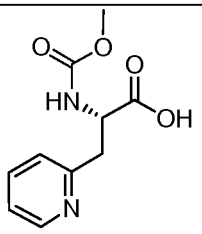
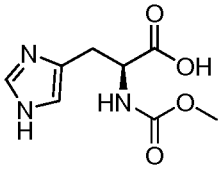
valine and the purity could not be estimated. The material was used as is in subsequent reactions. LCMS: Anal. Calcd. for $C_9H_{13}N_3O_2$: 195; found: 196 $(M+H)^+$.

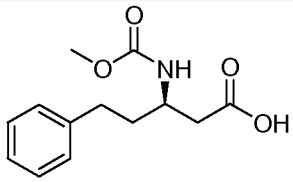
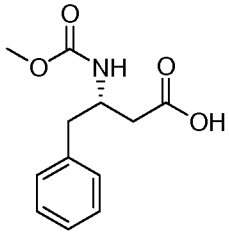
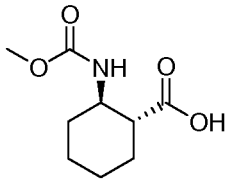
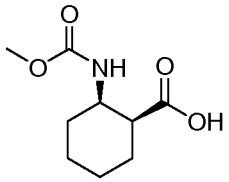
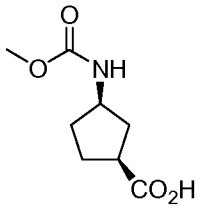
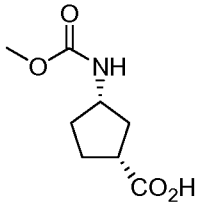
Cap–90

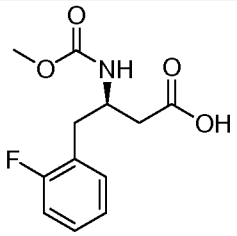
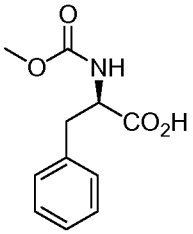
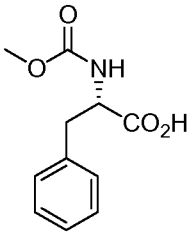
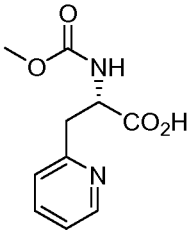
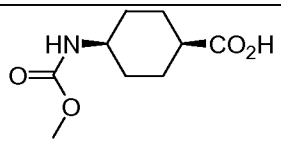
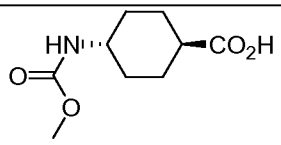


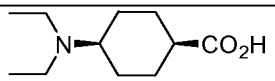
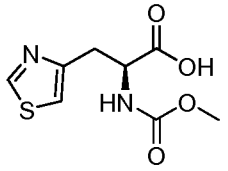
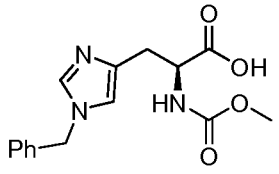
Cap-90 was prepared according to the method described for the preparation of *Cap*-1. The crude material was used as is in subsequent steps. LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 192 $(M-H)^-$.

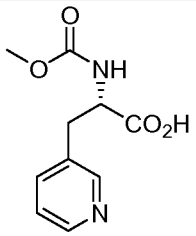
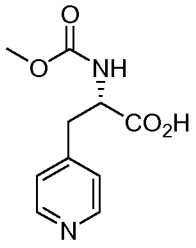
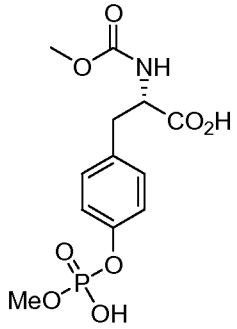
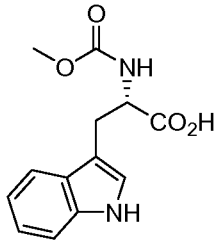
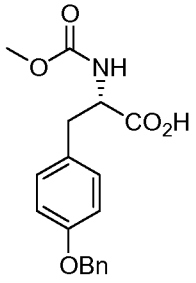
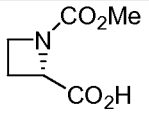
The following caps were prepared according to the method used for preparation of cap 51 unless noted otherwise:

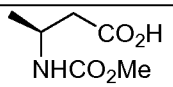
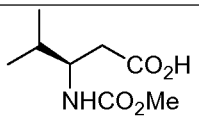
Cap	Structure	LCMS
Cap-91		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-92		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-93		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-94		LCMS: Anal. Calcd. for $C_8H_{11}N_3O_4$: 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 $(M-H)^-$.
Cap-98		LCMS: Anal. Calcd. for $C_9H_{15}NO_4$: 201; found: 202 $(M+H)^+$.
Cap-99		^{1}HNMR (400 MHz, CD_3OD) 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).
Cap-99a		^{1}HNMR (400 MHz, CD_3OD) 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).

Cap-100		LCMS: Anal. Calcd. for $C_{12}H_{14}NO_4F$: 255; found: 256 $(M+H)^+$.
Cap-101		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_3OD) 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_3OD) δ 3.60 (s, 3H), 3.33 – 3.35 (m, 1H, partially obscured by solvent), 2.37 – 2.41 and

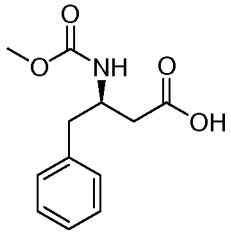
		2.16 – 2.23 (m, 1H), 1.94 – 2.01 (m, 4H), 1.43 – 1.53 (m, 2H), 1.17 – 1.29 (m, 2H).
Cap-106	 Prepared from cis-4-aminocyclohexane carboxylic acid and acetaldehyde by employing a similar procedure described for the synthesis of Cap-2. The crude HCl salt was passed through MCX ($MeOH/H_2O/CH_2Cl_2$ wash; 2 N NH_3/MeOH elution) to afford an oil, which was dissolved in CH_3CN/H_2O and lyophilized to afford a tan solid.	^{1}HNMR (400 MHz, CD_3OD) 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, 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 $C_8H_{10}N_2O_4S$: 230; found: 231 $(M+H)^+$.
Cap-108		LCMS: Anal. Calcd. for $C_{15}H_{17}N_3O_4$: 303; found: 304 $(M+H)^+$.

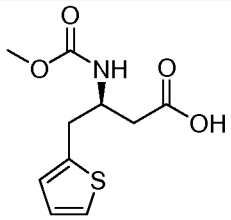
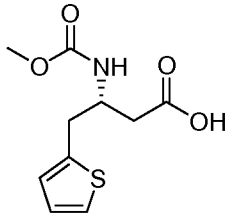
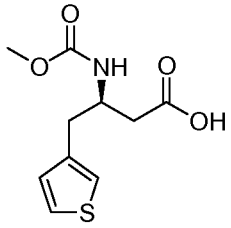
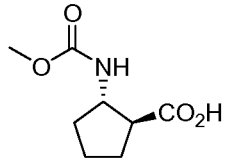
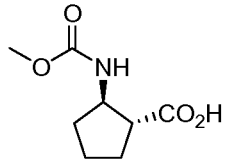
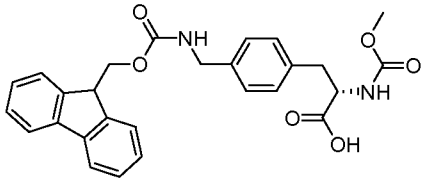
Cap-109		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-110		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-111		LCMS: Anal. Calcd. for $C_{12}H_{16}NO_8P$: 333; found: 334 $(M+H)^+$.
Cap-112		LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_4$: 262; 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, *J* = 5.0 Hz, 2H), 1.28 (d, *J* = 9.1 Hz, 3H).
Cap-116		^{1}HNMR (400 MHz, $CDCl_3$) δ 5.10 (d, *J* = 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).

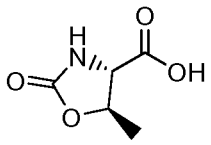
Cap-117 to Cap-123

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 CH_2Cl_2. 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
Cap-117		LCMS: Anal. Calcd. for $C_{12}H_{15}NO_4$: 237; found: 238 $(M+H)^+$.

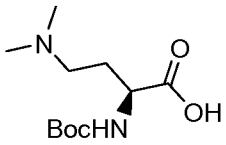
Cap-118		LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$.
Cap-119		LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$.
Cap-120		LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$.
Cap-121		^{1}HNMR (400 MHz, $CDCl_3$) δ 4.06 – 4.16 (m, 1H), 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 $C_{27}H_{26}N_2O_6$: 474; found: 475 $(M+H)^+$.

Cap-124



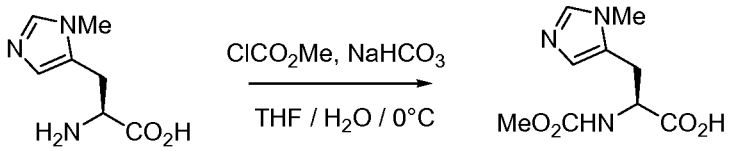
The hydrochloride salt of L-threonine tert-butyl ester was carbamoylated according to the procedure for *Cap*-51. The crude reaction mixture was acidified with 1N HCl to pH~1 and the mixture was extracted with EtOAc (2X50 mL). The combined organic phases were concentrated *in vacuo* to give a colorless 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-CH_2Cl_2-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. ^{1}HNMR (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 $C_5H_7NO_4$: 145; found: 146 $(M+H)^+$.

Cap-125



To a suspension of $Pd(OH)_2$, (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 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 $C_{11}H_{22}N_2O_4$: 246; found: 247 $(M+H)^+$.

Cap-126

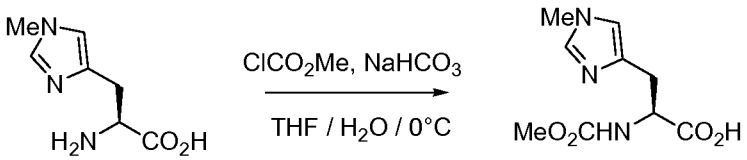


cj-25 *cap-126*

This procedure is a modification of that used to prepare *Cap*-51. To a 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.

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 H_2O (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 ^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. ^{1}HNMR (400 MHz, CD_3OD) 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, J = 9.0, 15.6 Hz, 1H).LCMS: Anal. Calcd. for $C_9H_{13}N_3O_4$: 227.09; found: 228.09 $(M+H)^+$.

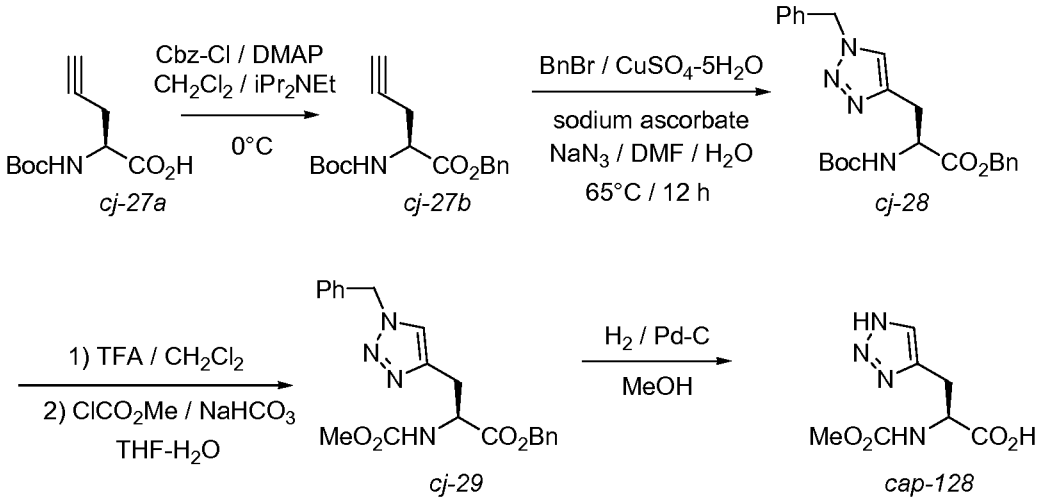
Cap-127



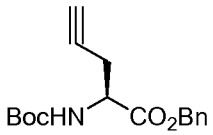
cj-26 *cap-127*

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), $NaHCO_3$ (1.21 g, 14.4 mmol) and $ClCO_2Me$ (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 crude mixture was used as is without further purification. ^1HNMR (400 MHz, CD_3OD) 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 $C_9H_{13}N_3O_4$: 227.09; found: 228 $(M+H)^+$.

Preparation of Cap-128



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

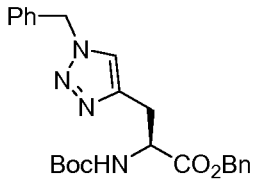


cj-27b

To a solution of *cj-27a* (1.01 g, 4.74 mmol), DMAP (58 mg, 0.475 mmol) and iPr_2NEt (1.7 mL, 9.8 mmol) in CH_2Cl_2 (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 $KHSO_4$, brine), dried (Na_2SO_4), 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. ^{1}HNMR (400 MHz, $CDCl_3$) 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 $C_{17}H_{21}NO_4$: 303; found: 304 $(M+H)^+$.

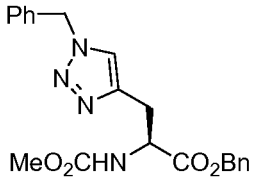
Step 2. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(tert-butoxycarbonylamino)propanoate (cj-28).



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), $CuSO_4$-$5H_2O$ (0.022 g, 0.09 mmol) and NaN_3 (0.13 g, 2.1 mmol) in DMF-H_2O (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 NaN_3 (100 mg) was added and heating was continued for 12h. The reaction was poured into EtOAc and H_2O and shaken. The layers were separated and the aqueous layer extracted 3x with EtOAc and the combined organic phases washed (H_2O x3, brine), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash (Biotage, 40+M 0-5% MeOH in CH_2Cl_2; TLC 3% MeOH in CH_2Cl_2) 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. ^{1}HNMR (400 MHz, DMSO-d_6) 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 $C_{24}H_{28}N_4O_4$: 436; found: 437 $(M+H)^+$.

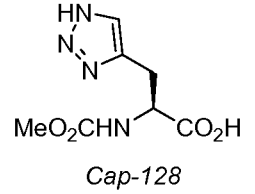
Step 3. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (cj-29).



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 CH_2Cl_2 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-H_2O and cooled to 0°C. Solid $NaHCO_3$ (0.25 g, 3.00 mmol) was added followed by $ClCO_2Me$ (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 H_2O-EtOAc. The layers were separated and the aq phase extracted 2x with EtOAc. The combined org layers were washed (H_2O, brine), dried (Na_2SO_4), 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. ^{1}HNMR (400 MHz, DMSO-d_6) 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 (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 $C_{21}H_{22}N_4O_4$: 394; found: 395 $(M+H)^+$.

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

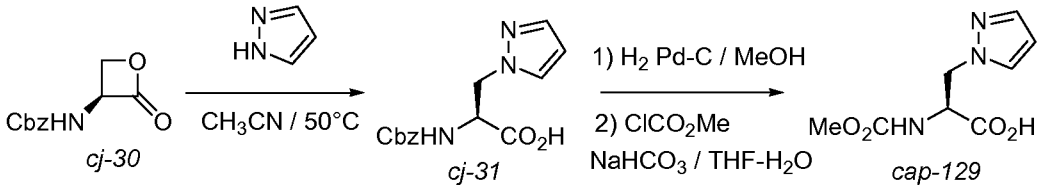


Cap-128

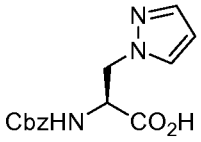
(S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (502 mg, 1.11 mmol) was hydrogenated in the presence of Pd-C (82 mg) in MeOH (5 mL) at atmospheric pressure for 12h. The mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo*. (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic 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. ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.78 (s, br, 1H), 7.59 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 4.19 – 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 $C_7H_{10}N_4O_4$: 214; found: 215 $(M+H)^+$.

Preparation of Cap-129



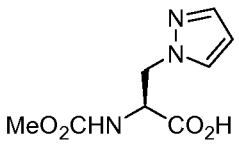
Step 1. Preparation of (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (cj-31).



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 CH_3CN (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 CH_3CN (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]. ^{1}HNMR (400 MHz, CD_3OD) 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 $C_{14}H_{15}N_3O_4$: 289; found: 290 $(M+H)^+$.

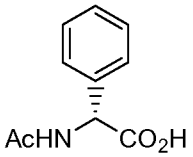
Step 2. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (*Cap-129*).



cap-129

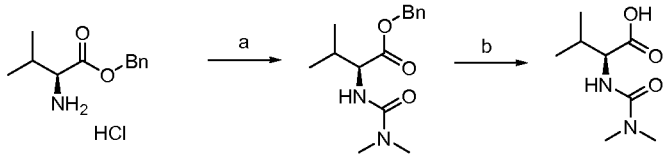
(S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (0.20 g, 0.70 mmol) was hydrogenated in the presence of Pd-C (45 mg) in MeOH (5 mL) at atmospheric pressure for 2h. The product appeared to be insoluble in MeOH, therefore the reaction mixture was diluted with 5mL H_2O and a few drops of 6N HCl. The homogeneous solution was filtered through diatomaceous earth (Celite®), and the MeOH removed *in vacuo*. The remaining solution was frozen and lyophyllized to give a yellow foam (188.9 mg). This material was suspended in THF-H_2O (1:1, 10mL) and then cooled to 0°C. To the cold mixture was added $NaHCO_3$ (146.0 mg, 1.74 mmol) carefully (evolution of CO_2). After gas evolution had ceased (ca. 15 min) $ClCO_2Me$ (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 (Na_2SO_4), filtered, and concentrated to give the title compound as a colorless solid (117.8 mg, 79%). ^{1}HNMR (400 MHz, DMSO-d_6) 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 $C_8H_{11}N_3O_4$: 213; found: 214 $(M+H)^+$.

Cap-130



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

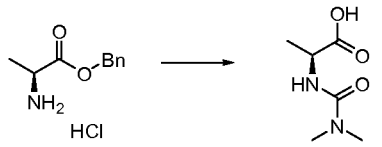
Cap-131



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 ($MgSO_4$), 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. ^{1}H NMR (300 MHz, DMSO-d_6) 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 $[M+H]^+$ $C_{16}H_{22}N_2O_3$: 279.17; found 279.03.

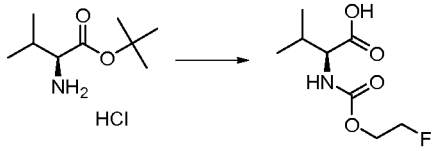
Step b: To a MeOH (50 mL) solution of the intermediate prepared above (2.35 g; 8.45 mmol) was added Pd/C (10%; 200 mg) and the resulting black suspension was flushed with N_2 (3x) and placed under 1 atm of H_2. The mixture was stirred at room temperature overnight and filtered though a microfiber filter 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. ^{1}H NMR (500 MHz, DMSO-d_6) 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 $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; found 189.04.

Cap-132



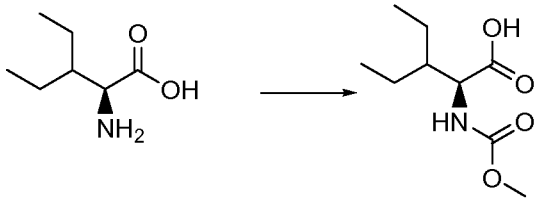
Cap-132 was prepared from (S)-benzyl 2-aminopropanoate hydrochloride according to the method described for *Cap-131*. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.27 (d, *J*=7.32 Hz, 3H), 2.80 (s, 6H), 4.06 (qt, 1H), 6.36 (d, *J*=7.32 Hz, 1H), 12.27 (s, 1H). LC (Cond. 1): RT = 0.15 min; MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{13}N_2O_3$: 161.09; found 161.00.

Cap-133



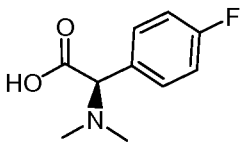
Cap-133 was prepared from (S)-*tert*-butyl 2-amino-3-methylbutanoate hydrochloride and 2-fluoroethyl chloroformate according to the method described for *Cap-47*. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.87 (t, *J* = 6.71 Hz, 6H), 1.97-2.10 (m, 1H), 3.83 (dd, *J*=8.39, 5.95 Hz, 1H), 4.14-4.18 (m, 1H), 4.20-4.25 (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



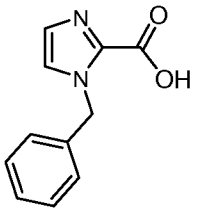
Cap-134 was prepared from (S)-diethyl alanine and methyl chloroformate according to the method described for *Cap-51*. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.72-0.89 (m, 6H), 1.15-1.38 (m, 4H), 1.54-1.66 (m, 1H), 3.46-3.63 (m, 3H), 4.09 (dd, *J* = 8.85, 5.19 Hz, 1H), 7.24 (d, *J* = 8.85 Hz, 1H), 12.55 (s, 1H). LC (Cond. 2): RT = 0.66 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{18}NO_4$: 204.12; found 204.02.

Cap-135



A solution of D-2-amino-(4-fluorophenyl)acetic acid (338 mg, 2.00 mmol), 1*N* 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%). ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.59 (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% homogenity index; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{13}FNO_2$: 198.09; found: 198.10.

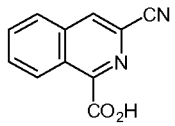
Cap-136



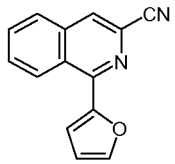
To a cooled (-50 °C) suspension of 1-benzyl-1*H*-imidazole (1.58 g, 10.0 mmol) in anhydrous diethyl ether (50 mL) under nitrogen was added *n*-butyl lithium (2.5 M in hexanes, 4.0 mL, 10.0 mmol) dropwise. After being stirred for 20 min at -50 °C, dry carbon dioxide (passed through Drierite) was bubbled 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 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%). ^{1}H 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% homogenity index; LRMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{12}N_2O_2$: 203.08; found: 203.11.

Cap-137

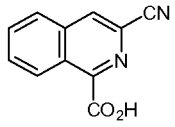


Cap-137, step a



A suspension of 1-chloro-3-cyanoisoquinoline (188 mg, 1.00 mmol; prepared 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 μL, 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 stirring for 1 h. The mixture was partitioned between ethyl acetate and water and the organic phase was separated, washed with brine, dried over Na_2SO_4, 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. Calc. for $[M+H]^+$ $C_{14}H_8N_2O$: 221.07; found: 221.12.

Cap-137

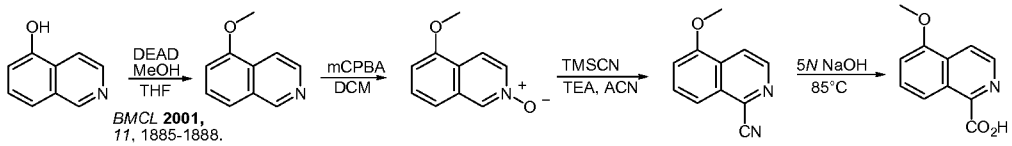


To a suspension of *Cap 137, step a*, (110 mg, 0.50 mmol) and sodium periodate (438 mg, 2.05 mmol) in carbon tetrachloride (1 mL), acetonitrile (1 mL) and water (1.5 mL) was added ruthenium trichloride hydrate (2 mg, 0.011 mmol).

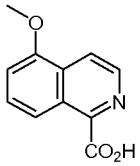
The mixture was stirred at 25 °C for 2 h and then partitioned between dichloromethane and water. The aqueous layer was separated, extracted twice more with dichloromethane and the combined dichloromethane extracts were dried over Na_2SO_4, filtered and concentrated. Trituration of the residue with hexanes 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 $[M+H]^+$ $C_{11}H_8N_2O_2$: 200.08; found: 200.08.

Caps 138 to *158*

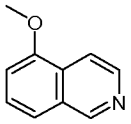
Synthetic Strategy. Method A.



Cap-138



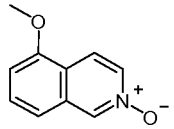
Cap-138, step a



To a stirred suspension of 5-hydroxisoquinoline (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 Na_2SO_4, filtered and concentrated. The residue was preabsorbed onto silica gel and purified (elution with 40% ethyl acetate/hexanes) to afford *Cap-*

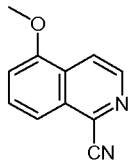
138, step a as a light yellow solid (1.00 g, 45%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.19 (s, 1H), 8.51 (d, *J* = 6.0 Hz, 1H), 7.99 (d, *J* = 6.0 Hz, 1H), 7.52-7.50 (m, 2H), 7.00-6.99 (m, 1H), 4.01 (s, 3H); R_t = 0.66 min (Cond. D2); 95% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_{10}NO$: 160.08; found 160.10.

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%). ^{1}H NMR ($CDCl_3$, 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% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_{10}NO_2$: 176.07; found: 176.0.

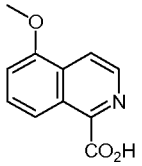
Cap-138, step c



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 trimethylsilylcyanide (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 Na_2SO_4 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

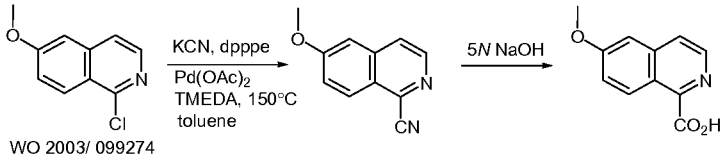
additional *Cap-138, step c* recovered from the filtrate. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.63 (d, *J* = 5.5 Hz, 1H), 8.26 (d, *J* = 5.5 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 4.04 (s, 3H); R_t = 1.75 min, (Cond.-D1); 90% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9N_2O$: 185.07; found: 185.10.

Cap-138



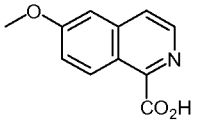
Cap-138, step c (0.45 g, 2.44 mmol) was treated with 5*N* sodium hydroxide solution (10 mL) and the resulting suspension was heated at 85 °C for 4 h, cooled to 25 °C, diluted with dichloromethane and acidified with 1*N* hydrochloric acid. The organic phase was separated, washed with brine, dried over Na_2SO_4, concentrated to ¼ volume and filtered to afford *Cap-138* as a yellow solid (0.44g, 88.9%). ^{1}H 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% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.

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

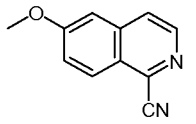


WO 2003/ 099274

Cap-139

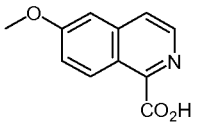


Cap-139, step a



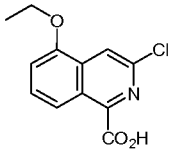
To a thick-walled, screw-top vial containing an argon-degassed suspension of 1-chloro-6-methoxyisoquinoline (1.2 g, 6.2 mmol; prepared according to the procedure in WO 2003/ 099274), potassium cyanide (0.40 g, 6.2 mmol), 1,5-bis(diphenylphosphino)pentane (0.27 g, 0.62 mmol) and palladium (II) acetate (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 Na_2SO_4, 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). ^{1}H NMR ($CDCl_3$, 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% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9N_2O$: 185.07; found: 185.20.

Cap-139

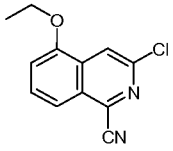


Cap-139 was prepared from the basic hydrolysis of *Cap-139, step a* with 5*N* NaOH according to the procedure described for *Cap 138*. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.63 (v br s, 1H), 8.60 (d, J = 9.3 Hz, 1H), 8.45 (d, J = 5.6 Hz, 1H), 7.95 (d, J = 5.9 Hz, 1H), 7.49 (d, J = 2.2 Hz, 1H), 7.44 (dd, J = 9.3, 2.5 Hz, 1H), 3.95 (s, 3H); R_t = 0.64 min (Cond.-D1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.

Cap-140

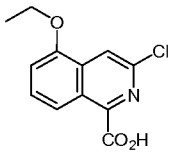


Cap-140, step a



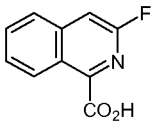
To a vigorously-stirred mixture of 1,3-dichloro-5-ethoxyisoquinoline (482 mg, 2.00 mmol; prepared according to the procedure in WO 2005/ 051410), palladium (II) acetate (9 mg, 0.04 mmol), sodium carbonate (223 mg, 2.10 mmol) and 1,5-bis(diphenylphosphino)pentane (35 mg, 0.08 mmol) in dry dimethylacetamide (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 □L 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 and water and the organic layer was separated, washed with brine, dried over Na_2SO_4, 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% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_9ClN_2O$: 233.05; found: 233.08.

Cap-140

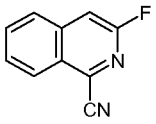


Cap-140 was prepared by the acid hydrolysis of *Cap-140, step a* with 12*N* HCl as described in the procedure for the preparation of *Cap 141*, described below. R_t = 2.24 min (Cond.-MS-W2); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{11}ClNO_3$: 252.04; found: 252.02.

Cap-141

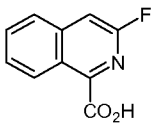


Cap-141, step a



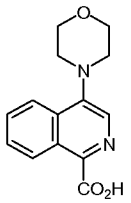
Cap-141, step a was prepared from 1-bromo-3-fluoroisoquinoline (prepared from 3-amino-1-bromoisoquinoline using the procedure outlined in *J. Med. Chem.* **1970**, *13*, 613) as described in the procedure for the preparation of *Cap-140, step a* (*vide supra*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, 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% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_6FN_2$: 173.05; found: 172.99.

Cap-141

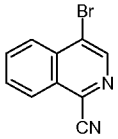


Cap-141, step a (83 mg, 0.48 mmol) was treated with 12*N* HCl (3 mL) and the resulting slurry was heated at 80 °C for 16 h before it was cooled to room temperature and diluted with water (3 mL). The mixture was stirred for 10 min and then filtered to afford *Cap-141* as an off-white solid (44.1 mg, 47.8%). The filtrate was diluted with dichloromethane and washed with brine, dried over Na_2SO_4, and concentrated to afford additional *Cap-141* which was sufficiently pure to be carried forward directly (29.30 mg, 31.8%). ^{1}H NMR (DMSO-d_6, 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% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 191.97.

Cap-142

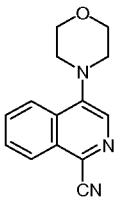


Cap-142, step a



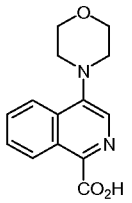
Cap-142, step a was prepared from 4-bromoisoquinoline N-oxide as described in the two-step procedure for the preparation of *Cap-138, steps b and c*. R_t = 1.45 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_6BrN_2$: 232.97; found: 233.00.

Cap-142, step b



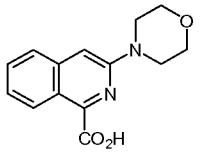
To an argon-degassed suspension of *Cap-142, step a* (116 mg, 0.50 mmol), potassium phosphate tribasic (170 mg, 0.80 mmol), palladium (II) acetate (3.4 mg, 0.015 mmol) and 2-(dicyclohexylphosphino)biphenyl (11 mg, 0.03 mmol) in anhydrous toluene (1 mL) was added morpholine (61 µL, 0.70 mmol). The mixture 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% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{14}N_3O$: 240.11; found: 240.13.

Cap-142

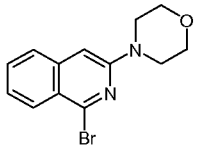


Cap-142 was prepared from *Cap-142, step b* with 5*N* sodium hydroxide as described in the procedure for *Cap 138*. R_t = 0.72 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; found: 259.08.

Cap-143

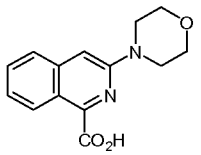


Cap-143, step a



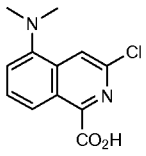
To a stirred solution of 3-amino-1-bromoisoquinoline (444 mg, 2.00 mmol) in anhydrous dimethylformamide (10 mL) was added sodium hydride (60%, unwashed, 96 mg, 2.4 mmol) in one portion. The mixture was stirred at 25 °C for 5 min before 2-bromoethyl ether (90%, 250 μL, 2.00 mmol) was added. The mixture 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% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{13}H_{14}BrN_2O$: 293.03; found: 293.04.

Cap-143

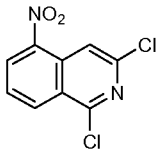


To a cold (-60 °C) solution of *Cap-143, step a* (154 mg, 0.527 mmol) in anhydrous tetrahydrofuran (5 mL) was added a solution of *n*-butyllithium in hexanes (2.5 M, 0.25 mL, 0.633 mmol). After 10 min, dry carbon dioxide was bubbled into the reaction mixture for 10 min before it was quenched with 1*N* 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 residue by a reverse phase HPLC (MeOH/water/TFA) afforded *Cap-143* (16 mg, 12%). R_t = 1.10 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; found: 259.08.

Cap-144

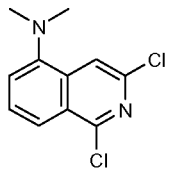


Cap-144, step a



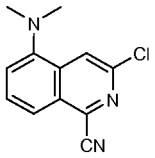
1,3-Dichloroisoquinoline (2.75 g, 13.89 mmol) was added in small portions to a cold (0 °C) solution of fuming nitric acid (10 mL) and concentrated sulfuric acid (10 mL). The mixture was stirred at 0 °C for 0.5 h before it was gradually warmed to 25 °C where it stirred for 16 h. The mixture was then poured 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 used directly. R_t = 2.01 min. (Cond.-D1); 95% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_9H_5Cl_2N_2O_2$: 242.97; found: 242.92.

Cap-144, step b



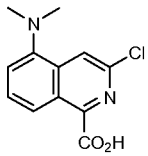
Cap-144, step a (0.30 g, 1.23 mmol) was taken up in methanol (60 mL) and treated with platinum oxide (30 mg), and the suspension was subjected to Parr hydrogenation at 7 psi H_2 for 1.5 h. Then formalin (5 mL) and additional platinum oxide (30 mg) were added, and the suspension was resubjected to Parr hydrogenation at 45 psi H_2 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% homogenity index; ^{1}H NMR (400 MHz, $CDCl_3$) 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 $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241.03; found: 241.02. HRMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241.0299; found: 241.0296.

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% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232.06; found: 232.03. HRMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232.0642; found: 232.0631.

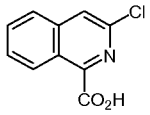
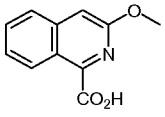
Cap-144

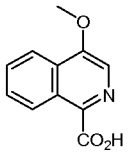
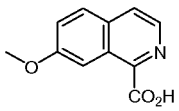
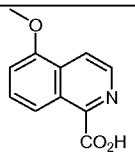


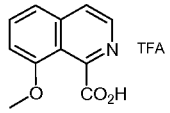
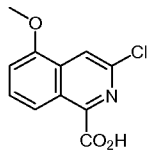
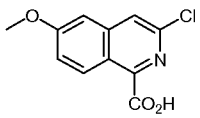
Cap-144 was prepared according to the procedure described for *Cap-141*. R_t = 2.36 min (Cond.-D1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{12}ClN_2O_2$: 238.01; found: 238.09.

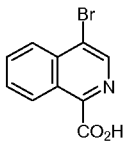
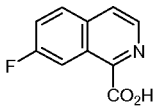
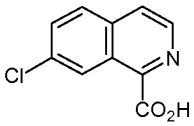
Caps-145 to 162

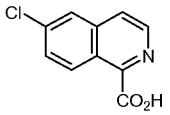
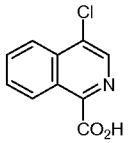
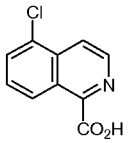
Caps-145 to *162* were prepared from the appropriate 1-chloroisoquinolines according to the procedure described for the preparation of *Cap-138* (Method A) or *Cap-139* (Method B) unless noted otherwise as outlined below.

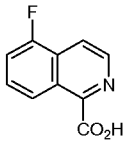
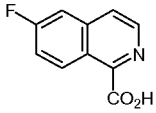
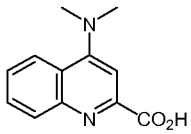
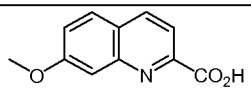
Cap #	Cap	Method	Hydrolysis	R_t (LC-Cond.); % homogeneity index; MS data
Cap-145	 Prepared from commercially available 1,3-dichloroisoquinoline	B	12*N* HCl	1.14 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.00.
Cap-146	 Prepared from commercially	A	5*N* NaOH	1.40 min (Cond.-D1); 95% ; LCMS: Anal.

	available 3-hydroxyisoquinoline			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	5*N* 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	5*N* 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	5*N* 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	 Prepared from 8-methoxy-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274	A	12*N* HCl	0.26 min (Cond.-D1); 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	12*N* HCl	1.78 min (Cond.-D1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9ClNO_3$: 238.03; found: 238.09.
Cap-152	 Prepared from commercially available 6-methoxy-1,3-dichloroisoquinoline	B	12*N* HCl	1.65 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9ClNO_3$: 238.00;

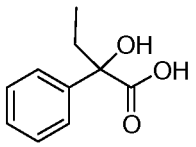
				found: 238.09.
Cap-153	 Prepared from 4-bromoisoquinoline, which can be synthesized following the procedure in WO 2003/062241	A	6*N* HCl	1.18 min (Cond.-MS-W1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7BrNO_2$: 251.97; found: 251.95.
Cap-154	 Prepared from 7-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274	B	5*N* 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-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/099274	B	5*N* 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-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274	B	5*N* NaOH	0.60 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.03.
Cap-157	 Prepared from 1,4-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 062241	B	12*N* HCl	1.49 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_{17}ClNO$: 208.02; found: 208.00.
Cap-158	 Prepared from 1,5-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274	B	5*N* NaOH	0.69 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 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	5*N* NaOH	0.41 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 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	5*N* NaOH	0.30 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 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 $[M+H]^+$ $C_{12}H_{13}N_2O_2$: 217.10; found: 217.06.
Cap-162		--	--	0.65 min (Cond.-M3);

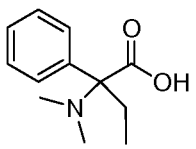
	Prepared from *m*-anisidine following the procedure described in *J. Hetero. Chem.* **1993**, 17 and *Heterocycles*, **2003**, *60*, 953.			95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 203.94.

Cap-163



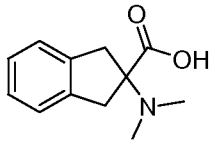
To a solution of 2-ketobutyric acid (1.0 g, 9.8 mmol) in diethylether (25 ml) was added phenylmagnesium bromide (22 ml, 1M in THF) dropwise. The reaction was stirred at ~25 °C under nitrogen for 17.5h. The reaction was acidified with 1N HCl and the product was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was washed with water followed by brine and dried over $MgSO_4$. After 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). ^{1}H NMR (DMSO-d_6, 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).

Cap-164



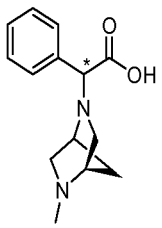
A mixture of 2-amino-2-phenylbutyric acid (1.5 g, 8.4 mmol), formaldehyde (14 mL, 37% in water), 1N HCl (10 mL) and 10% Pd/C (0.5 mg) in MeOH (40 mL) was exposed to H_2 at 50 psi in a Parr bottle for 42 h. The reaction was filtered over Celite and concentrated *in vacuo*, the residue was taken up in MeOH (36 mL) and the product was purified with a reverse phase HPLC (MeOH/H_2O/TFA) to afford the TFA salt of *Cap-164* as a white solid (1.7 g). ^{1}H NMR (DMSO-d_6, 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



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 (MeOH/H_2O/TFA) to afford the TFA salt of *Cap-165* as a viscous oil (120.2 mg). ^{1}H NMR (DMSO-d_6, 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 $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; found: 206.07.

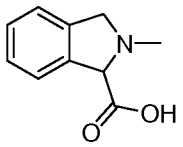
Cap-166a and -166b



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

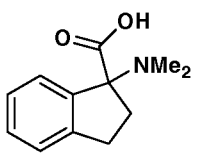
Caps-166a and *-166b* were prepared from (1S, 4S)-(+)-2-methyl-2,5-diazabicyclo[2.2.1]heptane (2HBr) according to the method described for the synthesis of *Cap-7a and Cap-7b*, with the exception that the benzyl ester intermediate was separated using a semi-prep Chrialcel OJ column, 20 x 250 mm, 10 μm eluting with 85:15 heptane/ethanol mixture at 10 mL/min elution rate for 25 min. *Cap-166b*: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 7.45 (d, J = 7.3 Hz, 2H), 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



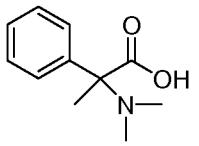
A solution of racemic Boc-1,3-dihydro-2H-isoindole carboxylic acid (1.0g, 3.8 mmol) in 20% TFA/CH_2Cl_2 was stirred at ~25 °C for 4h. All the volatile component was removed *in vacuo*. A mixture of the resultant crude material, formaldehyde (15 mL, 37% in water), 1N HCl (10 mL) and 10% Pd/C (10 mg) in 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). ^{1}H NMR (DMSO-d_6, δ = 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.

Cap-168



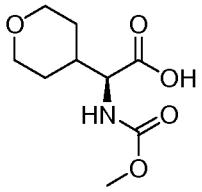
Racemic *Cap-168* was prepared from racemic Boc-aminoindane-1-carboxylic acid according to the procedure described for the preparation of *Cap-167*. The crude material was employed as such.

Cap-169



A mixture of 2-amino-2-phenylpropanoic acid hydrochloride (5.0 g, 2.5 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 g). ^{1}H NMR ($CDCl_3$, 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 $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; found: 194.12.

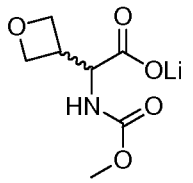
Cap-170



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 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* to afford *Cap-170* a colorless residue. ^{1}H 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



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. ^{1}H NMR (500 MHz, CHLOROFORM-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 placed on high vac overnite providing 55mg lithium 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate as a colorless solid. ^{1}H 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).

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 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.

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 (SiO_2) according to Still's flash 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:
Retention times were determined according to the following LC/MS conditions:

Condition I
Column: Phenomenex-Luna 4.6 X 50 mm S10
Start % B = 0
Final % B = 100

Gradient Time = 4 min

Flow Rate = 4 mL/min

Wavelength = 220

Solvent A = 10% CH_3OH – 90% H_2O – 0.1% TFA

Solvent B = 90% CH_3OH – 10% H_2O – 0.1% TFA

Condition II

Column: Phenomenex-Luna 3.0 X 50 mm S10

Start % B = 0

Final % B = 100

Gradient Time = 3 min

Flow Rate = 4 mL/min

Wavelength = 220

Solvent A = 10% CH_3OH – 90% H_2O – 0.1% TFA

Solvent B = 90% CH_3OH – 10% H_2O – 0.1% TFA

Condition III

Column: Xbridge C18 4.6 X 50 mm S5

Start % B = 0

Final % B = 100

Gradient Time = 3 min

Flow Rate = 4 mL/min

Wavelength = 220

Solvent A = H_2O : ACN 95% : 5% 10 mm Ammonium Acetate

Solvent B = H_2O : ACN 5% : 95% 10 mm Ammonium Acetate

Condition IV

Column: Phenomenex C18 10u 4.6 X 30 mm

Start % B = 0

Final % B = 100

Gradient Time = 3 min

Flow Rate = 4 mL/Min

Wavelength = 220

Solvent A = 10% CH_3OH – 90% H_2O – 0.1% TFA

Solvent B = 90% CH_3OH – 10% H_2O – 0.1% TFA

Condition V

Column: Phenomenex C18 10u 4.6 X 30 mm

Start % B = 0

Final % B = 100

Gradient Time = 10min

Flow Rate = 4 mL/Min

Wavelength = 220

Solvent A = H_2O : ACN 95% : 5% 10 mm Ammonium Acetate

Solvent B = H_2O : ACN 5% : 95% 10 mm Ammonium Acetate

Condition VI

Column: Phenomenex 10u 3.0 X 50 mm

Start % B = 0

Final % B = 100

Gradient Time = 3 min

Flow Rate = 4 mL/Min

Wavelength = 220

Solvent A = 10% CH_3OH – 90% H_2O – 0.1% TFA

Solvent B = 90% CH_3OH – 10% H_2O – 0.1% TFA

Condition VII

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min

Flow rate = 4mL/min

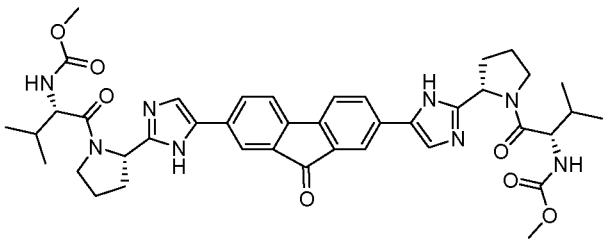
Wavelength = 220 nm

Solvent A = 10% CH_3OH / 90%H_2O / 0.1% TFA

Solvent B = 90% CH_3OH / 10% H_2O / 0.1% TFA

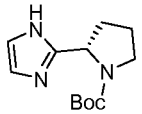
Column 2 = Phenomenex-Luna 3.0 x 50 mm S10

Example 1



methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-oxo-9H-fluoren-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

Example 1, Step a



1a

Glyoxal (2.0 mL of 40% in water) was added dropwise over 11 minutes to a CH_3OH solution of NH_4OH (32 mL) and (*S*)-Boc-prolinal (8.564 g, 42.98 mmol) and stirred at ambient temperature for 19 hours. The volatile component was removed *in vacuo* and the residue was purified by a flash chromatography (silica gel, EtOAc) followed by a recrystallization (EtOAc, room temperature) to afford imidazole 1a as a white fluffy solid (4.43g). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 11.68/11.59 (br s, 1H), 6.94 (s, 1H), 6.76 (s, 1H), 4.76 (m, 1H), 3.48 (m, 1H), 3.35-3.29 (m, 1H), 2.23-1.73 (m, 4H), 1.39/1.15 (s, 9H).

LC (Cond. VII): RT = 0.87 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{20}N_3O_2$ 238.16; found 238.22

Imidazole 1a had an ee of 98.9% when analyzed under chiral HPLC condition noted below.

Column: Chiralpak AD, 10 um, 4.6 x 50 mm

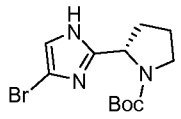
Solvent: 1.7% ethanol/heptane (isocratic)

Flow rate: 1 ml/min

Wavelength: either 220 or 256 nm

Relative retention time: 3.25min (*R*), 5.78 minutes (*S*)

Example 1, Step b



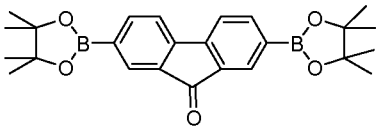
1b

N-bromosuccinimide (838.4 mg, 4.71 mmol) was added in batches, over 15 minutes, to a cooled (ice/water) CH_2Cl_2 (20 mL) solution of imidazole 1a (1.0689 g, 4.504 mmol), and stirred at similar temperature for 75 min. The volatile component was removed *in vacuo*, and the crude material was purified by a reverse phase HPLC system (H_2O/CH_3OH/TFA) to separate bromide 1b from its dibromo-analog and the non-consumed starting material. The HPLC elute was neutralized with excess NH_3/CH_3OH (2.0 M) and the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford 1b as a white solid (374 mg). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.12 (br s, 1H), 7.10 (m, 1H), 4.70 (m, 1H), 3.31 (m, 1H; overlapped with water signal), 2.25-1.73 (m, 4H), 1.39/1.17 (s, 3.8H + 5.2H).

LC (Cond. VII): RT = 1.10 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{19}BrN_3O_2$ 316.07; found 316.10

Example 1, Step c

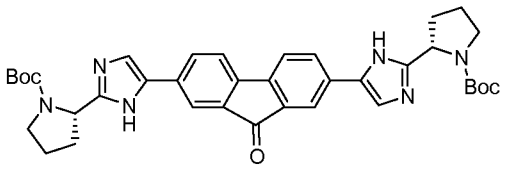


1c

$Pd(Ph_3P)_4$ (750 mg, 0.649 mmol) was added to a pressure tube containing the mixture of 2,7-dibromo-9*H*-fluoren-9-one (5.124 g, 15.16 mmol), bis(pinacolato)diboron (15.03 g, 59.19 mmol), and KOAc (3.526 g, 35.92 mmol) in dioxane (60 mL). The reaction vessel was flushed with nitrogen, capped, and heated at 90 °C for ~16 hr. The reaction mixture was allowed to cool to ambient temperature, the volatile component was removed *in vacuo* and the crude material was partitioned between CH_2Cl_2 (150 mL) and 50 % saturated $NaHCO_3$ solution (60 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant semi-solid oil was triturated from hexanes (100 mL), and the yellow

solid was filtered and washed with hexanes (100 mL) to afford impure bis-boronate 1c (5.011 g). The product was submitted to the coupling step without further purification. ^{1}H NMR ($CDCl_3$, δ = 7.24, 400 MHz): 8.11 (s, 2H), 7.93 (dd, J = 7.3, 1.0, 2H), 7.54 (d, J = 7.6, 2H), 1.33 (S, 24H).

Example 1, Step d



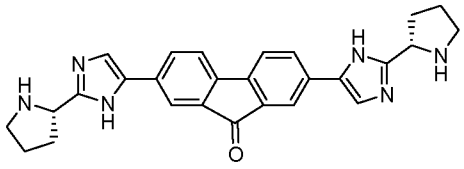
1d

$Pd(Ph_3P)_4$ (93.3 mg, 0.081 mmol) was added to a pressure tube containing bis-boronate 1c (508.7 mg, 1.177 mmol), bromoimidazole 1b (714 mg, 2.26 mmol), $NaHCO_3$ (635.6 mg, 7.566 mmol) in DME (18 mL) and water (6 mL). The pressure tube was purged with nitrogen, capped and heated at 80 °C for ~30 h, and then allowed to cool to ambient condition. The volatile component was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 and water. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and purified with a Biotage® (silica gel; EtOAc) followed by reverse phase HPLC (CH_3OH/H_2O/TFA). The HPLC elute was neutralized with excess NH_3/CH_3OH (2.0 N) and the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and ~3% saturated $NaHCO_3$ solution. The organic layer was dried (MgSO4), filtered, and concentrated *in vacuo* to afford carbamate 1d as a deep-red semi-solid (145 mg). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.26-11.94 (three br s, 2H), 7.97-7.41 (m, 8H), 4.85-4.77 (m, 2H), 3.55 (m, 2H), 3.37 (m, 2H), 2.30-1.79 (m, 8H), 1.40 (s, 7.5 H), 1.16 (s, 10.5H).

LC (Cond. VII): RT = 1.37 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{43}N_6O_5$ 651.33; found 651.26

Example 1, Step e



1e

Carbamate 1d (184 mg, 0.283 mmol) was treated with 25% TFA/CH_2Cl_2 (4.0 mL) and the reaction mixture was stirred at ambient condition for 6 hours. The volatile component was removed *in vacuo* and the residue was free-based with MCX (2 g; CH_3OH wash; 2.0 M NH_3/CH_3OH elution) to afford pyrrolidine 1e as a red foam (129.8 mg; ~3 mg above the theoretical yield). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 11.91 (br s, 2H), 7.96-7.94 (m, 4H), 7.69 (d, J = 8.1, J = 8.1, 2H), 7.61 (s, 2H), 4.16 (m, 2H), 2.99-2.93 (m, 2H), 2.89-2.83 (m, 2H), 2.10-2.01 (m, 2H), 1.94-1.86 (m, 2H), 1.82-1.66 (m, 4H).

LC (Cond. VII): RT = 1.01 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{27}N_6O$ 451.22; found 451.27.

Example 1

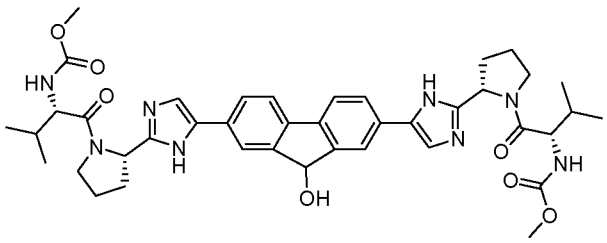
HATU (216.3 mg, 0.569 mmol) was added in one batch to a DMF (4.0 mL) solution of pyrrolidine 1e (126 mg, 0.280 mmol), (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (109.6 mg, 0.626 mmol) and *i*-Pr_2EtN (0.12 mL, 0.689 mmol), and the resulting mixture was stirred at ambient condition for ~6 hours. The volatile component was removed *in vacuo*, and the residue was purified first by MCX (methanol wash; 2.0 M NH_3/methanol elution) and then by a reverse phase HPLC system (H_2O/methanol/TFA) to provide the TFA salt of Example 1 as a reddish orange foam (208.9 mg). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 8.18-7.99 (m, 8H), 7.33 (d, J = 8.5, 2H), 5.53 (m, 0.16H), 5.13 (m, 1.84H), 4.12 (m, 2H), 3.91-3.80 (m, 4H), 2.42-2.33 (m, 2H), 2.25-1.94 (m, 8H), 0.91-0.79 (m, 12H).

LC (Cond. VII): RT = 1.26 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{49}N_8O_7$ 765.37; found 765.39.

HRMS: Anal. Calcd. for $[M+H]^+$ 765.3724; found 765.3723

Example 2



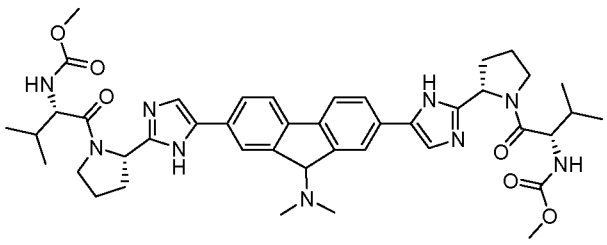
methyl ((1S)-1-(((2S)-2-(5-(9-hydroxy-7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9H-fluoren-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

$NaBH_4$ (41 mg, 1.08 mmol) was added to a cooled (ice/water) CH_3OH (3 mL) solution the TFA salt of Example 1 (165 mg, 0.166 mmol) and stirred for 25 min. The reaction mixture was directly passed through MCX column (6g; washed with 50% H_2O/CH_3OH, followed by CH_3OH; eluted with 2.0 N NH_3/CH_3OH), and then purified with a reverse phase HPLC (CAN/H_2O/NH_4OAc) to afford Example 2, containing about ~2 equiv of acetic acid, as a beige foam (91 mg). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 7.97/7.92 (two br s, 2H), 7.76-7.65 (m, 4H), 7.52/7.45 (two br s, 2H), 7.29 (d, J = 8.3, ~2H), 5.48/5.46 (two s, 1H), 5.26 (m, 0.26H), 5.09 (m, 1.74 H), 4.07 (m, 2H), 3.81/3.54-3.45 (m, 10H), 2.23-1.89 (10H), 0.9 (d, J = 6.8, 6H), 0.85 (d, J = 6.5, 6H).

LC (Cond. VII): RT = 1.21 min; >95% homogeneity index

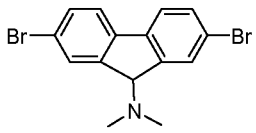
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{51}N_8O_7$ 767.39; found 767.26

Example 3



methyl ((1S)-1-(((2S)-2-(5-(9-(dimethylamino)-7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9H-fluoren-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

Example 3, Step a



3a

A heterogeneous mixture of 2,7-dibromo-9*H*-fluorene (4.98 g, 15.37 mmol) and *N*-bromosuccinimide (2.77 g, 15.56 mmol) was refluxed for ~5.5 hours. Additional *N*-bromosuccinimide (0.41 g, 2.30 mmol) was added and refluxing was continued for an additional 1h. The reaction mixture was allowed to cool to ambient temperature, and the volatile component was removed *in vacuo*.

A portion of the above crude material (~ 5.1g) was added over 10 minutes to a cooled (ice/water) THF solution of dimethylamine (30 mL of 2.0 M), and the cooling bath was removed and the heterogeneous mixture was stirred for 2 hours. The volatile component was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 and water, and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was submitted to a Biotage purification (0-5% CH_3OH/CH_2Cl_2) to afford amine 3a as a dark yellow viscous oil that slowly yielded a dense solid (1.327). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 7.83 (d, J = 8.4, 2H), 7.73 (app br s, 2H), 7.61 (dd, J = 8.1, 1.3, 2H), 4.98 (s, 1H), 2.22 (s, 6H).

LC (Cond. VII): RT = 1.32 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{15}H_{14}Br_2N$: 367.95; found 367.81 (for the dominant isotope)

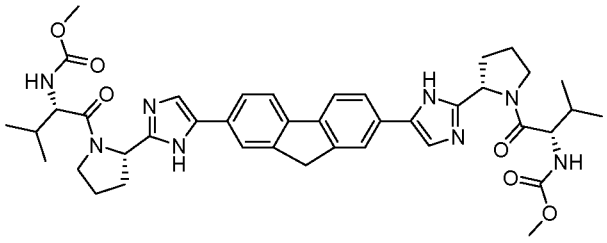
Example 3

Example 3 (TFA salt) was prepared starting from amine 3a according to the procedure described for the synthesis of Example 1 from 2,7-dibromo-9*H*-fluoren-9-one. ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 8.27-7.99 (m, 8H), 7.33 (d, J = 8.3, 1.88H), 6.91 (br s, 0.12H), 5.92 (br s, ~1H), 0.12 (br s, 0.12H), 5.17 (m, 1.88 H), 4.12 (m, 1.88H), 3.91-3.79 (m, 4H), 3.55 (s, ~6H), 2.75 (app br s, 6H), 2.43-2.35 (m, 2H), 2.24-1.95 (m, 8H), 0.91-0.78 (m, 12H). [Note: some of the chemical shifts of the minor rotamer were not identified, and that is partly why approximate values are given for some of the integrations].

LC (Cond. VII): RT = 1.09 minutes, >95% homogeneity index

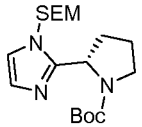
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{56}N_9O_6$: 794.43; found 794.29.

Example 4



methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9H-fluoren-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

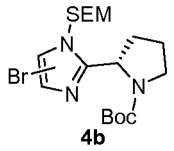
Example 4, Step a



4a

NaH (243 mg of 60%, 6.08 mmol) was added in one batch to a DMF (15 mL) semi-solution of imidazole 1a (1.228 g, 5.17 mmol), and stirred for 75 min. SEM-Cl (1.0 mL, 5.65 mmol) was added dropwise over 7 minutes, and the reaction mixture was stirred for an additional 3.5 hours. The volatile component, including the solvent, was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was purified with a Biotage® (100 g silica gel; 60-100% EtOAc/hexanes) to afford imidazole 1a as a colorless viscous oil (1.649 g). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 7.16/7.13 (overlapping singlets, 1H), 6.80/6.78 (overlapping singlets, 1H), 5.61 (d, J = 10.8, 0.41H), 5.38 (d, J = 11.1, 0.59 H), 5.26 (d, J = 11.4, 1H), 4.95-4.85 (m, 1H), 3.51-3.33 (m, 4H), 2.25-2.00 (m, 2H), 1.90-1.77 (m, 2H), 1.35 (s, 3.79H), 1.12 (s, 5.21 H), 0.91-0.76 (m, 2H), -0.04 (s, 9H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{34}N_3O_3Si$: 368.24; found 368.23.

Example 4, Step b



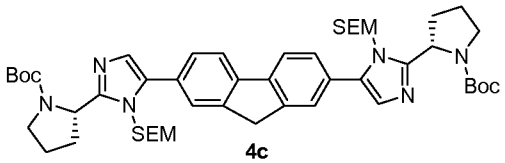
4b

A CH_3CN (6 mL) solution of NBS (573 mg, 3.22 mmol) was added dropwise over 8 minutes to a cooled (ice/water) CH_3CN (10 mL) solution of amine 4a, and stirred for 95 min. The cooling bath was removed and stirring was continued for an additional 35 min. The volatile component was removed *in vacuo*, and the resulting crude material was directly submitted to a Biotage® purification (100 g silica gel; 40-50% EtOAc/hexanes) to afford bromide 4b as light-yellow viscous oil (0.895 g). According to ^1H NMR the product appears to be a mixture of regioisomers (in a ratio of 7.1:1.0), and was submitted to the next step as such.

LC (Cond. VII): RT = 1.77 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{33}BrN_3O_3Si$: 446.15; found 446.07

Example 4, Step c



4c

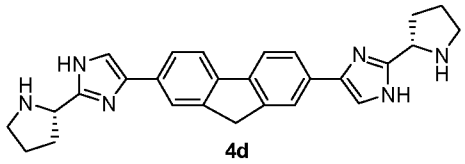
Carbamate 4c was prepared starting from 2,7-dibromo-9*H*-fluoren-9-one and bromide 4b, via a Suzuki coupling, according to the procedure described for the synthesis of carbamate 1d. The above SEM regiochemical assignment for the main product is based on NOE studies, albeit it is inconsequential for the current purpose.

^1H NMR (DMSO-d_6, δ = 2.50, 500 MHz): 8.04-8.02 (m, 2H), 7.74-7.70 (m, 2H), 7.56-7.49 (m, 2H), 7.06 (br s, 2H), 5.62-5.60 (m, 0.82H), 5.43-5.41 (m, 1.18H), 5.27 (m, 2H), 5.09 (m, 0.86H), 1.14 (m, 1.14H), 4.02 (s, 2H), 3.63-3.38 (m, 8H), 2.33-2.09 (m, 4H), 2.01-1.84 (m, 4H), 1.39 (s, 7.56H), 1.18 (s, 10.44H), 0.92-0.81 (m, 4H), -0.04 (s, 18H).

LC (Cond. VII): RT = 1.92 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{73}N_6O_6Si_2$: 897.51; found 897.37

Example 4, Step d



4d

Dioxane solution of HCl (3 mL of 4.0 N, 12 mmol) was added to compound 4c (133 mg, 0.148 mmol) and the resultant heterogeneous reaction mixture was stirred for ~14 h, and then CH_3OH (1.0 mL) was added and stirring continued for an additional ~4.5 hours. The volatile component was removed *in vacuo*, and dried under high vacuum, and submitted to the next step without purification.

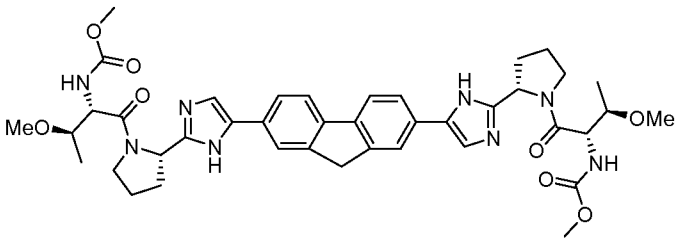
Example 4

Pyrrolidine 4d was elaborated to the TFA salt of Example 4 according to the protocol described for the synthesis of Example 1, with a notable exception that 6 mol equiv of *i*-Pr_2EtN was employed. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 8.11-7.82 (m, 8H), 7.34 (d, J = 8.3, 1.89H), 6.92 (app br s, 0.11H), 5.55 (m, 0.14H), 5.16-5.13 (m, 1.86H), 4.14-3.74 (m, 8H), 3.55/3.35 (two s, 6H), 2.45-2.34 (m, 2H), 2.20-1.74 (m, 8H), 0.91-0.78 (m, 12H).

LC (Cond. VII): RT = 1.28 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{51}N_8O_6$: 751.39; found 751.24

Example 5



methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9H-fluoren-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

The TFA salt of Example 5 was prepared from pyrrolidine 4d and appropriate acid according to the procedure described for Example 4. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 8.11-7.82 (m, 8H), 7.23 (d, J = 8.3, 1.87H), 6.75 (app br s, 0.13H),

5.65 (m, 0.17H), 5.17-5.13 (m, 1.83H), 4.33-4.22 (m, 2H), 4.09 (s, 2H), 3.93-3.72 (m, 4H), 3.61-3.19 (m, 14H), 2.44-2.33 (m, 2H), 2.21-1.72 (m, 6H), 1.10 (d, J = 6.3, 0.58H), 5.42 (d, J = 6.0, 5.42H).

LC (Cond. VII): RT = 1.17 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{51}N_8O_8$: 783.38; found 783.23

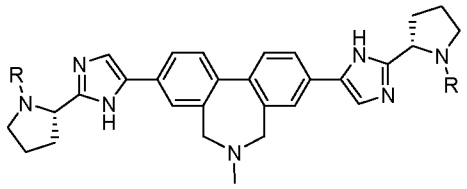
Example 6-7

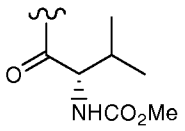
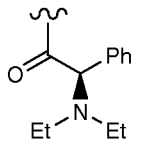
$MeNH_2$ (4.9 mL, 9.87 mmol) and Na_2CO_3 (0.349 g, 3.29 mmol) were added to a THF (6.5 mL) solution of 4,4'-dibromo-2,2'-bis(bromomethyl)biphenyl (0.328 g, 0.658 mmol), and the reaction mixture was refluxed for 3 hours. The volatile component was removed *in vacuo*, and the residue was passed through MCX (CH_3OH wash; 2.0 M NH_3/CH_3OH elution) to afford 3,9-dibromo-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine as a white solid (0.24 g). ^1H NMR (DMSO-d_6, δ = 2.50, 500 MHz): 2.31 (s, 3 H), 3.24 (s, 4 H), 7.47 (d, J = 7.9, 2 H), 7.55-7.82 (m, 4 H).

LC (Cond.III): RT = 2.42 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{15}H_{14}Br_2N$: 367.95; found 368.17 (for dominant isotope)

Example 6-7 were prepared starting from 3,9-dibromo-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine by employing the procedures described for the synthesis of Example 4 from 2,7-dibromo-9*H*-fluoren-9-one.



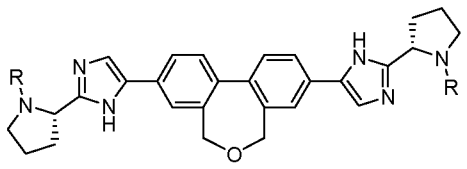
Example	Compound Name	R	RT (LC-Cond.); % homogeneity index; MS data
6	*methyl ((1S)-1-(((2S)-2-(5-(9-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-3-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate*		1.98 minutes (Cond. IV); >95% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{56}N_9O_6$: 794.43; found 795.27
7	*(1S,1'S)-2,2'-((6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine-3,9-diyl)bis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine)*		1.82 minutes (Cond. III); >95% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{53}H_{64}N_9O_2$: 858.52; found 859.07.

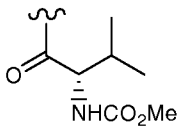
Example 8-12

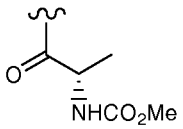
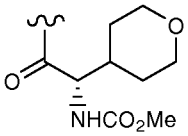
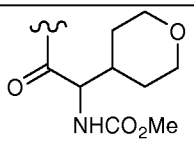
HBr (11 mL, 97 mmol) was added to a THF (10 mL) solution of (4,4'-dibromobiphenyl-2,2'-diyl)dimethanol (for preparation, see: *Tetrahedron Letters* 2004, *45*, 2801; 1.3 g, 3.49 mmol), and the mixture was refluxed for six hours and then allowed to cool to ambient temperature. Most of the organic component was removed with a rotervap, and the residue was extracted with CH_2Cl_2 (10 mL, 3x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a brown oil, which when dissolved in 5 mL acetone and allowed to stand at

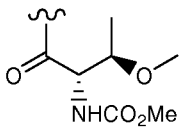
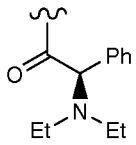
ambient condition for 1 h afforded a precipitate. Filtration and drying *in vacuo* afforded 3,9-dibromo-5,7-dihydrodibenzo[c,e]oxepine as a white solid (0.628 g, 51 % yield). ^{1}H NMR (DMSO-d_6, δ = 2.50, 500 MHz): 4.23-4.29 (m, 4H), 7.53-7.60 (m, 2H), 7.74 (dd, J = 7.9, 2.1, 2H) 7.79 (d, J = 2.1, 2H).

Example 8-12 were prepared starting from 3,9-dibromo-5,7-dihydrodibenzo[c,e]oxepine by employing the procedures described for the synthesis of Example 4 from 2,7-dibromo-9*H*-fluoren-9-one and appropriate substrates.

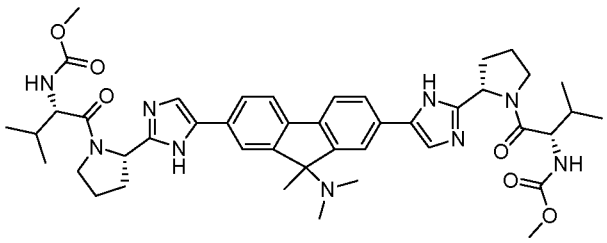


Example	R	Compound Name	RT (LC-Cond.); % homogeneity index; MS data
8		*methyl ((1S)-1-(((2S)-2-(5-(9-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-5,7-dihydrodibenzo[c,e]oxepin-3-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate*	2.31 minutes (Cond. IV); >95% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{53}N_8O_7$: 781.40; found 781.59

9		*methyl ((1S)-2-((2S)-2-(4-(9-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-5,7-dihydrodibenzo[c,e]oxepin-3-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate*	2.05 minutes (Cond. IV); >95% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{45}N_8O_7$: 725.34; found 725.32
10		*dimethyl (5,7-dihydrodibenzo[c,e]oxepine-3,9-diylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate*	2.06 minutes (Cond. IV); >95% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{57}N_8O_9$: 865.42; found 865.89.
10A		*dimethyl (5,7-dihydrodibenzo[c,e]oxepine-3,9-diylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate*	2.09 minutes (Cond. IV); >95% LC/MS: Anal.

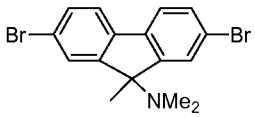
			Calcd. for $[M+H]^+$ $C_{46}H_{57}N_8O_9$: 865.42; found 865.22.
11		*methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(4-(9-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-5,7-dihydrodibenzo[c,e]oxepin-3-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate*	2.15 minutes (Cond. IV); >95% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{53}N_8O_9$: 813.39; found 814.31
12		*(1S,1'S)-2,2'-(5,7-dihydrodibenzo[c,e]oxepine-3,9-diylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine)*	1.26 minutes (Cond. II); >95% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{52}H_{61}N_8O_3$: 845.49; found 845.22.

Example 13



methyl ((1S)-1-(((2S)-2-(5-(9-(dimethylamino)-7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-methyl-9H-fluoren-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

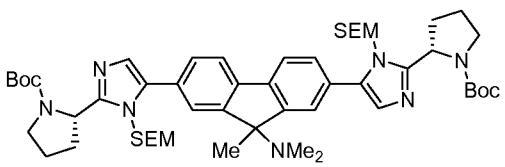
Example 13, Step a



13a

$NaN(TMS)_2$ (3.40 ml of 1.0 M/THF, 3.4 mmol) was added dropwise over 2 minutes to a THF solution of amine 3a (1.14 g, 3.10 mmol), and stirred for 20 min. Then MeI (0.27 mL, 4.33 mmol) was added dropwise over 3 minutes, and stirring was continued for ~65 min. The reaction was treated with excess CH_3OH and all the volatile component was removed *in vacuo*. The resultant crude material was purified with a flash chromatography (10% EtOAc/hexanes) to afford amine 13a as off-white solid (793 mg). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 7.80 (d, J = 8.0, 2H), 7.67 (d, J = 1.7, 2H), 7.58 (dd, J = 8.1, 1.8, 2H), 2.06 (s, 6H), 1.58 (s, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{16}H_{16}Br_2N$: 381.96; found 381.90 (for the dominant isotope).

Example 13, Step b



13b

$Pd(OAc)_2$ (5.3 mg, 0.024 mmol) was added to the mixture of dibromide 13a (101.8 mg, 0.267 mmol), imidazole 13a (145.6 mg, 0.396 mmol), Ph_3P (12.5 mg,

0.048 mmol) and K_2CO_3 (116 mg, 0.839 mmol) in dioxane (2.5 mL), and nitrogen was bubbled through it for 1 minute and then heated at 140 °C (microwave) for 3 hours. The mixture was treated with CH_3OH (2 mL), filtered through a cotton plug and the volatile component was removed *in vacuo*. The crude material was purified by a reverse phase HPLC system (H_2O/CH_3OH/TFA), and the HPLC elute was neutralized with excess NH_3/CH_3OH and the volatile component was removed *in vacuo*. The resultant material was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford 13b as a white foam (56.1 mg). The regiochemical make up of 13b was not determined as it is inconsequential for the current purpose. LC/MS: Anal. Calcd. for $[M\text{-SEM}+H]^+$ $C_{46}H_{66}N_7O_5Si$: 824.49; found 824.34.

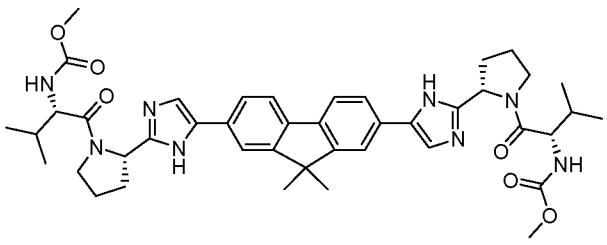
Example 13

The TFA salt of Example 13 was prepared starting from compound 13b by employing the procedures described for the synthesis of Example 4 from intermediate 4c, with the exception that the corresponding pyrrolidine precursor employed for the last step was free-based with MCX, and that only 2 mol equiv of *i*-Pr_2EtN was employed for the HATU-coupling step. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 8.24-7.96 (m, 8H), 7.32 (m, 1.89H), 6.89 (app br s, 0.11H), 5.52 (app br s, 0.12H), 5.17-5.14 (m, 1.88H), 4.13-4.09 (m, 2H), 3.85 (m, 2H), 3.54/3.36 (two s, 6H), 2.63 (app br s, 6H), 2.43-1.93 (m, 13H), 0.91-0.78 (m, 12H).

LC (Cond. VII): RT = 1.14 min

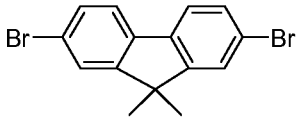
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{58}N_9O_6$: 808.45; found 808.32

Example 14



methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9,9-dimethyl-9H-fluoren-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

Example 14, Step a

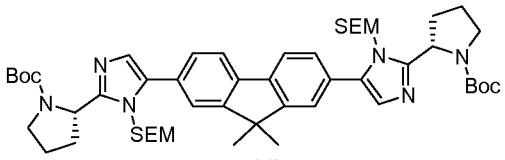


14a

Powdered KOH (0.970 g, 17.3 mmol) was added in batches over 1 minute to a heterogeneous mixture of 2,7-dibromo-9*H*-fluorene (1.30 g, 4.01 mmol) and MeI (0.560 mL, 9.00 mmol) in DMSO (10 mL), and stirred at ambient condition for ~17.5 hours. The mixture was diluted with water (100 mL) and extracted with hexanes (100 mL). The organic layer was washed with water (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified with a flash chromatography (sample was loaded as a silica gel mesh; hexanes) to afford 14a (728 mg) contaminated with the corresponding mono-methyl intermediate in a 12:1 ratio (^{1}H NMR).

$NaN(TMS)_2$ (0.5 mL of 1.0 M/THF, 0.50 mmol) was added to a THF (4.0 mL) solution of the above mixture (702 mg) and stirred for 10 min. Then MeI (0.15 mL, 2.41 mmol) was added dropwise over a few minutes and stirred for 75 min. It was then quenched with CH_3OH (10 mL) and the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford 14a as a light yellow solid, free of the mono-methylated impurity. The crude material was submitted to the next step without purification. ^{1}H NMR ($CDCl_3$, δ = 7.24, 400 MHz): 7.53 (d, J = 7.8, 2H), 7.53 (d, J = 2, 2H) 7.45 (dd, J = 8.1, 1.8, 2H), 1.45 (s, 6H).

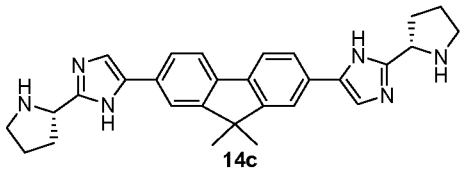
Example 14, Step b



14b

Compound 14b was prepared from dibromide 14a according to the procedure described for the synthesis of 13b from dibromide 6a. LC/MS: Anal. Calcd. for [M-SEM+H]$^+$ $C_{45}H_{63}N_6O_5Si$: 795.46; found 795.33.

Example 14, Step c



14c

HCl/dioxane (5 mL of 4N, 20 mmol) was added to compound 14b (124.5 mg, 0.135 mmol) and stirred to effect total dissolution. The solution was cooled with ice/water bath and treated with 1 mL of 33% concentrated HCl solution dropwise over 2 min. Then the cooling bath was removed and the reaction mixture was stirred for ~22.5 hours. The volatile component was removed *in vacuo*, and the residue was first free-based with MCX (2 g; CH_3OH wash; 2.0 N NH_3/CH_3OH elution) and then purified with a reverse phase HPLC (CH_3OH/H_2O/TFA). The HPLC elute was concentrated and the resultant product was free-based with MCX as noted above to afford pyrrolidine 14c as a reddish-orange foam, contaminated with unidentified impurity (38.7 mg). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 1.83 (s, 2H), 7.74-7.69 (m, 4H), 7.49 (app br s, 2H), 4.24-4.20 (m, 2H), 3.04-2.98 (m, 2H), 2.93-2.87 (m, 2H), 2.13-2.05 (m, 2H), 1.95-1.70 (6H), 1.48 (s, 6H).

LC (Cond. VII): RT = 1.03 min

LC/MS: Anal. Calcd. for [M+H]$^+$ $C_{29}H_{33}N_6$: 465.28, found 465.21.

Example 14

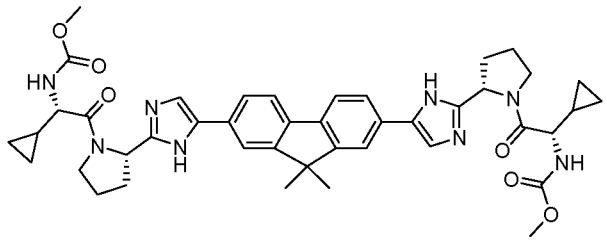
Example 14 was prepared as a TFA salt starting from 14c according to the procedure described for the synthesis of Example 1 from intermediate 1e. ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 8.13 (s, 2H), 8.06-8.01 (m, 2H), 7.85-7.79 (m, 2H),

7.39-7.33 (m, 1.89H), 6.93 (m, 0.11H), 5.61 (m, 0.14H), 5.17-5.14 (m, 1.86H), 4.15-4.06 (m, 2H), 3.91-3.80 (m, 4H), 3.54/3.33 (two s, 6H), 2.46-2.38 (m, 2H), 2.22-1.99 (m, 8H), 1.53 (s, 6H), 0.92-0.78 (m, 12H).

LC (Cond. VII): RT = 1.37 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{55}N_8O_6$: 779.42; found 779.23

Example 15



dimethyl ((9,9-dimethyl-9H-fluorene-2,7-diyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate

Example 15 (TFA salt) was prepared according to the protocol described for Example 14 by employing the appropriate acid for the final step. ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 8.11-8.01 (m, 6H), 7.83-7.79 (2H), (d, J = 7.8, 1.84H), 7.47 (m, 0.16H), 5.46 (m, 0.19H), 5.18-5.15 (m, 1.81H), 3.89-3.72 (m, 6H), 3.55/3.33 (two s, 6H), 2.45-2.34 (m, 2H), 2.23-1.95 (m, 6H), 1.54 (s, 6H), 1.21-1.04 (m, 2H), 0.51-0.23 (m, 8H).

LC (Cond. VII): RT = 1.25 min

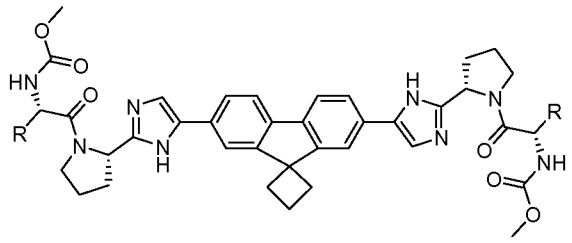
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_6$: 775.39; found 775.36

Example 16-17

Powdered KOH (983 mg, 17.5 mmol) was added in batches over 1 minute to a heterogeneous mixture of 2,7-dibromo-9*H*-fluorene (1.31 g, 4.04 mmol) and 1,3-dibromopropane (837 mg, 4.15 mmol) in DMSO (20 mL), and stirred at ambient condition for ~5 days. The mixture was diluted with water (200 mL) and extracted with 10% CH_2Cl_2/hexanes (100 mL, 2x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified with a column chromatography (sample was loaded as a silica gel mesh; hexanes, with gravity elution) to afford 2',7'-dibromospiro[cyclobutane-1,9'-fluorene] as a white fluffy solid (600 mg). ^{1}H NMR ($CDCl_3$, δ = 7.24, 400 MHz): 7.86 (d, J

1.8, 2H), 7.48 (d, *J* = 8.0, 2H), 7.44 (dd, *J* = 8.1, 1.8, 2H), 2.61 (app t, *J* = 8.1, 4H), 2.42-2.34 (m, 2H).

Example 16-17 (TFA salt) were prepared starting from 2',7'-dibromospiro[cyclobutane-1,9'-fluorene] by employing the procedure described for the synthesis of Example 14 from dibromide 14a.

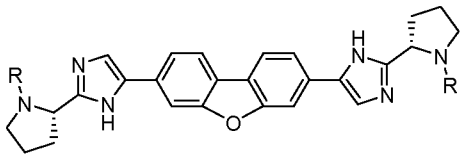


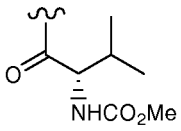
Example	R	Compound Name	RT (LC-Cond.); % homogeneity index; MS data
16		*methyl ((1S)-1-(((2S)-2-(5-(7'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)spiro[cyclobutane-1,9'-fluoren]-2'-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate*	1.38 minutes (Cond. VII); >95% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{55}N_8O_6$: 791.42; found 791.32
17		*methyl ((1S)-2-((2S)-2-(5-(7'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)spiro[cyclobutane-1,9'-*	1.22 minutes (Cond. VII); >95% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; found 735.28.

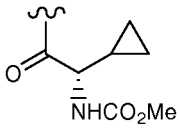
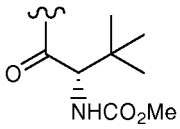
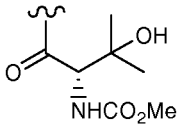
		fluoren]-2'-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	

Examples 18-21

Example 18-21 were prepared starting from 3,7-dibromodibenzo[b,d]furan (which in turn was prepared according to *Eur. J. Med. Chem.* 1999, *34*, 205) by employing the procedures described for the synthesis of Example 14 from dibromide 14a.

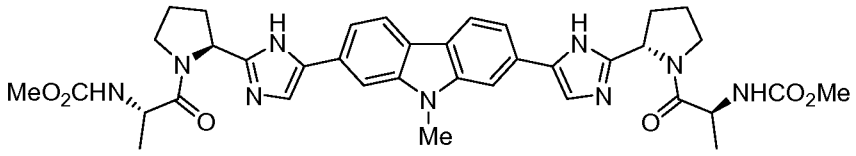


Example	R	Compound Name	RT (LC-Cond.); % homogeneity index; MS data
18		*methyl ((1S)-1-(((2S)-2-(4-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)dibenzo[b,d]furan-3-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate*	^{1}H NMR (DMSO-d_6, δ = 2.50, 500 MHz): 14.60 (s, 2H), 8.32 (d, J = 7.9, 2H), 8.14-8.24 (m, 4H), 7.87 (d, J = 8.2, 2H), 7.34 (d, J = 8.5, 2H), 5.17 (app t, J = 7.2, 2H), 4.13 (t, J = 7.9, 2H), 3.79-3.92 (m, 4H), 3.55 (s, 6H), 2.41(m, 2H), 1.94-2.26 (m, 8H), 0.71 - 0.95 (m, 12 H)

			2.27 minutes (Cond. VI); >95% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{49}N_8O_7$: 753.37; found 753.88
19		*dimethyl (dibenzo[b,d]furan-3,7-diylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate*	2.18 minutes (Cond. VI); >95% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}N_8O_7$: 749.34; found 749.78
20		*methyl ((1S)-1-(((2S)-2-(4-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)dibenzo[b,d]furan-3-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate*	2.51 minutes (Cond. VI); >95% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{53}N_8O_7$: 781.40; found 781.85
21		*methyl ((1S)-2-hydroxy-1-(((2S)-2-(4-(7-(2-((2S)-1-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)dibenzo[b,d]furan-3-*	2.16 minutes (Cond. VI); >95% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{49}N_8O_9$: 785.36; found 785.89

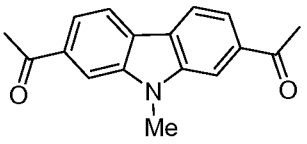
		yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	

Example 22



methyl ((1S)-2-((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-methyl-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate

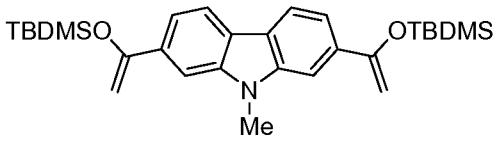
Example 22, Step a



22a

To a stirred solution of 2,7-dibromo-9-methyl-9*H*-carbazole (1.52 g, 4.47 mmol) in anhydrous THF (150 mL) at -78°C was added *n*-BuLi (1.06 M in hexane, 12.6 mL, 13.4 mmol) over 10 min. The resulting suspension was stirred at -78 °C for 6 h, after which *N*-methyl-*N*-methoxyacetamide (1.43 mL, 13.4 mmol) was added. Stirring was continued as the reaction mixture was allowed to warm to room temperature over 18 hours. The mixture was then quenched with 2 N NaH_2PO_4, extracted with ethyl acetate and the organic phase was dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by column chromatography (Biotage® Horizon system/ 2-55% ethyl acetate-hexanes) to afford 22a (0.560 g, 47%) as a yellow solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 8.09 Hz, 2H), 8.27 (s, 2H), 7.86 (m, 1H), 7.84 (m, 1H), 4.05 (s, 3H), 2.72 (s, 6H). LC/MS: Anal. Calcd. for $C_{17}H_{15}NO_2$: 265; found: 266 $(M+H)^+$.

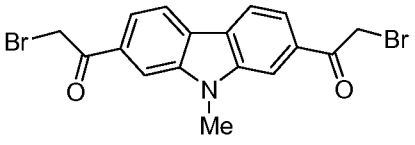
Example 22, Step b



22b

To an ice-cold suspension of 22a (0.661 g, 2.49 mmol) in toluene (20 mL) was added triethylamine (1.39 mL, 9.96 mmol) and then *tert*-butyldimethylsilyl triflate (1.72 mL, 7.47 mmol). Stirring was continued at 0 °C for 10 minutes and then the reaction mixture was allowed to warm to room temperature. After 3 h the reaction mixture was partitioned with EtOAc-H_2O and the organic phase was dried ($MgSO_4$), filtered, and concentrated to dryness to give 22b as a light brown solid in essentially quantitative yield. This material was used as such in the next step without further manipulation.

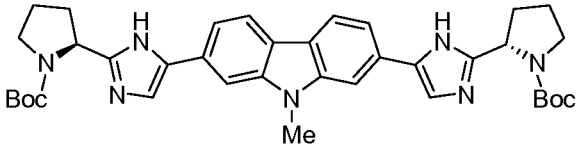
Example 22, Step c



22c

To a stirred solution of 22b in anhydrous THF (25 mL) at 0 °C was added *N*-bromosuccinimide (0.709 g, 3.98 mmol) in one portion. Stirring was continued at 0 °C for an additional 30 minutes and the resulting suspension was filtered. The filter-cake was air-dried to give 22c (1.05 g, 100%) as a yellow solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.41 (d, J = 8.59 Hz, 2H), 8.37 (s, 2H), 7.89 (m, 2H), 5.10 (s, 4H), 4.07 (s, 3H). LC/MS: Anal. Calcd. for $C_{17}H_{13}Br_2NO_2$: 421; found: 422 $(M+H)^+$.

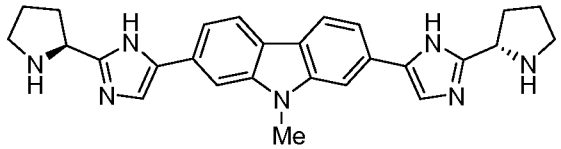
Example 22, Step d



22d

A mixture of 22c (1.05 g, 2.49 mmol), Boc-*L*-proline (1.07 g, 4.98 mmol) and DIEA (0.867 mL, 4.98 mmol) in acetonitrile (20 mL) was heated at 85 °C in a sealed tube for 2 hours. The cooled mixture was then concentrated to dryness to give a solid residue. A mixture of this material and NH_4OAc (1.92 g, 0.025 mol) in toluene (32 mL) was heated at 120 °C in a sealed tube for 2.5 h and then the cooled reaction mixture was partitioned with EtOAc-brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated and the residue was purified by preparative HPLC (C18/ CH_3CN-H_2O+0.1% TFA) to give the TFA salt of 22d (as 0.840 g, 34% overall) as a yellow solid. ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 8.28 (m, 2H), 7.95 (m, 4H), 7.60 (m, 2H), 5.14 (m, 2H), 4.03 (s, 3H), 2.56 (m, 2H), 2.09 (m, 6H), 1.93 (m, 2H), 1.48 (s, 8H), 1.30 (s, 10H). LC/MS: Anal. Calcd. for $C_{37}H_{45}N_7O_4$: 651; found: 652 $(M+H)^+$.

Example 22, Step e



22e

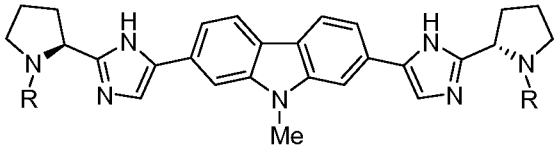
To a solution of the TFA salt of 22d (0.840 g, 0.845 mmol) in dichloromethane (5 mL) was added TFA (15 mL) and the mixture was stirred at room temperature for 3 hours. The mixture was then concentrated to dryness and the residue was dissolved in CH_3OH and applied to a plug of MCX extraction gel (12 g, pre-conditioned with CH_3OH-dichloromethane, 1:1). The plug was eluted with CH_3OH- dichloromethane (1:1) and then 2 N NH_3 in CH_3OH, and the product-containing fractions were combined and concentrated to give 22e as a yellow solid (quantitative yield). This material was used as such in subsequent steps.

Example 22

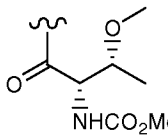
To a mixture of (*S*)-2-(methoxycarbonylamino)propanoic acid (0.022 g, 0.150 mmol) and HATU (0.057 g, 0.150 mmol) in DMF (1 mL) was added DIEA (0.104 mL, 0.60 mmol), and the mixture was stirred at room temperature for 15 min. A solution of 22e (0.034 g, 0.075 mmol) in DMF (2.5 mL) was then added and stirring was continued at room temperature for 2 hours. The mixture was then partitioned

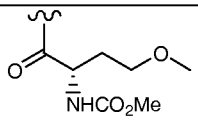
with ethyl acetate-water (1:1) and the organic phase was dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by preparative HPLC (C-18/ MeCN-H_2O+0.1%TFA) and product-containing fractions were concentrated to dryness. The residue was lyophilized from CH_3CN-H_2O (1:1) to give the TFA salt of Example 22 (0.0064 g, 8%) as a yellow solid. ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 8.25 (d, J = 8.08 Hz, 2H), 7.93 (m, 4H), 7.58 (d, J = 8.08 Hz, 2H), 5.30 (m, 2H), 4.49 (quart, J = 7.07 Hz, 2H), 4.20 – 3.98 (m, 1.5 H), 4.00 (s, 3H), 3.88 (m, 2H), 3.65 (s, 6H), 2.55 (m, 2H), 2.23 (m, 6H), 1.34 (d, J = 7.07 Hz, 6H). LC/MS: Anal. Calcd. for $C_{37}H_{45}N_7O_4$: 709; found: 710 $(M+H)^+$.

Example 23-24



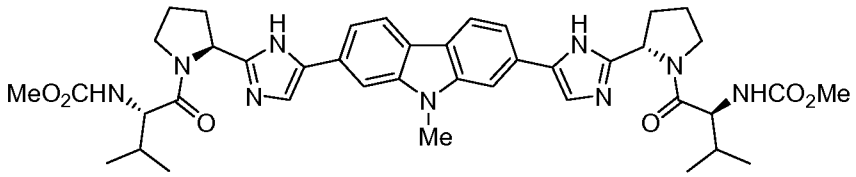
Example 23-24 were prepared according to the general method noted in Example 22, by using appropriate acids.

Example	R	Compound Name	Description (Yield) ^{1}H NMR and LC/MS data
23		*methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-methyl-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate*	Yellow solid (0.011 g, 12%); ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 8.25 (m, 2H), 7.94 (m, 4H), 7.59 (d, J = 8.08 Hz, 2H), 5.31 (m, 2H), 4.49 (m, 2H), 4.07 (m, 2H), 3.99 (m,

			3H), 3.91 (m, 2H), 3.73 (m, 2H), 3.67 (s, 6H), 2.59 (m, 2H), 2.22 (m, 6H), 1.14 (m, 2H). LC/MS: Anal. Calcd. for $C_{41}H_{51}N_9O_8$: 797; found: 798 $(M+H)^+$.
24		*methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-methyl-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate*	Yellow solid (0.0203 g, 26%). ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 8.26 (d, *J* = 8.08 Hz, 2H), 7.94 (s, 4H), 7.59 (d, *J* = 8.59 Hz, 2H), 5.31 (m, 2H), 4.59 (quart, *J* = 4.55 Hz, 2H), 4.02 – 3.99 (m, 2.5 H), 4.01 (s, 3H), 3.90 (m, 3H), 3.65 (s, 6H), 3.45 (m, 5H), 2.57 (m, 2H), 2.23 (m, 6H), 2.08 (m, 3H), 1.81 (m, 3H).

			LC/MS: Anal. Calcd. for $C_{41}H_{51}N_9O_8$: 797; found: 798 $(M+H)^+$.

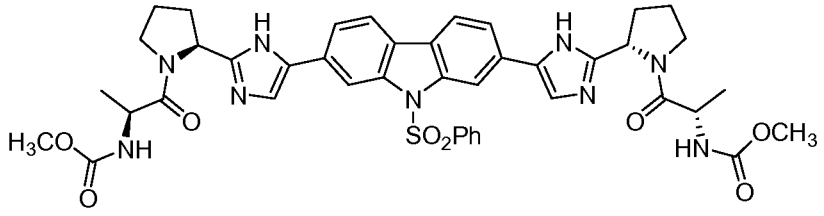
Example 25



methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-methyl-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

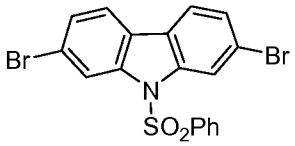
The crude product obtained according to the general method noted in Example 22, using (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.024 g, 0.138 mmol) and 9-methyl-2,7-bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)-9*H*-carbazole (0.021 g, 0.046 mmol), was purified by prep HPLC (C-18/ MeCN-H_2O-NH_4OAc) to afford Example 25 (0.0207 g, 59%) as a white solid. ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 7.98 (m, 3H), 7.82 (m, 0.6H), 7.74 (m, 2.4H), 7.53 (d, *J* = 7.07 Hz, 0.5H), 7.64 (m, 2.5H), 7.39 (m, 0.6H), 7.34 (m, 2.4H), 5.34 (m, 0.6H), 5.20 (dd, *J* = 5.31, 7.83 Hz, 2.4H), 4.24 (d, *J* = 7.07 Hz, 2H), 4.01 (m, 2H), 3.65 (s, 6H), 2.37 – 2.19 (m, 6H), 2.09 – 2.02 (m, 4H), 0.94 (m, 12H). LC/MS: Anal. Calcd. for $C_{41}H_{51}N_9O_6$: 765; found: 766 $(M+H)^+$.

Example 26



methyl ((1S)-2-((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-(phenylsulfonyl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate

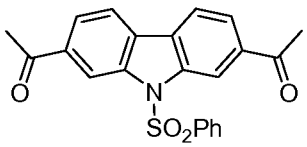
Example 26, Step a



26a

A mixture of freshly pulverized KOH (1.31 g, 23.4 mmol) in DMSO (28 mL) was stirred vigorously at ambient temperature for 10 minutes, after which solid 2,7-dibromocarbazole (1.90 g, 5.85 mmol) was added in one portion. The mixture stirred for 1 h and then benzenesulfonyl chloride (1.49 mL, 11.7 mmol) was added and stirring was continued for 18 hours. The mixture was then diluted with water (150 mL) and the resulting precipitate was filtered off and the filter-cake was washed with water and air-dried. The resulting beige powder was triturated with dichloromethane-hexanes, filtered and dried *in vacuo* to give 26a (2.10 g, 77%) as a beige solid. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 1.52 Hz, 2H), 7.83 (d, J = 8.59 Hz, 2H), 7.72 (d, J = 8.59 Hz, 2H), 7.50 (m, 3H), 7.40 (t, J = 8.08 Hz, 2H). LC/MS: Anal. Calcd. for $C_{18}H_{11}Br_2NO_2S$:463; found: 464 $(M+H)^+$.

Example 26, Step b

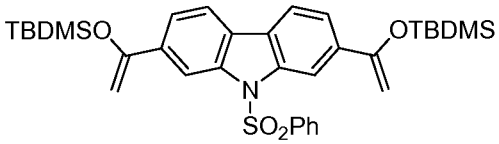


26b

To a solution of 26a (2.086 g, 4.48 mmol) in dry THF (60 mL) at -78 °C under argon was added n-BuLi (1.29M in hexanes, 10.4 mL, 13.4mmol) dropwise over 5 min. The resulting mixture was stirred at -78 °C for 70 minutes and then *N*-methoxy-*N*-methylacetamide (1.43 mL, 13.45 mmol) was added and the cooling bath was allowed to warm to room temperature over 18 hours. The reaction was then quenched with 2N NaH_2PO_4 and extracted with EtOAc. The organic phase was dried

($MgSO_4$), filtered, and concentrated to dryness to give a tan-colored solid. This solid was triturated with hexanes-acetonitrile and the resulting precipitate was filtered and dried *in vacuo* to give 26b (1.16g, 66%) as a light beige solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.79 (s, 2H), 8.40 (d, J = 8.08 Hz, 2H), 8.10 (d, J = 8.08 Hz, 2H), 7.85 (d, J = 7.07 Hz, 2H), 7.64 (m, 2H), 7.50 (m, 3H), 2.74 (s, 6H). LC/MS: Anal. Calcd. for $C_{22}H_{17}NO_4S$:391; found: 392 $(M+H)^+$.

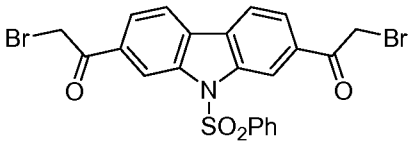
Example 26, Step c



26c

To an ice-cold suspension of 26b (1.16 g, 2.96 mmol) and triethylamine (1.65 mL, 11.8 mmol) in toluene (50 mL) was added TBDMSOTf (2.04 mL, 8.88 mmol) and the mixture was stirred for 2 h at 0 °C and then it was then allowed to warm to room temperature over 18 hours. The mixture was then partitioned with EtOAc-water and the organic phase was dried ($MgSO_4$), filtered, and concentrated to give 26c as an orange oil in a quantitative yield. This material was used as such in the next step without purification. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 1.52 Hz, 2H), 7.79 (m, 4H), 7.62 (dd, J = 1.52, 8.59 Hz, 2H), 7.44 (m, 1H), 7.29 (m, 2H), 7.17 (m, 1H), 5.03 (d, J = 2.02 Hz, 2H), 4.53 (d, J = 2.02 Hz, 2H), 1.07 (s, 18H), 0.27 (s, 12H). LC/MS: Anal. Calcd. for $C_{34}H_{45}NO_4SSi_2$: 619; found: 620 $(M+H)^+$.

Example 26, Step d



26d

To a solution of 26c (2.96 mmol) in THF (40 mL) was added NBS (0.948 g, 5.34 mmol) and the mixture was stirred at room temperature for 24 hours. The dark amber-colored reaction mixture was then concentrated to near dryness and hexanes was added until a brown precipitate had formed. The mixture was filtered to give (after drying *in vacuo*) 26d as a brown solid in a quantitative yield. This material was

used as such in the next step without purification. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.84 (s, 2H), 8.44 (d, *J* = 8.08 Hz, 2H), 8.14 (d, *J* = 8.59 Hz, 2H), 7.93 (d, *J* = 7.07 Hz, 2H), 7.65 (m, 1H), 7.51 (m, 2H), 5.13 (s, 4H).

Example 26, Step e

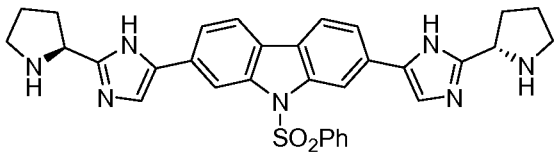


26e

A solution of 26d (2.96 mmol), *N*-BOC-*L*-proline (1.27 g, 5.92 mmol), and DIEA (1.03 mL, 5.92 mmol) in acetonitrile (40 mL) was heated in a sealed tube at *ca.* 85 °C for 2 hours. After being allowed to cool to room temperature, the mixture was concentrated to dryness to give a brown oil.

A mixture of the crude oil obtained above and NH_4OAc (2.28 g, 29.6 mmol) in toluene (40 mL) was heated at 125 °C in a sealed tube for 3 hours. The cooled mixture was partitioned with EtOAc-water and the organic phase was dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by column chromatography (Biotage® Horizon system/ 0-10% methanol-dichloromethane) to give 26e (1.09 g, 47%) as a brown solid. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 7.80 (d, *J* = 7.58 Hz, 6H), 7.39 (m, 3H), 7.28 (m, 2H), 5.01 (m, 2H), 3.55 – 3.43 (m, 5H), 3.06 (br s, 2H), 2.19 (m, 4H), 1.99 (m, 3H), 1.51 (s, 18H). LC/MS: Anal. Calcd. for $C_{42}H_{47}N_7O_6S$: 777; found: 778 $(M+H)^+$.

Example 26, step f



26f

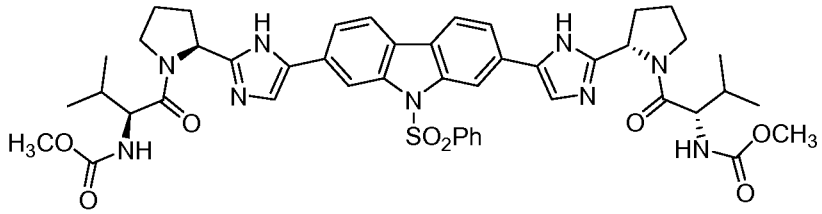
To a solution of 26f (0.868 g, 1.12 mmol) in dichloromethane (20 mL) was added TFA (5 mL) and the mixture was stirred at room temperature for 2 h and then concentrated to dryness. The residue was taken up in CH_3OH and applied to a pre-conditioned (CH_3OH) pad of SCX extraction gel (3cm x 3cm). The pad was washed

with CH_3OH and then eluted with 2M NH_3 in CH_3OH. Product-containing fractions were concentrated to give 9-(phenylsulfonyl)-2,7-bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)-9*H*-carbazole (0.582 g, 90%.) as a dark amber solid which was immediately used in the next step.

Example 26

To a solution of (*S*)-2-(methoxycarbonylamino)propanoic acid (0.061 g, 0.412 mmol) and HATU (0.157 g, 0.412 mmol) in DMF (5 mL) was added DIEA (0.359 mL, 2.06 mmol) and the mixture was stirred at room temperature for 10 min. To this solution was added a crude 26f (0.119 g, 0.206 mmol) and stirring was continued for 2 hours. The reaction mixture was then partitioned with EtOAc-water (1:1) and the organic phase was dried ($MgSO_4$), filtered and concentrated to dryness. The resulting residue was purified by preparative HPLC (C-18/ CH_3CN-H_2O-NH_4OAc) and product-containing fractions were concentrated to dryness. The residue was lyophilized from H_2O-CH_3CN (7:3) to give Example 26 (0.122 g, 66%) as a white solid. ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 8.64 (s, 0.5H), 8.59 (s, 1.5H), 7.89 (m, 4H), 7.74 (d, J = 8.08 Hz, 0.5H), 7.66 (d, J = 8.08 Hz, 1.5H), 7.48 (m, 1.5H), 7.36 (m, 3.5H), 5.25 (m, 2H), 4.50 (quart, J = 6.91 Hz, 1.5H), 4.27 (m, 0.5H), 3.89 (t, J = 6.57 Hz, 3H), 3.59 (m, 6H), 2.48 – 1.99 (m, 9H), 1.36 (m, 6H). LC/MS: Anal. Calcd. for $C_{42}H_{45}N_9O_8S$: 835; found: 836 $(M+H)^+$.

Example 27

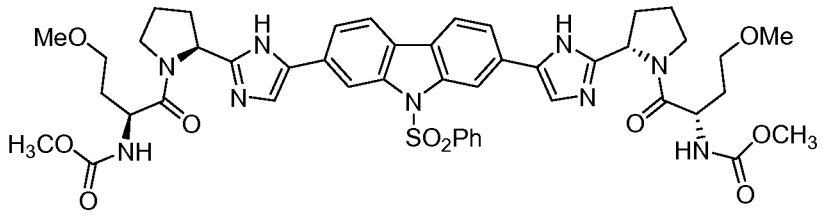


methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-(phenylsulfonyl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

To a solution of (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.045 g, 0.256 mmol) and HATU (0.097 g, 0.256 mmol) in DMF (1 mL) was added DIEA (0.223 mL, 1.28 mmol) and the mixture was stirred at ambient temperature for 10

min. To this mixture was added a solution of 26f (0.074 g, 0.128 mmol) in DMF (2 mL). The reaction mixture was stirred at room temperature for 5 h and then water (5 mL) was added and the mixture was concentrated to dryness *in vacuo*. The residue was purified by prep HPLC (C-18/ CH_3CN - H_2O + 0.1% TFA) and the product-containing fractions were concentrated to dryness and repurified by prep HPLC (C-18/ CH_3CN-H_2O-NH_4OAc) to give Example 27 (0.0591 g, 52 %) as a beige solid. ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 8.63 (s, 0.5H), 8.58 (s, 1.5H), 7.90 (m, 4H), 7.74 (m, 0.5H), 7.67 (m, 1.5H), 7.48 (m, 1.5H), 7.36 (m, 3.5H), 5.22 (dd, *J* = 5.05, 7.58 Hz, 2H), 4.25 (d, *J* = 7.58 Hz, 2H), 4.02 (m, 2H), 3.92 (m, 2H), 3.65 (s, 5H), 3.47 (s, 1H), 2.41 – 2.20 (m, 5.5H), 2.12 – 2.04 (m, 4.5H), 0.96 (m, 12H). LC/MS: Anal. Calcd. for $C_{46}H_{53}N_9O_8S$: 891; found: 892 $(M+H)^+$.

Example 28

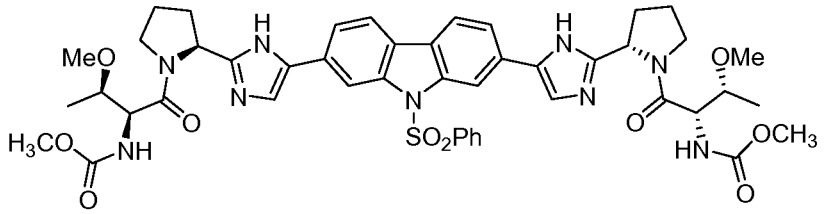


methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-(phenylsulfonyl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

To a solution of (*S*)-4-methoxy-2-(methoxycarbonylamino)butanoic acid (0.076 g, 0.398 mmol) and HATU (0.151 g, 0.398 mmol) in DMF (5 mL) was added DIEA (0.348 mL, 1.99 mmol) and the mixture was stirred at room temperature for 10 min. To this mixture was added 26f (0.115 g, 0.199 mmol), stirring was continued for 2 h and then the reaction mixture was partitioned with EtOAc-brine (1:1). The organic phase was dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by prep HPLC (C-18/ CH_3CN-H_2O-NH_4OAc) and product-containing fractions were lyophilized to give Example 28 (0.122 g, 66%) as a white solid. ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 8.64 (s, 0.5H), 8.59 (s, 1.5H), 7.90 (m, 4H), 7.68 (m, 2H), 7.49 (m, 1.5H), 7.37 (m, 3.5H), 5.40 (m, 0.5H), 5.25 (dd, *J* = 4.04, 8.08 Hz, 1.5H), 4.61 (m, 1.5H), 4.40 (m, 0.5H), 3.93 (m, 3H), 3.65 (s, 4.5H), 3.54 (s, 1.5H), 3.49 (m, 4H), 3.34 (m, 2H), 2.49 (m, 1H), 2.38 – 2.32 (m, 2H), 2.27 – 2.08 (m, 8H),

2.04 – 1.80 (6H). LC/MS: Anal. Calcd. for $C_{46}H_{53}N_9O_{10}S$: 923; found: 463 $[(M/2)+H)^+$.

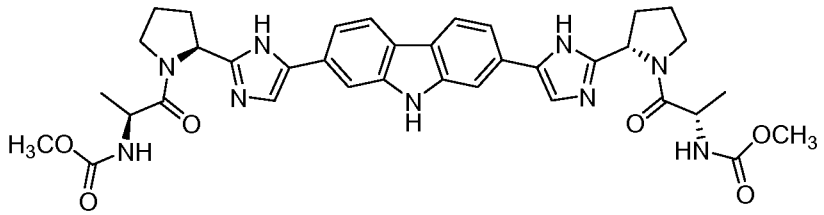
Example 29



methyl rac-((1R,2S)-2-methoxy-1-(((2R)-2-(5-(7-(2-((2R)-1-(N-(methoxycarbonyl)-O-methyl-D-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-(phenylsulfonyl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

Example 29 was prepared according to the method described for Example 28, and was isolated as a white solid (0.083 g, 44%). ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 8.63 (s, 0.5H), 8.58 (s, 1.5H), 7.89 (m, 4H), 7.72 (m, 0.5H), 7.66 (m, 1.5H), 7.47 (m, 1.5H), 7.37 (m, 3.5H), 5.56 (m, 0.4H), 5.25 (dd, *J* = 4.80, 7.83 Hz, 1.6H), 4.47 (d, *J* = 5.56 Hz, 1.5H), 4.35 (m, 0.5H), 3.94 (m, 3H), 3.83 (m, 1H), 3.73 – 3.69 (m, 1.3H), 3.66 (s, 6H), 3.61 – 3.56 (m, 0.7H), 2.40 – 2.22 (m, 6H), 2.07 (m, 3H), 1.21 (d, *J* = 6.06 Hz, 6H). LC/MS: Anal. Calcd. for $C_{46}H_{53}N_9O_{10}S$: 923, found: 463 $[(M/2)+H]^+$.

Example 30



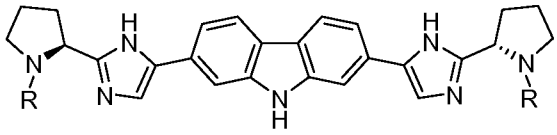
methyl ((1S)-2-((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate

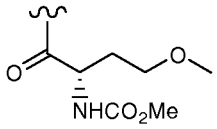
To a mixture of Exampe 26 (0.033 g, 0.039 mmol) and Na_2HPO_4 (0.022 g, 0.051 mmol) in absolute EtOH (2 mL) was added freshly pulverized 6% Na amalgam (0.079 g). The resulting suspension was stirred at ambient temperature for 6 h then it was filtered using a 0.45 μM syringe filter. The filtrate was concentrated *in vacuo* and the residue was taken up in CH_3OH (2 mL) and purified by preparative HPLC

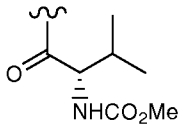
(C-18/ CH_3CN-H_2O-NH_4OAc). Product-containing fractions were concentrated to dryness and the residue was lyophilized from H_2O-CH_3CN (7:3) to give Example 30 (0.014 g, 53%) as a beige solid. ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 7.98 (m, 2H), 7.79 (s, 0.5H), 7.71 (s, 1.5H), 7.52 (m, 0.5H), 7.44 (d, *J* = 8.08 Hz, 1.5H), 7.37 (s, 0.5H), 7.28 (s, 1.5H), 5.21 (dd, *J* = 4.29, 7.83 Hz, 2H), 4.48 (quart, *J* = 7.07 Hz, 1.5H), 4.27 (m, 0.5H), 3.87 (t, *J* = 6.32 Hz, 3H), 3.64 (s, 4H), 3.57 (s, 2H), 2.48 – 1.92 (m, 9H), 1.33 (d, *J* = 7.07 Hz, 6H). LC/MS: Anal. Calcd. for $C_{36}H_{41}N_9O_6$: 695; found: 696 $(M+H)^+$.

Example 31-32

Example 31-32 were prepared from the respective sulphonamide precursors by employing the procedure described for the synthesis of Example 30.

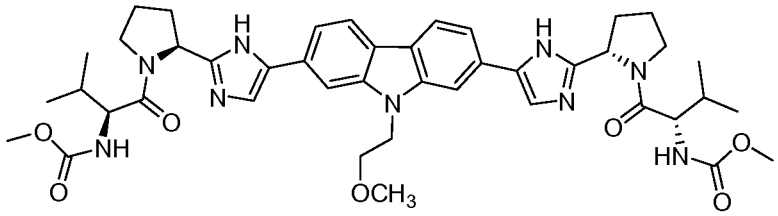


Example	R	Compound Name	Product description (Yield) ^{1}H NMR and LC/MS data
31		*methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate*	Yellow solid (0.029 g, 26%); ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 8.22 (d, *J* = 8.59 Hz, 2H), 7.90 (s, 0.35H), 7.86–7.84 (m, 3.65H), 7.60 (m, 0.3H), 7.54 (d, *J* = 8.08 Hz, 1.7H),

			5.66 (m, 0.3H), 5.29 (dd, *J* = 5.56, 8.08 Hz, 1.7H), 4.58 (dd, *J* = 4.55, 9.09 Hz, 1.7H), 4.33 (m, 0.3H), 4.02–3.87 (m, 4H), 3.65 (s, 6H), 3.47 (m, 5H), 3.34 (m, 2H), 2.55 (m, 2H), 2.26–2.16 (m, 7H), 2.12–2.04 (m, 4H), 1.85–1.77 (m, 2H). LC/MS: Anal. Calcd. for $C_{40}H_{49}N_9O_8$:783; found: 784 $(M+H)^+$.
32		*methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate*	Light yellow solid (0.003 g, 1.6%); ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 8.22 (d, *J* = 8.59 Hz, 2H), 7.84 (d, *J* = 3.54 Hz, 3.5H), 7.76 (m, 0.5H), 7.61 (m, 0.3H), 7.53 (d, *J* = 8.59 Hz,

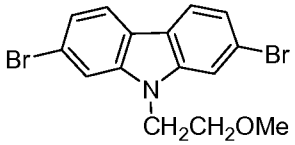
			1.7H), 7.15 (m, 1.5H), 5.26 (t, *J* = 7.07 Hz, 2H), 4.24 (m, 2H), 4.10 (m, 2H), 3.88 (m, 2H), 3.65 (s, 5H), 3.43 (s, 1H), 2.57 (m, 2H), 2.37–1.95 (m, 10H), 0.94 (d, *J* = 7.07 Hz, 6H), 0.90 (d, *J* = 7.07 Hz, 6H). LC/MS: Anal. Calcd. for $C_{40}H_{49}N_9O_6$: 751; found: 752 $(M+H)^+$.

Example 33



methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-(2-methoxyethyl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

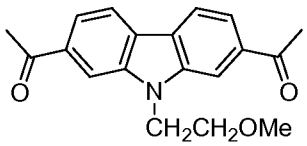
Example 33, Step a



33a

To an ice-cold suspension of NaH (60% in oil, 0.201 g, 5.02 mmol; previously washed with 3x5 mL of hexanes under Ar) in DMF (5 mL) was added a solution of 2,7-dibromo-9*H*-carbazole (1.419 g, 4.37 mmol) in DMF (25 mL). The mixture was stirred at 0 °C for 5 minutes and then 2-chloroethyl methyl ether (1.40 mL, 15.3 mmol) was added and the reaction mixture was warmed to 60 °C and stirred for 40 min. The cooled mixture was then poured into ice water (300 mL) and the resulting white precipitate was filtered off and dried under vacuum to afford 33a (1.54 g, 92%) as a white solid which was used without further purification. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.08 Hz, 2H), 7.59 (s, 2H), 7.34 (dd, *J* = 8.34, 1.77 Hz, 2H), 4.37 (t, *J* = 5.81 Hz, 2H), 3.74 (t, *J* = 5.81 Hz, 2H), 3.29 (s, 3H).LC/MS: Anal. Calcd. for $C_{15}H_{13}Br_2NO$: 381; found: 382 $(M+H)^+$.

Example 33, Step b

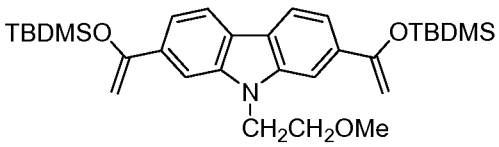


33b

To a stirred solution of crude 33a (1.577 g, 4.12 mmol) in dry THF (40 mL) at -78 °C under Ar was added n-BuLi (1.29M in hexane, 9.53 mL, 12.3 mmol) drop-wise over 5 min. Stirring was continued at the same temperature for 2 h and then *N*-methoxy-*N*-methylacetamide (1.31 mL, 12.3 mmol) was added and the cooling bath was allowed to warm to room temperature over 18 hours. The reaction mixture was then quenched with 2N Na_2HPO_4 and extracted with ethyl acetate (2x30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated to dryness to give an amber colored oil which was purified by column chromatography (Biotage, 40+M column/ 10–60% ethyl acetate-hexanes). Product-containing fractions were combined, filtered, and concentrated to give 33b (0.967 g, 76%) as a yellow solid.

^{1}HNMR (400 MHz, $CDCl_3$) δ 8.11 (m, 3H), 7.83 (dd, *J* = 8.34, 1.26 Hz, 1H), 7.55–7.47 (m, 2H), 7.28–7.24 (m, 1H), 4.52 (t, *J* = 5.81 Hz, 2H), 3.78 (t, *J* = 5.81 Hz, 2H), 3.29 (s, 3H), 2.73 (s, 3H). LC/MS: Anal. Calcd. for $C_{19}H_{19}NO_3$: 309; found: 310 $(M+H)^+$.

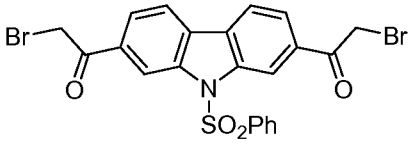
Example 33, Step c



33c

To an ice-cold suspension of 33b (0.967 g, 3.12 mmol) and triethylamine (1.74 mL, 12.5 mmol) in toluene (50 mL) was added TBDMSOTf (2.15 mL, 9.38 mmol) and the mixture was stirred for 20 minutes at 0 °C and then it was allowed to warm to room temperature over 24 hours. The mixture was partitioned with EtOAc-water and the organic phase was dried ($MgSO_4$), filtered, filtered, and concentrated to give 33c as an oil in a quantitative yield. This material was not stable to ^{1}HNMR or LC/MS analysis and was used as such in the next step without purification.

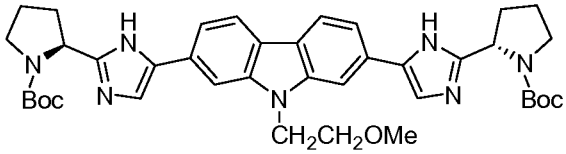
Example 33, Step d



33d

To a solution of 33c (3.12 mmol) in THF (20 mL) was added NBS (1.00 g, 5.62 mmol) and the mixture was stirred at room temperature for 45 min. The resulting yellow slurry was filtered, the fliter-cake was washed with a minimum volume of THF and the solid was dried *in vacuo* to give 33d (0.66 g, 45%) as a yellow solid. This material was used as such in the next step without further purification. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.40 (m, 4H), 7.88 (dd, *J* = 8.34, 1.26 Hz, 2H), 5.08 (s, 4H), 4.77 (t, *J* = 5.31 Hz, 2H), 3.77 (t, *J* = 5.31 Hz, 2H), 3.18 (s, 3H). LCMS: Anal. Calcd. for $C_{19}H_{17}Br_2NO_3$: 465; found: 466 $(M+H)^+$.

Example 33, Step e

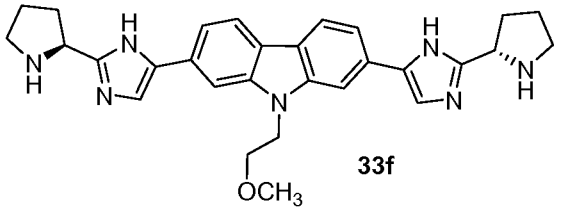


33e

A solution of 33d (0.662 g, 1.42 mmol), N-BOC-L-proline (0.611 g, 2.84 mmol), and DIEA (0.495 mL, 2.84 mmol) in acetonitrile (20 mL) was heated in a sealed tube at *ca.* 85 °C for 2.5 hours. After being allowed to cool to room temperature, the mixture was concentrated to dryness to give a yellow solid. LC/MS: Anal. Calcd. for $C_{39}H_{49}N_3O_{11}$: 735; found: 736 $(M+H)^+$.

A mixture of the above solid and NH_4OAc (1.09 g, 14.2 mmol) in toluene (20 mL) was heated at 125 °C in a sealed tube for 3 hours. The cooled mixture was concentrated under reduced pressure, partitioned with EtOAc-brine, and then the organic phase was dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by preparative HPLC (C-18/ MeCN-H2O+0.1% TFA) to give 33e (0.810 g, 82%) as a beige solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.31 (d, J = 8.08 Hz, 2H), 8.20 (m, 1H), 8.14 (m, 1H), 8.08 (s, 2H), 7.66 (d, J = 8.59 Hz, 2H), 5.06 (m, 2H), 4.63 (t, J = 5.31 Hz, 2H), 3.80 (m, 2.5H), 3.64–3.58 (m, 2.5H), 3.48–3.39 (m, 2.5H), 3.18 (s, 3H), 2.45–2.40 (m, 2H), 2.11–1.94 (m, 7.5H), 1.79 (m, 1H), 1.41 (s, 8H), 1.19 (s, 10H). LC/MS: Anal. Calcd. for $C_{36}H_{41}N_9O_6$: 695; found: 696 $(M+H)^+$.

Example 33, Step f



33f

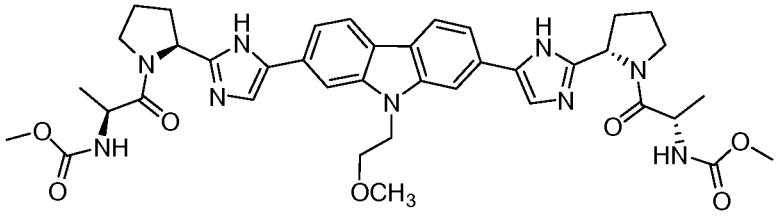
To a solution of 33e (0.810 g, 1.16 mmol) in dichloromethane (20 mL) was added TFA (8 mL) and the mixture was stirred at room temperature for 24 h and then concentrated to dryness. The residue was taken up in CH_3OH and applied to a pre-conditioned (CH_3OH) pad of SCX extraction gel (3cm x 5cm). The pad was washed with CH_3OH and then eluted with 2M NH_3 in CH_3OH. Product-containing fractions were concentrated to give 33f (0.380 g, 66%.) as an orange solid which was used as

such in the next step. ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 8.01 (d, J = 8.08 Hz, 2H), 7.86 (s, 2H), 7.54 (dd, J = 8.34, 1.26 Hz, 2H), 7.49 (s, 2H), 4.68 (t, J = 8.08 Hz, 2H), 4.57 (t, J = 5.56 Hz, 2H), 3.83 (t, J = 5.56 Hz, 2H), 3.43–3.36 (m, 2H), 3.33–3.28 (m, 2H), 3.26 (s, 3H), 2.48–2.05 (m, 8H). LC/MS: Anal. Calcd. for $C_{29}H_{33}N_7O$: 495; found: 496 $(M+H)^+$.

Example 33

To a solution of (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.051 g, 0.29 mmol) and HATU (0.110 g, 0.29 mmol) in DMF (3 mL) was added DIEA (0.252 mL, 1.45 mmol) and the mixture was stirred at room temperature for 10 min. To this solution was added 33f (0.072 g, 0.145 mmol) and stirring was continued for 4 hours. The reaction mixture was then partitioned with EtOAc-brine (1:1) and the organic phase was dried ($MgSO_4$), filtered and concentrated to dryness. The resulting residue was purified by preparative HPLC (C-18/ CH_3CN-H_2O+0.1% TFA) and product-containing fractions were concentrated to dryness. This afforded the TFA salt of Example 33 (0.055 g, 37%) as a yellow solid. ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 8.25 (d, J = 8.08 Hz, 2H), 7.96 (s, 2H), 7.94 (s, 2H), 7.58 (d, J = 8.08 Hz, 2H), 5.28 (t, J = 7.33 Hz, 2H), 4.67 (t, J = 5.05 Hz, 2H), 4.24 (d, J = 7.58 Hz, 2H), 4.14–4.09 (m, 2H), 3.93–3.86 (m, 4H), 3.65 (s, 6H), 3.25 (s, 3H), 2.62–2.57 (m, 2H), 2.31–2.04 (m, 8H), 0.94 (d, J = 6.57 Hz, 6H), 0.90 (d, J = 7.07 Hz, 6H). LC/MS: Anal. Calcd. for $C_{43}H_{55}N_9O_7$: 809; found: 810 $(M+H)^+$.

Example 34

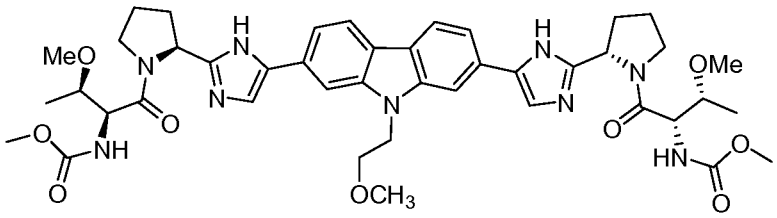


methyl ((1S)-2-((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-(2-methoxyethyl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate

The TFA salt of Example 34 was prepared according to the procedure described for Example 33, and was retrieved as a yellow solid (0.0387 g, 27%).

^{1}HNMR (400 MHz, CH_3OH-d_4) δ 8.26 (d, *J* = 8.08 Hz, 2H), 7.96 (s, 2H), 7.92 (s, 2H), 7.58 (dd, *J* = 8.08, 1.52 Hz, 2H), 5.29 (m, 2H), 4.68 (m, 2H), 4.49 (m, 2H), 4.00 (m, 2H), 3.88 (m, 4H), 3.65 (s, 6H), 3.25 (s, 3H), 2.61–2.53 (m, 2H), 2.26–2.18 (m, 6H), 1.34 (d, *J* = 7.07 Hz, 6H). LC/MS: Anal. Calcd. for $C_{39}H_{47}N_9O_7$: 753; found: 754 $(M+H)^+$.

Example 35



methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-(2-methoxyethyl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

The TFA salt of Example 35 was prepared according to the procedure described for Example 33. This material was repurified by preparative HPLC (C-18/ MeCN-H_2O-NH_4OAc) to give the free base as a beige solid (0.031 g, 25%). ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 7.99 (m, 2H), 7.86 (m, 0.5H), 7.80 (s, 1.5H), 7.54 (d, *J* = 8.59 Hz, 0.5H), 7.47 (d, *J* = 8.08 Hz, 1.5H), 7.41 (m, 0.5H), 7.36 (s, 1.5H), 5.54 (m, 0.5H), 5.23 (dd, *J* = 7.83, 4.8 Hz, 1.5H), 4.60–4.54 (m, 2H), 4.46 (d, *J* = 5.05 Hz, 1.5H), 4.35 (d, *J* = 5.05 Hz, 0.5H), 4.00–3.82 (m, 6H), 3.70–3.63 (m, 7H), 3.49 (s, 1H), 3.37 (s, 2H), 3.28 (m, 7H), 2.39–2.02 (m, 8H), 1.18 (d, *J* = 6.06 Hz, 6H). LC/MS: Anal. Calcd. for $C_{43}H_{55}N_9O_7$: 841; found: 842 $(M+H)^+$.

BIOLOGICAL ACTIVITY

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

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 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

Example	**Range/ Value**
1	9 pM
2	C
3	C
4	D
5	D
6	2 nM
7	C
8	D
9	D
10	C
10A	B
11	146 pM
12	C
13	D
14	D
15	52 pM
16	D
17	D
18	D
19	D
20	D
21	D
22	B
23	D
24	C
25	D
26	D
27	D
28	D
29	D
30	20 nM
31	B
32	C
33	D
34	B
35	662 pM

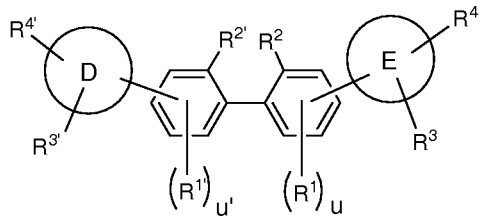
It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects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

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. 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;

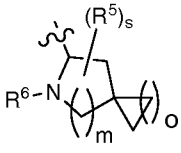
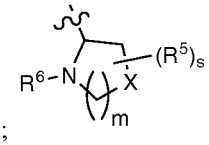
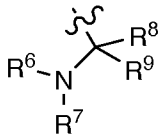
D and E are each five-membered aromatic rings containing one, two, or three heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^1 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;

R^2 and $R^{2'}$, together with the carbon atoms to which they are attached, form a five- to eight-membered unsaturated ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the five- to eight-membered unsaturated 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^3 and $R^{3'}$ are each independently selected from hydrogen, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, heterocyclylalkyl, hydroxyalkyl, (NR^aR^b)carbonyl, and trialkylsilylalkoxyalkyl;

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



; and  ; wherein

each m is independently 0, 1, or 2;

each o is independently 1, 2, or 3;

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

each X is independently selected from O, S, S(O), SO_2, CH_2, CHR^5, and $C(R^5)_2$; provided that when n is 0, X is selected from CH_2, CHR^5, and $C(R^5)_2$;

each R^5 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^6 is independently selected from hydrogen and R^{10}-C(O)-, and R^{10}-C(S)-;

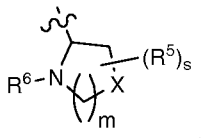
R^7 is selected from hydrogen and alkyl;

R^8 and R^9 are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and (NR^aR^b)alkyl; or,

R^8 and R^9, 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^{10} 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, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

2. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^4 and $R^{4'}$ are each



3. A compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein each m is 1.

4. A compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein each X is CH_2.

5. A compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein s is 0.

6. A compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein each R^6 is R^{10}-C(O)-.

7. A compound of claim 6 wherein each R^{10} is independently selected from arylalkyl, (cycloalkyl)alkyl, and (NR^cR^d)alkyl.

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

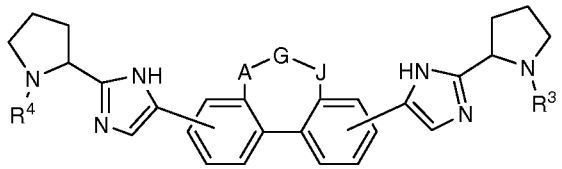
9. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 and $R^{3'}$ are each hydrogen.

10. A compound of claim 1 wherein R^2 and $R^{2'}$, together with the atoms to which they are attached, form a five-membered ring optionally containing an oxygen or nitrogen atom, wherein said ring is optionally substituted with one or two 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, and oxo.

11. A compound of claim 1 wherein R^2 and $R^{2'}$, together with the atoms to which they are attached, form a seven-membered ring containing a heteroatom selected from oxygen and nitrogen, wherein said 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, and oxo.

12. A compound of Formula (II)



(II);

or a pharmaceutically acceptable salt thereof, wherein

A is absent or $CR^{11}R^{12}$;

G is selected from $CR^{11}R^{12}$, O, and NR^{13};

J is absent or $CR^{11}R^{12}$;

R^3 and R^4 are each independently selected from hydrogen and R^{10}-C(O)-;

each R^{10} is independently selected arylalkyl, (cycloalkyl)alkyl, and (NR^cR^d)alkyl;

each R^{11} and R^{12} are independently selected from hydrogen, alkyl, and -NR^aR^b; or

R^{11} and R^{12} together form an oxo group; or

R^{11} and R^{12}, together with the carbon atom to which they are attached, form a three- to eight-membered spirocycle; and

each R^{13} is independently selected from hydrogen, alkoxyalkyl, alkyl, and arylsulfonyl.

13. A compound selected from:

methyl ((1S)-1-(((2S)-2-(5-(9-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepin-3-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-oxo-9H-fluoren-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(9-hydroxy-7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9H-fluoren-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(9-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-5,7-dihydrodibenzo[c,e]oxepin-3-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(9-(dimethylamino)-7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9H-fluoren-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-methyl-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9H-fluoren-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(9-(dimethylamino)-7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-methyl-9H-fluoren-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-methyl-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-methyl-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-methyl-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-(phenylsulfonyl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1S,1'S)-2,2'-((6-methyl-6,7-dihydro-5H-dibenzo[c,e]azepine-3,9-diyl)bis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine);

methyl ((1S)-2-((2S)-2-(4-(9-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-5,7-dihydrodibenzo[c,e]oxepin-3-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-(phenylsulfonyl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl rac-((1R,2S)-2-methoxy-1-(((2R)-2-(5-(7-(2-((2R)-1-(N-(methoxycarbonyl)-O-methyl-D-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-(phenylsulfonyl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-(phenylsulfonyl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9H-fluoren-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9,9-dimethyl-9H-fluoren-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

dimethyl ((9,9-dimethyl-9H-fluorene-2,7-diyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((2S)-2-(5-(7'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)spiro[cyclobutane-1,9'-fluoren]-2'-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(7'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)spiro[cyclobutane-1,9'-fluoren]-2'-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

dimethyl (5,7-dihydrodibenzo[c,e]oxepine-3,9-diylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate;

dimethyl (5,7-dihydrodibenzo[c,e]oxepine-3,9-diylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(4-(9-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-5,7-dihydrodibenzo[c,e]oxepin-3-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

(1S,1'S)-2,2'-(5,7-dihydrodibenzo[c,e]oxepine-3,9-diylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine);

methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(5-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-(2-methoxyethyl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-(2-methoxyethyl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(7-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-9-(2-

methoxyethyl)-9H-carbazol-2-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)dibenzo[b,d]furan-3-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (dibenzo[b,d]furan-3,7-diylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((2S)-2-(4-(7-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)dibenzo[b,d]furan-3-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate; and

methyl ((1S)-2-hydroxy-1-(((2S)-2-(4-(7-(2-((2S)-1-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)dibenzo[b,d]furan-3-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate.

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

15. The composition of claim 14 further comprising one or two additional compounds having anti-HCV activity.

16. The composition of claim 15 wherein at least one of the additional compounds is an interferon or a ribavirin.

17. The composition of claim 16 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

18. The composition of claim 15 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'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

19. 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.

20. 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.

21. The method of claim 20 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.

22. The method of claim 21 wherein at least one of the additional compounds is an interferon or a ribavirin.

23. The method of claim 22 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

24. The method of claim 21 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'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

25. The method of claim 21 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.