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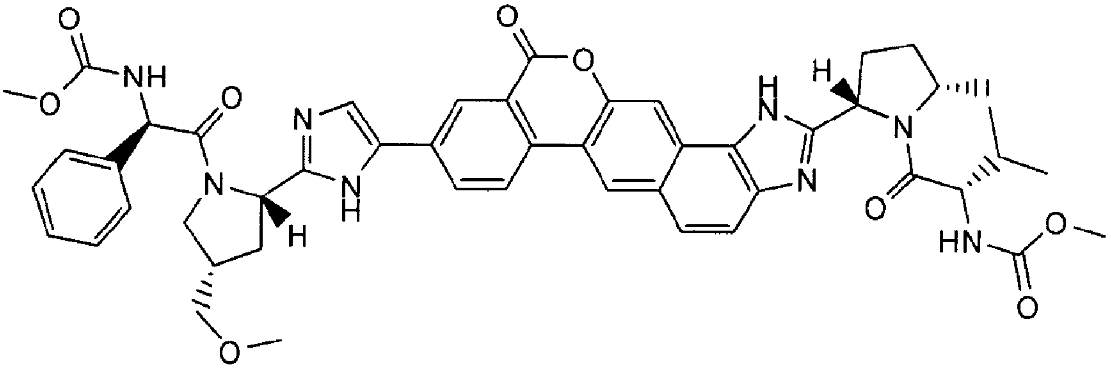
(54) Titre : COMPOSES ANTIVIRAUX
(54) Title: ANTIVIRAL COMPOUNDS



(57) Abrégé/Abstract:

The disclosure is related to anti-viral compounds of formula (I), compositions containing such compounds, and therapeutic methods that include the administration of such compounds, as well as to processes and intermediates useful for preparing such compounds.

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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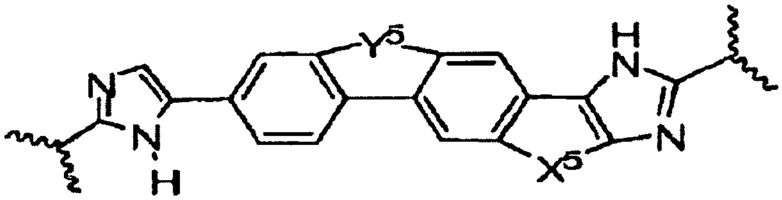
**Declarations under Rule 4.17**:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

**Published**:
— *with international search report (Art. 21(3))*

# (54) **Title**: ANTIVIRAL COMPOUNDS INHIBITORS OF HCV NS5B



(I)

(57) **Abstract**: The disclosure is related to anti-viral compounds of formula (I), compositions containing such compounds, and therapeutic methods that include the administration of such compounds, as well as to processes and intermediates useful for preparing such compounds.

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# DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.**

**CECI EST LE TOME __1___ DE __2 __**

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

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# JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.**

**THIS IS VOLUME __1___ OF __2___**

NOTE: For additional volumes please contact the Canadian Patent Office.

# ANTIVIRAL COMPOUNDS

## BACKGROUND

Hepatitis C is recognized as a chronic viral disease of the liver which is characterized by liver disease. Although drugs targeting the liver are in wide use and have shown effectiveness, toxicity and other side effects have limited their usefulness. Inhibitors of hepatitis C virus (HCV) are useful to limit the establishment and progression of infection by HCV as well as in diagnostic assays for HCV.

There is a need for new HCV therapeutic agents. In particular, there is a need for HCV therapeutic agents that have broad activity against HCV genotypes (e.g. genotypes 1a, 1b, 2a, 3a, 4a). There is also a particular need for agents that are less susceptible to viral resistance. Resistance mutations to inhibitors have been described for HCV NS5A for genotypes 1a and 1b in Antimicrobial Agents and Chemotherapy, September 2010, Volume 54, p. 3641-3650.

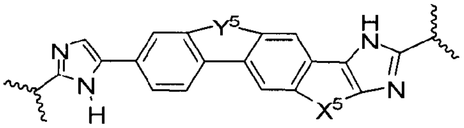
## SUMMARY

In one embodiment the disclosure provides a compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{-}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

$W^{1a}$ is



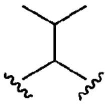
and $W^{1a}$ is optionally substituted with one or more groups independently selected from halo, alkyl, haloalkyl, optionally substituted aryl, optionally substituted heterocycle, and cyano;

$Y^5$ is -O-$CH_2$-, -$CH_2$-O-, -O-C(=O)-, or -C(=O)-O-; $X^5$ is -$CH_2$-$CH_2$- or -CH=CH-;

$E^{1a}$ is -N(H)(alkoxycarbonyl), -N(H)(cycloalkylcarbonyl) or -N(H)(cycloalkyloxycarbonyl); or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is -N(H)(alkoxycarbonyl), -N(H)(cycloalkylcarbonyl) or -N(H)(cycloalkyloxycarbonyl); or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ and $V^{1b}$ are each independently selected from: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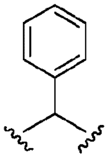
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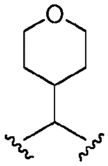
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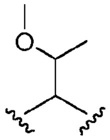
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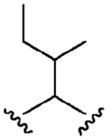
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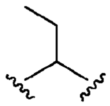
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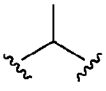
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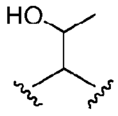
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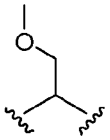
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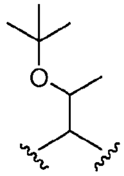
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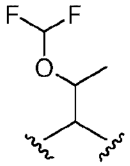
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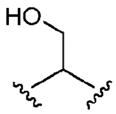
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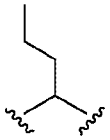
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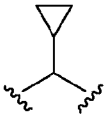
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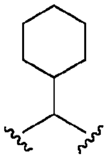
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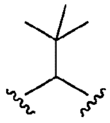
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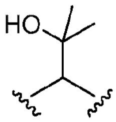
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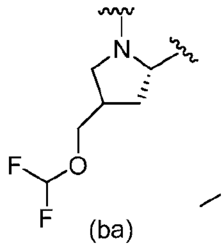
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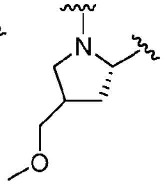
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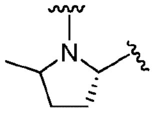
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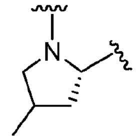
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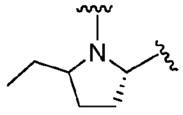
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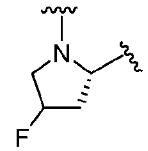
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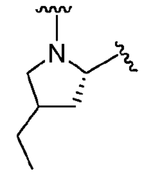
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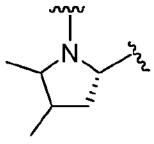
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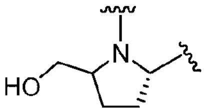
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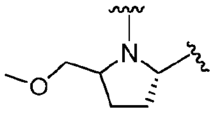
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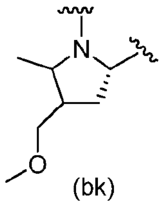
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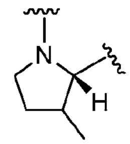
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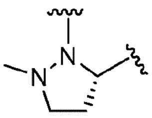
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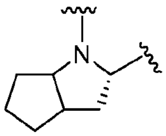
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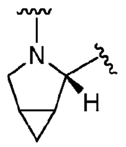
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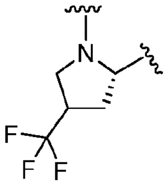

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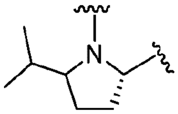
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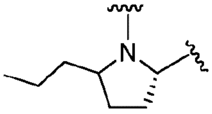
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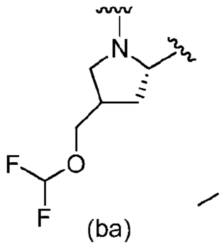

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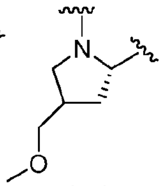
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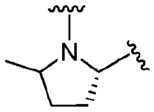
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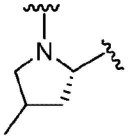
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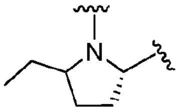
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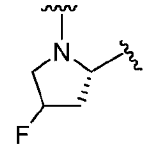

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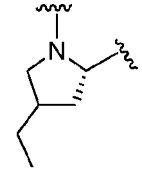
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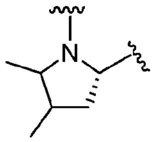
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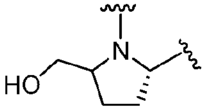

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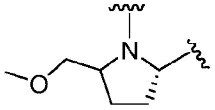
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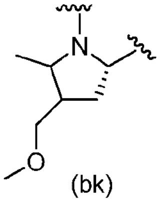
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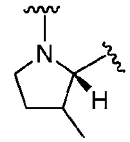
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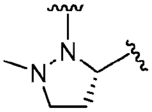
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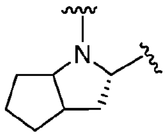
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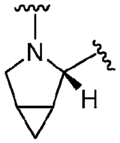
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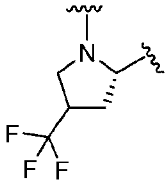

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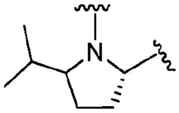
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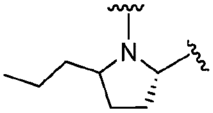
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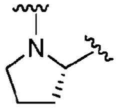
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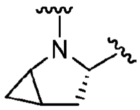
or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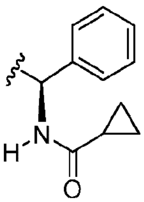
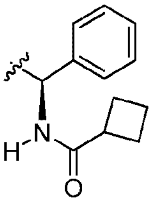
and

$R^{9a}$ and $R^{9b}$ are each independently selected from:



or



;

or a pharmaceutically acceptable salt or prodrug thereof;

provided that when $Y^5$ is -O-$CH_2$-, or -$CH_2$-O-, then at least one of the following occurs:

(1) at least one of $V^{1a}$ and $V^{1b}$ is selected from (af), (ag), (ah), (ai), (aj), (ak), (al), (am), (an), (ao), (ap) or (aq); or

(2) $P^{1a}$ is selected from (be), (bf), (bg), (bh), (bi), (bj), (bk), (bl), (bm), (bn), (bo), (bq) or (br); or

(3) $P^{1b}$ is selected from (be), (bf), (bg), (bh), (bi), (bj), (bk), (bl), (bm), (bn), (bo), (bp), (bq) or (br).

The disclosure also provides isotopically enriched compounds that are compounds of the disclosure that comprise an enriched isotope at one or more positions in the compound.

The present disclosure also provides a pharmaceutical composition comprising a compound of the disclosure or a pharmaceutically acceptable salt or prodrug thereof and at least one pharmaceutically acceptable carrier.

The present disclosure also provides a pharmaceutical composition for use in treating hepatitis C (HCV). In one embodiment the composition comprises at least one additional therapeutic agent for treating HCV. In one embodiment, the therapeutic agent is selected from ribavirin, an NS3 protease inhibitor, a nucleoside or nucleotide inhibitor of HCV NS5B polymerase, an alpha-glucosidase 1 inhibitor, a hepatoprotectant, a non-nucleoside inhibitor of HCV polymerase, or combinations thereof. In one embodiment, the composition further comprises a nucleoside or nucleotide inhibitor of HCV NS5B polymerase. In one embodiment, the nucleoside or nucleotide inhibitor of HCV NS5B polymerase is selected from ribavirin, viramidine, levovirin, a L-nucleoside, or isatoribine.

In one embodiment, provided is a pharmaceutical composition comprising a compound as described herein and at least one nucleoside or nucleotide inhibitor of HCV NS5B polymerase, and at least one pharmaceutically acceptable carrier. In one embodiment, the composition further comprises an interferon, a pegylated interferon, ribavirin or combinations thereof. In one embodiment, the nucleoside or nucleotide inhibitor of HCV NS5B polymerase is sofosbuvir. In one embodiment, provided is a pharmaceutical composition comprising a compound as described herein and at least one NS3 protease inhibitor, and at least one pharmaceutically acceptable carrier. In one embodiment, the composition further comprises sofosbuvir.

The present disclosure also provides a pharmaceutical composition further comprising an interferon or pegylated interferon.

The present disclosure also provides a pharmaceutical composition further comprising a nucleoside analog.

The present disclosure also provides for a pharmaceutical composition wherein said nucleoside analogue is selected from ribavirin, viramidine, levovirin, an L-nucleoside, and isatoribine and said interferon is α-interferon or pegylated α-interferon.

The present disclosure also provides for a method of treating hepatitis C, said method comprising administering to a human patient a pharmaceutical composition which comprises a therapeutically effective amount of a compound of the disclosure.

The present disclosure also provides a method of inhibiting HCV, comprising administering to a mammal afflicted with a condition associated with HCV activity, an amount of a compound of the disclosure, effective to inhibit HCV.

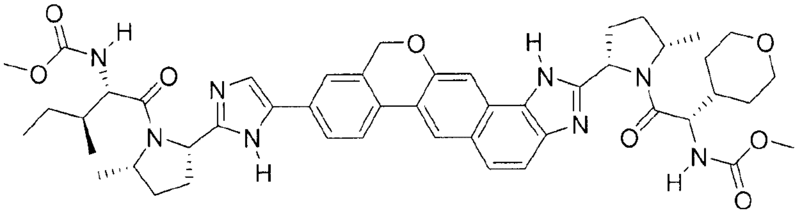
The present disclosure also provides a compound of the disclosure for use in medical therapy (e.g. for use in inhibiting HCV activity or treating a condition associated with HCV activity), as well as the use of a compound of the disclosure for the manufacture of a medicament useful for inhibiting HCV or the treatment of a condition associated with HCV activity in a mammal.

The present disclosure also provides synthetic processes and novel intermediates disclosed herein which are useful for preparing compounds of the disclosure. Some of the compounds of the disclosure are useful to prepare other compounds of the disclosure.
In another aspect the disclosure provides a compound of the disclosure, or a pharmaceutically acceptable salt or prodrug thereof, for use in the prophylactic or therapeutic treatment of hepatitis C or a hepatitis C associated disorder.

In another aspect the disclosure provides a method of inhibiting HCV activity in a sample comprising treating the sample with a compound of the disclosure.

Compounds of formula (I) have been found to possess useful activity against several HCV genotypes. Additionally certain compounds of formula (I) exhibit significant potency against resistant variants in, e.g., GT1.

According to one aspect of the present invention, there is provided a compound of formula:



or a pharmaceutically acceptable salt thereof.

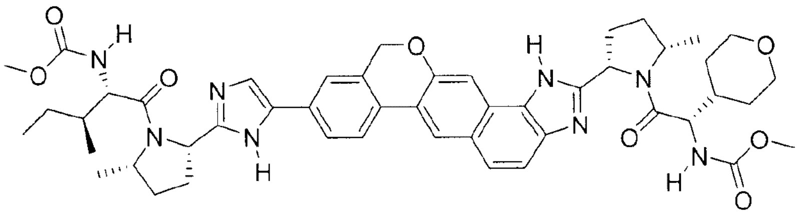
According to another aspect of the present invention, there is provided a pharmaceutical composition comprising the compound described herein and a pharmaceutically acceptable diluent or carrier, or combination thereof.

According to still another aspect of the present invention, there is provided the compound described herein for use in the prophylactic or therapeutic treatment of hepatitis C.

According to yet another aspect of the present invention, there is provided use of the compound described herein in the manufacture of a medicament for the treatment of hepatitis C.

According to a further aspect of the present invention, there is provided the pharmaceutical composition described herein for use in the prophylactic or therapeutic treatment of hepatitis C.

According to yet a further aspect of the present invention, there is provided a compound of formula:



.

According to still a further aspect of the present invention, there is provided a pharmaceutical composition comprising the compound described herein and a pharmaceutically acceptable diluent or carrier, or combination thereof.

According to another aspect of the present invention, there is provided the compound described herein for use in the prophylactic or therapeutic treatment of hepatitis C.

According to yet another aspect of the present invention, there is provided use of the compound of described herein in the manufacture of a medicament for the treatment of hepatitis C.

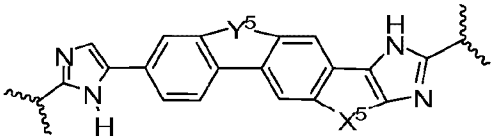
According to yet a further aspect of the present invention, there is provided the pharmaceutical composition described herein for use in the prophylactic or therapeutic treatment of hepatitis C.

## DETAILED DESCRIPTION

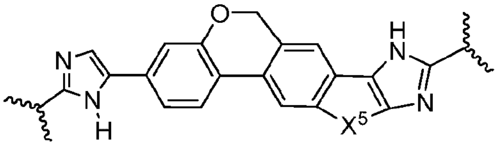
Reference will now be made in detail to certain embodiments of the disclosure, examples of which are illustrated in the accompanying structures and formulas. While the disclosure will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the disclosure to those embodiments. On the contrary, the disclosure is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present disclosure as defined by the embodiments.

### Compounds

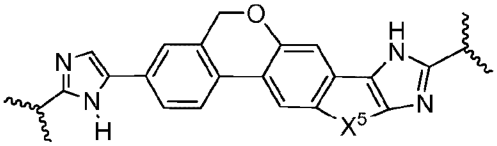
The "P" groups (eg $P^{1a}$ and $P^{1b}$) defined for formula (I) herein have one bond to a -C(=O)- of formula (I) and one bond to a $W^{1a}$ group. It is to be understood that a nitrogen of the P group is connected to the -C(=O)- group of formula (I) and that a carbon of the P group is connected to the $W^{1a}$ group.



In the $W^{1a}$ group a $Y^5$ group is present. When that $Y^5$ group is defined as -O-$CH_2$-, or -$CH_2$-O- group, those $Y^5$ groups have a directionality. The $Y^5$ group is connected to the $W^{1a}$ group in the same left to right directionality that each is drawn. So for example, when $Y^5$ is -O-$CH_2$-, the directly following structure is intended:



For example, when $Y^5$ is -$CH_2$-O-, the directly following structure is intended:

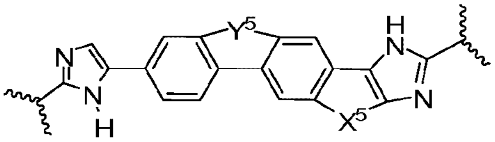


In the structure I, the $W^{1a}$ group has a left-to-right directionality as depicted in I and $W^{1a}$ as they drawn.

$$E^{1a}\text{-}V^{1a}\text{-}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b}\ (I)$$

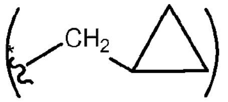
wherein:

$W^{1a}$ is



For example, the $P^{1a}$ group is connected to the imidazole group of $W^{1a}$, and the P1b group is connected to the pentacyclic ring system of $W^{1a}$.

"Alkyl" is $C_1$-$C_{18}$ hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, and cyclopropylmethyl



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"Alkenyl" is $C_2$-$C_{18}$ hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, $sp^2$ double bond. Examples include, but are not limited to, ethylene or vinyl ($-CH=CH_2$), allyl ($-CH_2CH=CH_2$), cyclopentenyl ($-C_5H_7$), and 5-hexenyl ($-CH_2\ CH_2CH_2CH_2CH=CH_2$).

"Alkynyl" is $C_2$-$C_{18}$ hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, *sp* triple bond. Examples include, but are not limited to, acetylenic ($-C\equiv CH$) and propargyl ($-CH_2C\equiv CH$).

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to, methylene ($-CH_2-$) 1,2-ethyl ($-CH_2CH_2-$), 1,3-propyl ($-CH_2CH_2CH_2-$), 1,4-butyl ($-CH_2CH_2CH_2CH_2-$), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene ($-CH=CH-$).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. Typical alkynylene radicals include, but are not limited to, acetylene ($-C\equiv C-$), propargyl ($-CH_2C\equiv C-$), and 4-pentynyl ($-CH_2CH_2CH_2C\equiv CH$).

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

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

The term "cycloalkyl," as used herein, refers to a saturated monocyclic, hydrocarbon ring system having three to seven carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. The cycloalkyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, nitro, and $-NR^xR^y$ wherein the aryl and the heterocyclyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

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

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

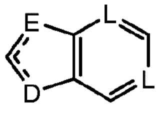
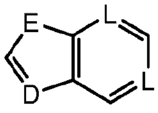
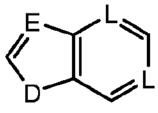
The term “cycloalkyloxycarbonyl,” as used herein, refers to a cycloalkyloxy group attached to the parent molecular moiety through a carbonyl group.

“Aryl” means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, radicals derived from benzene, substituted benzene, naphthalene, anthracene, biphenyl, and the like.

“Arylalkyl” refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or *sp*$^3$ carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group comprises 6 to 20 carbon atoms, *e.g.*, the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the arylalkyl group is 1 to 6 carbon atoms and the aryl moiety is 5 to 14 carbon atoms.

“Substituted alkyl”, “substituted aryl”, and “substituted arylalkyl” mean alkyl, aryl, and arylalkyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to: halo (e.g. F, Cl, Br, I), -R, -OR, -SR, -NR$_2$, -CF$_3$, -CCl$_3$, -OCF$_3$, -CN, -NO$_2$, -N(R)C(=O)R, -C(=O)R, -OC(=O)R, -C(O)OR, -C(=O)NRR, -S(=O)R, -S(=O)$_2$OR, -S(=O)$_2$R, -OS(=O)$_2$OR, -S(=O)$_2$NRR, and each R is independently -H, alkyl, aryl, arylalkyl, or heterocycle. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

The term “optionally substituted” in reference to a particular moiety of the compound of formula (I), (e.g., an optionally substituted aryl group) refers to a moiety having 0, 1, 2, or more substituents.

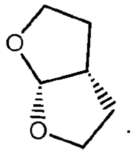
The symbol “-----“ in a ring structure means that a bond is a single or double bond. In a non-limiting example,  can be  or .

“Haloalkyl” as used herein includes an alkyl group substituted with one or more halogens (e.g. F, Cl, Br, or I). Representative examples of haloalkyl include trifluoromethyl, 2,2,2-trifluoroethyl, and 2,2,2-trifluoro-1-(trifluoromethyl)ethyl.

“Heterocycle” or “heterocyclyl” as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; Principles of Modern

Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. In one specific embodiment, "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (*e.g.* 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (*e.g.* O, N, or S). The term heterocycle also includes "heteroaryl" which is a heterocycle wherein at least one heterocyclic rings is aromatic.

Examples of heterocycles include by way of example and not limitation pyridyl, dihydropyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4H-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, isatinoyl, and bis-tetrahydrofuranyl:



By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Carbocycle" refers to a saturated, unsaturated or aromatic ring having up to about 25 carbon atoms. Typically, a carbocycle has about 3 to 7 carbon atoms as a monocycle, about 7 to 12 carbon atoms as a bicycle, and up to about 25 carbon atoms as a polycycle. Monocyclic carbocycles typically have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles typically have 7 to 12 ring atoms, *e.g.*, arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. The term carbocycle includes "cycloalkyl" which is a saturated or unsaturated carbocycle. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

The term "amino," as used herein, refers to $-NH_2$.

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

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.*, melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as, for example, electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

The term "treatment" or "treating," to the extent it relates to a disease or condition includes preventing the disease or condition from occurring, inhibiting the disease or condition, eliminating the disease or condition, and/or relieving one or more symptoms of the disease or condition.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes (D and L) or (R and S) are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity. The disclosure includes all stereoisomers of the compounds described herein.

***Prodrugs***

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates a compound of the disclosure that inhibits HCV activity ("the active inhibitory compound"). The compound may be formed from the prodrug as a result of: (i) spontaneous chemical reaction(s), (ii) enzyme catalyzed chemical reaction(s), (iii) photolysis, and/or (iv) metabolic chemical reaction(s).

"Prodrug moiety" refers to a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, "Design and Application of Prodrugs" in A Textbook of Drug Design and Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the prodrug compounds of the disclosure include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy. A prodrug moiety may include an active metabolite or drug itself.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-CH_2OC(=O)R^{99}$ and acyloxymethyl carbonates $-CH_2OC(=O)OR^{99}$ where $R^{99}$ is $C_1-C_6$ alkyl, $C_1-C_6$ substituted alkyl, $C_6-C_{20}$ aryl or $C_6-C_{20}$ substituted aryl. The acyloxyalkyl ester was first used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al. (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. Subsequently, the acyloxyalkyl ester was used to deliver phosphonic acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the disclosure. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-CH_2OC(=O)C(CH_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-CH_2OC(=O)OC(CH_3)_3$.

***Protecting Groups***

In the context of the present disclosure, protecting groups include prodrug moieties and chemical protecting groups.

"Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. Chemical protecting groups and strategies for protection/deprotection are well known in the art. *See e.g.*, Protective Groups in Organic Chemistry, Theodora W. Greene, John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, *e.g.*, making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as, for example, the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as, for example, passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro,* in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, *e.g.*, alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, *i.e.* routes or methods to prepare the compounds of the disclosure. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group “PG” will be dependent upon the chemistry of the reaction to be protected against (*e.g.*, acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. PGs do not need to be, and generally are not, the same if the compound is substituted with multiple PG. In general, PG will be used to protect functional groups such as, for example, carboxyl, hydroxyl, thio, or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

Various functional groups of the compounds of the disclosure may be protected. For example, protecting groups for –OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) include “ether- or ester-forming groups”. Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Synthesis, Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994). In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below.

***Stereoisomers***

The compounds of the disclosure may have chiral centers, *e.g.*, chiral carbon or phosphorus atoms. The compounds of the disclosure thus include all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the disclosure include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the non-racemic or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the disclosure. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, *e.g.*, acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material or through enantioselective reactions.

The compounds of the disclosure can also exist as tautomeric isomers in certain cases. Although only one tautomer may be depicted, all such forms are contemplated within the scope of the disclosure. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the disclosure.

***Salts and Hydrates***

Examples of physiologically or pharmaceutically acceptable salts of the compounds of the disclosure include salts derived from an appropriate base, such as, for example, an alkali metal (for example, sodium), an alkaline earth metal (for example, magnesium), ammonium and $NX_4^+$ (wherein X is $C_1$–$C_4$ alkyl). Physiologically acceptable salts of a hydrogen atom or an amino group include salts of organic carboxylic acids such as, for example, acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as, for example, methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as, for example, hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as, for example, $Na^+$ and $NX_4^+$ (wherein X is independently selected from H or a $C_1$–$C_4$ alkyl group).

For therapeutic use, salts of active ingredients of the compounds of the disclosure will typically be physiologically acceptable, *i.e.* they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present disclosure.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this disclosure. Examples of metal salts which are prepared in this way are salts containing $Li^+$, $Na^+$, and $K^+$. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic acids, *e.g.*, HCl, HBr, $H_2SO_4$, $H_3PO_4$ or organic sulfonic acids, to basic centers, typically amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise compounds of the disclosure in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this disclosure are the salts of the parental compounds with one or more amino acids. Any of the natural or unnatural amino acids are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, *e.g.*, lysine, arginine or glutamic acid, or a neutral group such as, for example, glycine, serine, threonine, alanine, isoleucine, or leucine.

## Methods of Inhibition of HCV

Another aspect of the disclosure relates to methods of inhibiting the activity of HCV comprising the step of treating a sample suspected of containing HCV with a compound or composition of the disclosure.

The treating step of the disclosure comprises adding the compound of the disclosure to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of HCV after application of the compound can be observed by any method including direct and indirect methods of detecting HCV activity. Quantitative, qualitative, and semiquantitative methods of determining HCV activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as, for example, observation of the physiological properties of a living organism are also applicable.

Many organisms contain HCV. The compounds of this disclosure are useful in the treatment or prophylaxis of conditions associated with HCV activation in animals or in man.

However, in screening compounds capable of inhibiting HCV activity it should be kept in mind that the results of enzyme assays may not always correlate with cell culture assays. Thus, a cell based assay should typically be the primary screening tool.

## Pharmaceutical Formulations

The compounds of this disclosure are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as, for example, those set forth in the Handbook of Pharmaceutical Excipients (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as, for example, EDTA, carbohydrates such as, for example, dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10. Typically, the compound will be administered in a dose from 0.01 milligrams to 2 grams.

In one embodiment, the dose will be from about 10 milligrams to 450 milligrams. It is contemplated that the compound may be administered once, twice or three times a day.

In some embodiments, the compound is administered for about 12 weeks or less. In further embodiments, the compound is administered for about 12 weeks or less, about 8 weeks or less, about 8 weeks or less, about 6 weeks or less, or about 4 weeks or less. The compound may be administered once daily, twice daily, once every other day, two times a week, three times a week, four times a week, or five times a week.

In further embodiments, a sustained virologic response is achieved at about 12 weeks, at about 8 weeks, at about 6 weekes, or at about 4 weeks, or at about 4 months, or at about 5 months, or at about 6 months, or at about 1 year, or at about 2 years.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the disclosure comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefore and optionally other therapeutic ingredients. The carrier(s) must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington’s Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present disclosure suitable for oral administration may be presented as discrete units such as, for example, capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as, for example, a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For administration to the eye or other external tissues *e.g.*, mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as, for example, 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, *i.e.* an alcohol having two or more hydroxyl groups such as, for example, propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this disclosure may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the disclosure include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as, for example, di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as, for example, white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present disclosure comprise one or more compounds of the disclosure together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as, for example, calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as, for example, maize starch, or alginic acid; binding agents, such as, for example, cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as, for example, magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as, for example, glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as, for example, peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the disclosure contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as, for example, a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as, for example, ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as, for example, sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as, for example, liquid paraffin. The oral suspensions may contain a thickening agent, such as, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as, for example, those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as, for example, ascorbic acid.

Dispersible powders and granules of the disclosure suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as, for example, olive oil or arachis oil, a mineral oil, such as, for example, liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as, for example, gum acacia and gum tragacanth, naturally occurring phosphatides, such as, for example, soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as, for example, sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as, for example, polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as, for example, glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the disclosure may be in the form of a sterile injectable preparation, such as, for example, a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as, for example, a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as, for example, oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as, for example, gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as, for example, 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as, for example, compounds heretofore used in the treatment or prophylaxis of conditions associated with HCV activity.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are 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 injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this disclosure 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 disclosure further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefore.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the disclosure can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the disclosure also provides compositions comprising one or more compounds of the disclosure formulated for sustained or controlled release.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses), the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies.

## Routes of Administration

One or more compounds of the disclosure (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this disclosure is that they are orally bioavailable and can be dosed orally.

## HCV Combination Therapy

In another embodiment, non-limiting examples of suitable combinations include combinations of one or more compounds of formula (I) and (A1-A4) with one or more interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophillin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers, and other drugs or therapeutic agents for treating HCV.

More specifically, one or more compounds of the present as described herein may be combined with one or more compounds selected from the group consisting of

1) interferons, *e.g.*, pegylated rIFN-alpha 2b (PEG-Intron®), pegylated rIFN-alpha 2a (Pegasys®), rIFN-alpha 2b (Intron® A), rIFN-alpha 2a (Roferon®-A), interferon alpha (MOR-22, OPC-18, Alfaferone®, Alfanative®, Multiferon®, subalin), interferon alfacon-1 (Infergen®), interferon alpha-n1 (Wellferon), interferon alpha-n3 (Alferon®), interferon-beta (Avonex®, DL-8234), interferon-omega (omega DUROS®, Biomed® 510), albinterferon alpha-2b (Albuferon®), IFN alpha-2b XL, BLX-883 (Locteron®), DA-3021, glycosylated interferon alpha-2b (AVI-005), PEG-Infergen, PEGylated interferon lambda-1 (PEGylated IL-29), and belerofon®;

2) ribavirin and its analogs, *e.g.*, ribavirin (Rebetol®, Copegus®), and taribavirin (Viramidine®);

3) HCV NS3 protease inhibitors, *e.g.*, boceprevir (SCH-503034, SCH-7), telaprevir (VX-950), TMC435350, BI-1335, BI-1230, MK-7009, VBY-376, VX-500, GS-9256, GS-9451, BMS-605339, PHX-1766, AS-101, YH-5258, YH5530, YH5531, ABT-450, ACH-1625, ITMN-191, AT26893, MK5172, MK6325, and MK2748;

4) alpha-glucosidase 1 inhibitors, *e.g.*, celgosivir (MX-3253), Miglitol, and UT-231B;

5) hepatoprotectants, *e.g.*, emericasan (IDN-6556), ME-3738, GS-9450 (LB-84451), silibilin, and MitoQ;

6) nucleoside or nucleotide inhibitors of HCV NS5B polymerase, *e.g.*, R1626, R7128 (R4048), IDX184, IDX-102, BCX-4678, valopicitabine (NM-283), MK-0608, sofosbuvir (GS-7977 (formerly PSI-7977)), VLX-135 (formerly ALS-2200), and INX-189 (now BMS986094);

7) non-nucleoside inhibitors of HCV NS5B polymerase, *e.g.,* PF-868554, VCH-759, VCH-916, JTK-652, MK-3281, GS-9190, VBY-708, VCH-222, A848837, ANA-598, GL60667, GL59728, A-63890, A-48773, A-48547, BC-2329, VCH-796 (nesbuvir), GSK625433, BILN-1941, XTL-2125, ABT-072, ABT-333, GS-9669, PSI-7792, and GS-9190;

8) HCV NS5A inhibitors, *e.g.*, AZD-2836 (A-831), BMS-790052, ACH-3102, ACH-2928, MK8325, MK4882, MK8742, PSI-461, IDX719, GS-5885, and A-689;

9) TLR-7 agonists, *e.g.*, imiquimod, 852A, GS-9524, ANA-773, ANA-975 (isatoribine), AZD-8848 (DSP-3025), and SM-360320;

10) cyclophillin inhibitors, *e.g.*, DEBIO-025, SCY-635, and NIM811;

11) HCV IRES inhibitors, *e.g.*, MCI-067;

12) pharmacokinetic enhancers, *e.g.*, BAS-100, SPI-452, PF-4194477, TMC-41629, GS-9350 (cobicistat), GS-9585, and roxythromycin; and

13) other drugs for treating HCV, *e.g.*, thymosin alpha 1 (Zadaxin), nitazoxanide (Alinea, NTZ), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), GS-9525, KRN-7000, civacir, GI-5005, XTL-6865, BIT225, PTX-111, ITX2865, TT-033i, ANA 971, NOV-205, tarvacin, EHC-18, VGX-410C, EMZ-702, AVI 4065, BMS-650032, BMS-791325, Bavituximab, MDX-1106 (ONO-4538), Oglufanide, and VX-497 (merimepodib).

In yet another embodiment, the present application discloses pharmaceutical compositions comprising a compound as described herein, or a pharmaceutically acceptable salt, prodrug, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or excipient.

In another embodiment is provided a pharmaceutical composition comprising a compound of formula (I) as described herein and sofosbuvir and/or GS-5885 and optionally an interferon or ribavirin.

In another embodiment is provided a pharmaceutical composition comprising a compound of formula (I) as described herein and a nucleoside or nucleotide inhibitor of HCV NS5B polymerase and optionally an interferon or ribavirin.

It is contemplated that additional therapeutic agents will be administered in a manner that is known in the art and the dosage may be selected by someone of skill in the art. For example, additional therapeutic agents may be administered in a dose from about 0.01 milligrams to about 2 grams per day.

## Metabolites of the Compounds

Also falling within the scope of this disclosure are the *in vivo* metabolic products of the compounds described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the disclosure includes compounds produced by a process comprising contacting a compound of this disclosure with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (*e.g.*, $C^{14}$ or $H^{3}$) compound of the disclosure, administering it parenterally in a detectable dose (*e.g.*, greater than about 0.5 mg/kg) to an animal such as, for example, rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, *e.g.*, by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the disclosure even if they possess no HCV –inhibitory activity of their own.

Methods for determining stability of compounds in surrogate gastrointestinal secretions are known.

## Exemplary Methods of Making the Compounds

The disclosure also relates to methods of making the compositions of the disclosure. The compositions are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in Compendium of Organic Synthetic Methods (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, Jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., Advanced Organic Chemistry, Third Edition, (John Wiley & Sons, New York, 1985), Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes, Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing). Other methods suitable for preparing compounds of the disclosure are described in International Patent Application Publication Number WO 2006/020276.

A number of exemplary methods for the preparation of the compositions of the disclosure are provided in the schemes and examples below. These methods are intended to illustrate the nature of such preparations and are not intended to limit the scope of applicable methods.

Generally, the reaction conditions such as, for example, temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0°C to -100°C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as, for example, azeotropic removal of reaction by-products and use of anhydrous reaction conditions (*e.g.*, inert gas environments) are common in the art and will be applied when applicable.

The terms "treated", "treating", "treatment", and the like, when used in connection with a chemical synthetic operation, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was “treated”, “reacted”, “allowed to react”, etc., with compound two. For example, treating indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis is used in selecting the conditions and apparatus for “treating” in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes and in the Examples (hereafter “exemplary schemes”) leads to various analogs of the specific exemplary materials produce. The above-cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as, for example, activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as, for example, antibodies, binding proteins, selective chelators such as, for example, crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

A single stereoisomer, *e.g.*, an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as, for example, formation of diastereomers using optically active resolving agents (Stereochemistry of Carbon Compounds, (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113, 3) 283-302). Racemic mixtures of chiral compounds of the disclosure can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as, for example, brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as, for example, carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as, for example, camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

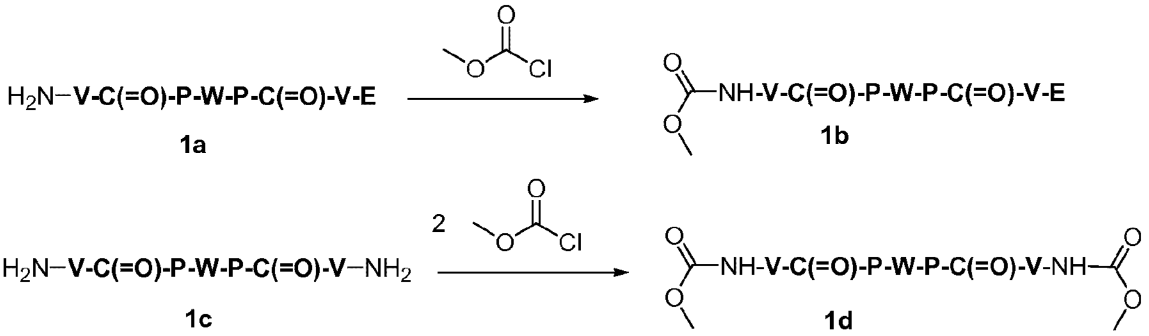
Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as, for example, menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched substrate. A method of determining optical purity involves making chiral esters, such as, for example, a menthyl ester, *e.g.*, (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as, for example, optical rotation and circular dichroism.

### *Schemes and Examples*

General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

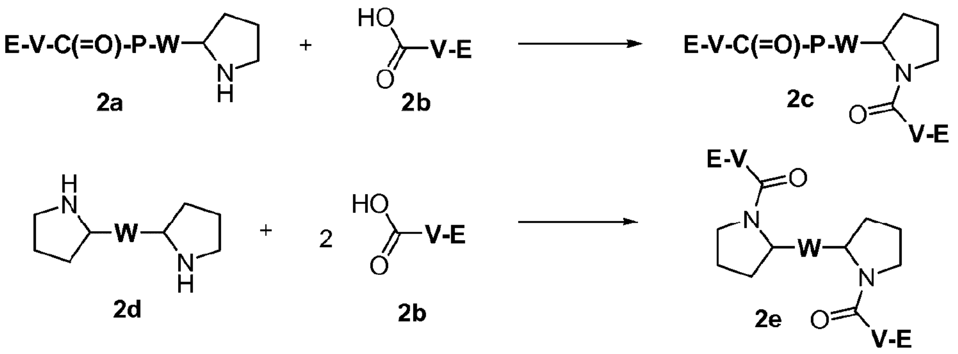
A number of exemplary methods for the preparation of compounds of the disclosure are provided herein, for example, in the Examples below. These methods are intended to illustrate the nature of such preparations and are not intended to limit the scope of applicable methods. Certain compounds of the disclosure can be used as intermediates for the preparation of other compounds of the disclosure. In the exemplary methods described herein, the fragment **E-V-** can also be written as **R9-**. PG represents a protecting group common for the given functional group that it is attached. The installation and removal of the protecting group can be accomplished using standard techniques, such as, for example, those described in Wuts, P. G. M., Greene, T. *Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons, Inc.: Hoboken, New Jersey, 2007.

**Scheme 1. Representative synthesis of E-V-C(=O)-P-W-P-C(=O)-V-E**



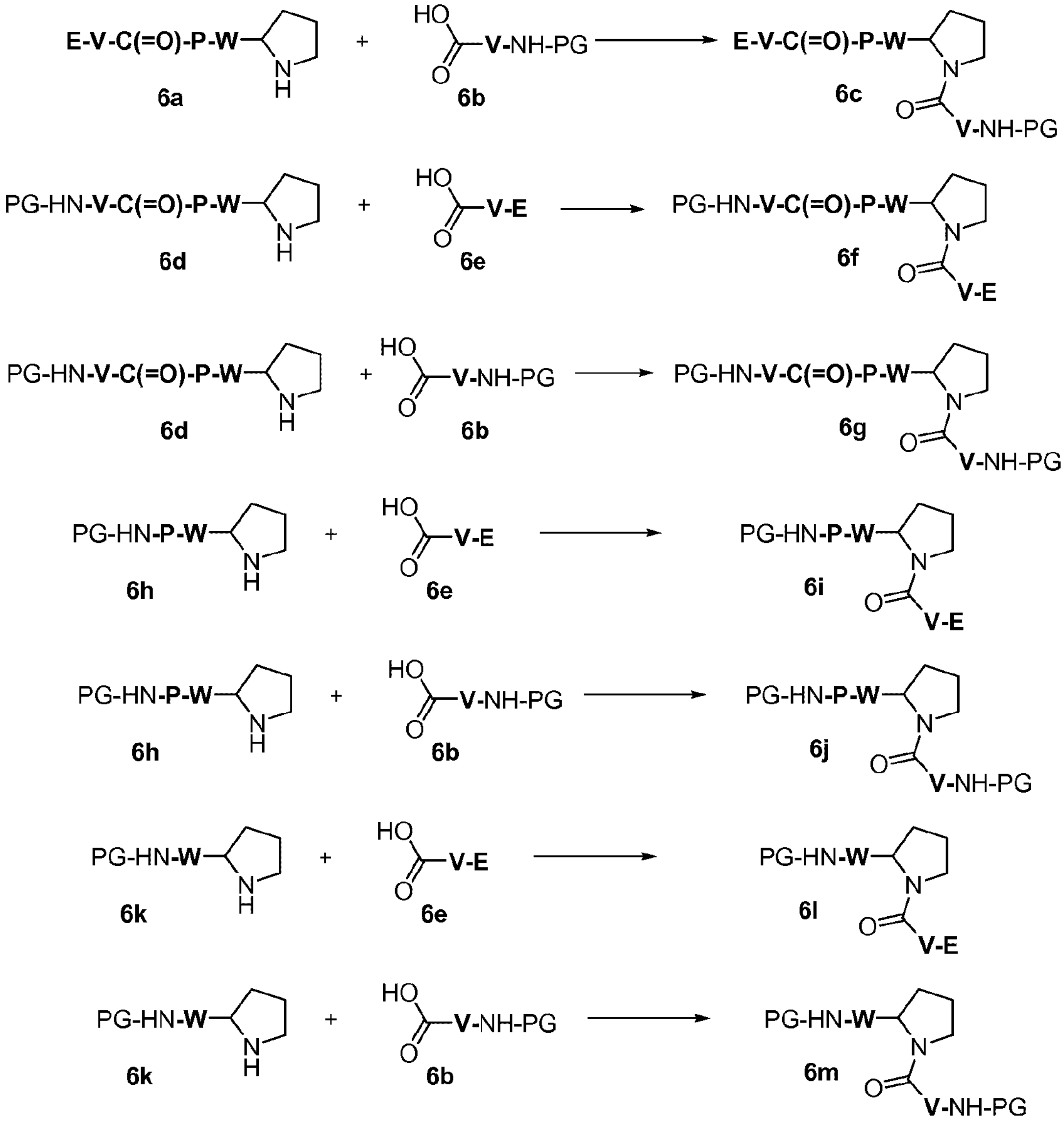
Scheme 1 shows a general synthesis of an **E-V-C(=O)-P-W-P-C(=O)-V-E** molecule of the invention wherein, for illustrative purposes, **E** is methoxycarbonylamino. The treatment of either **1a** or **1c** with one or two equivalents respectively of methyl chloroformate under basic conditions (e.g. sodium hydroxide) provides the molecule **1b** or **1d**.

**Scheme 2. Representative synthesis of E-V-C(=O)-P-W-P-C(=O)-V-E**



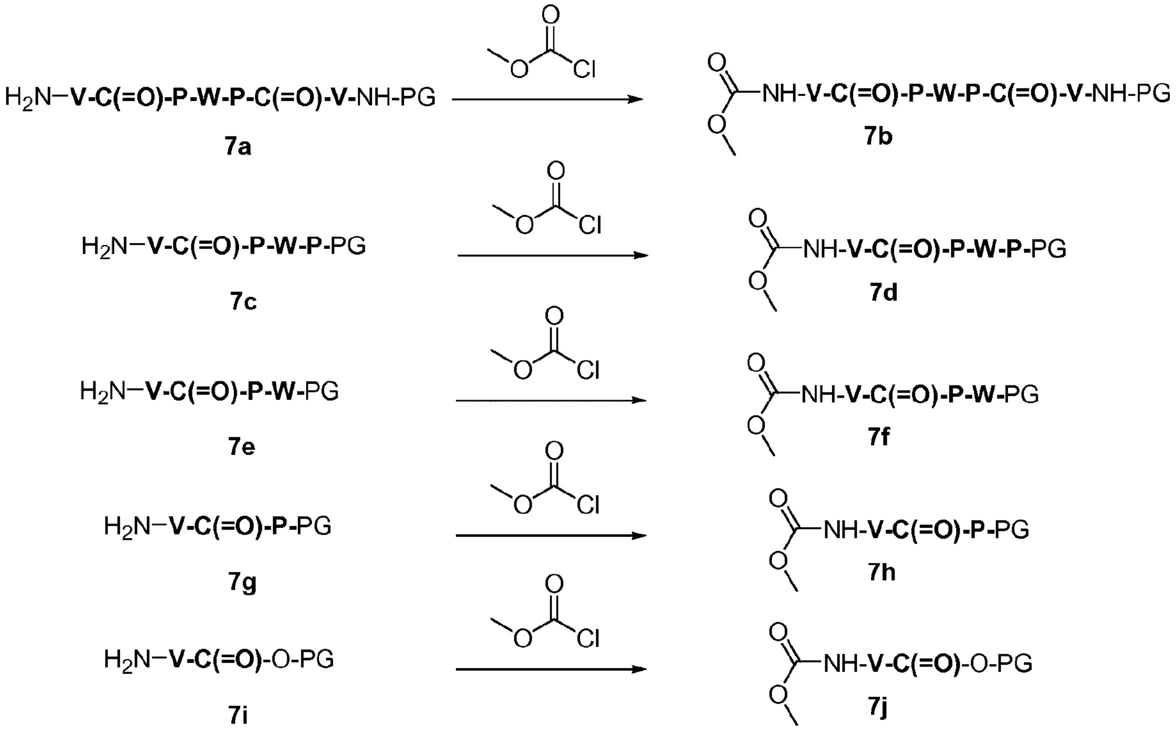
Scheme 2 shows a general synthesis of an **E-V-C(=O)-P-W-P-C(=O)-V-E** molecule of the invention wherein, for illustrative purposes, **P** is pyrrolidine. Coupling of amine **2a** with acid **2b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **2c**. Alternatively, amine **2d** is coupled with two equivalents of **2b** under similar conditions to provide **2e**.

**Scheme 6. Representative synthesis of R$^1$-V-C(=O)-P-R$^2$**



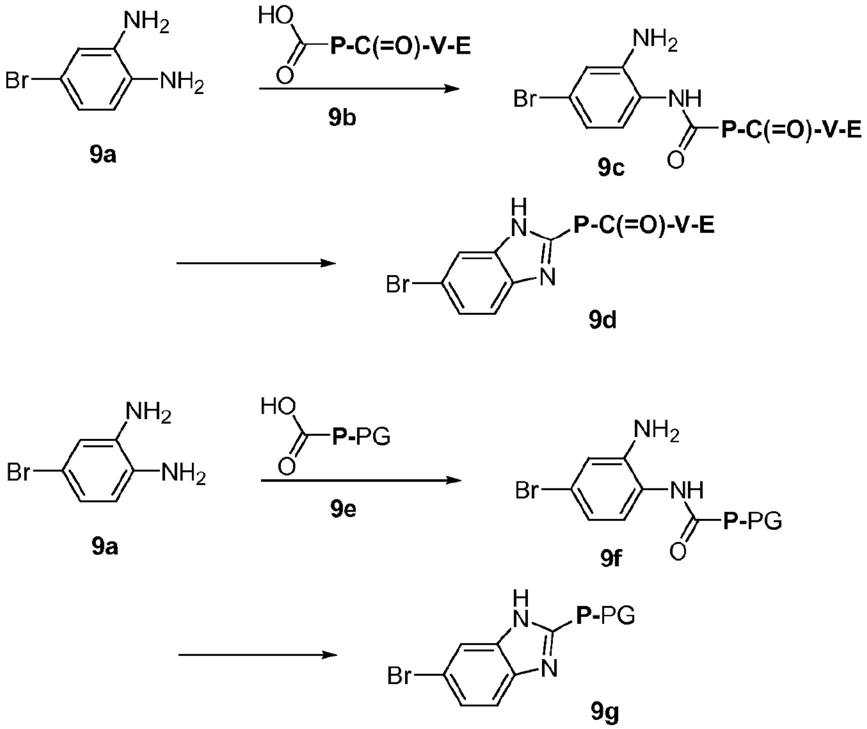
Scheme 6 shows a general synthesis of an R$^1$-**V-C(=O)-P**-R$^2$ intermediate wherein, for illustrative purposes, **P** is pyrrolidine, R$^1$ is a generic group that is depicted as either -**E** or a amino protecting group, and R$^2$ is a generic group that is depicted as -**W-P-C(=O)-V-E**, -**W-P-C(=O)-V**-NH-PG, -**W-P**-NH-PG, or -**W**-NH-PG. Coupling of amine **6a** (or **6d**, **6h**, **6k**) with acid **6b** or **6e** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **6c** (or **6f**, **6g**, **6i**, **6j**, **6l**, **6m**) respectively.

**Scheme 7. Representative synthesis of E-V-C(=O)-R$^1$**



Scheme 7 shows a general synthesis of an **E-V-C(=O)**-R$^1$ intermediate wherein, for illustrative purposes, **E** is methoxycarbonylamino and R$^1$ is a generic group that is depicted as either **-P-W-P-**C(**=O**)**-V**-NH-PG, **-P-W-P-**PG, **-P-W-**PG, **-P-**PG, or -O-PG. Treatment of **7a** (or **7c**, **7e**, **7g**, **7i**) with methyl chloroformate under basic conditions (e.g. sodium hydroxide) provides the molecule **7b** (or **7d**, **7f**, **7h**, **7j**).

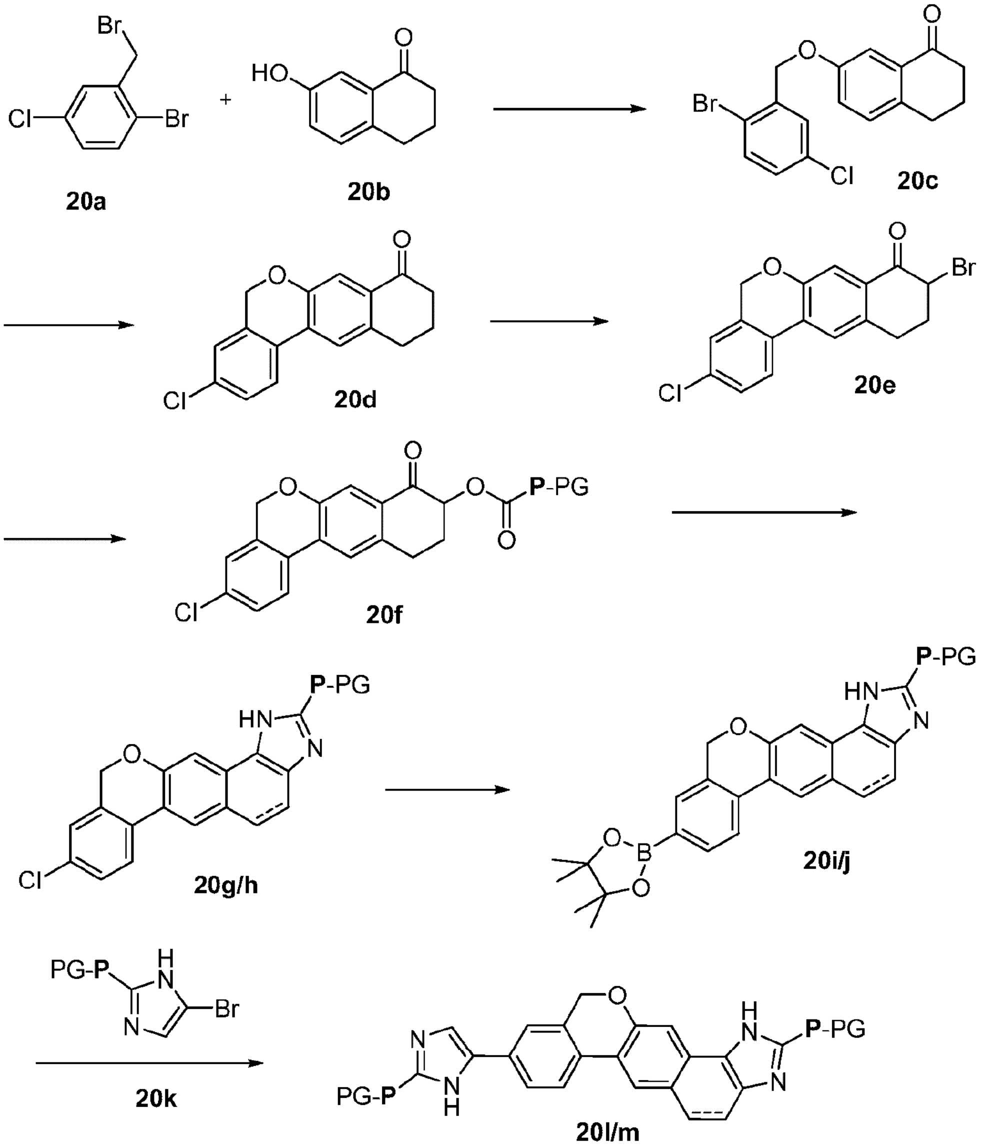
### Scheme 9. Representative synthesis of R$^1$-P-R$^2$



Scheme 9 shows a general synthesis of an R$^1$-**P**-R$^2$ intermediate wherein, for illustrative purposes, R$^1$ is **-C(=O)-V-E** or a protecting group and R$^2$ is a substituted benzamidazole. The formation of the benzimidazole is accomplished by coupling the acid **9b** or **9e** with an arylamine **9a**, using a peptide coupling reagent such as HATU, to afford **9c** or **9d**. Cyclization of the amide in the presence an acid (such as acetic acid) affords the benzimidazole containing molecule **9d** or **9g**.

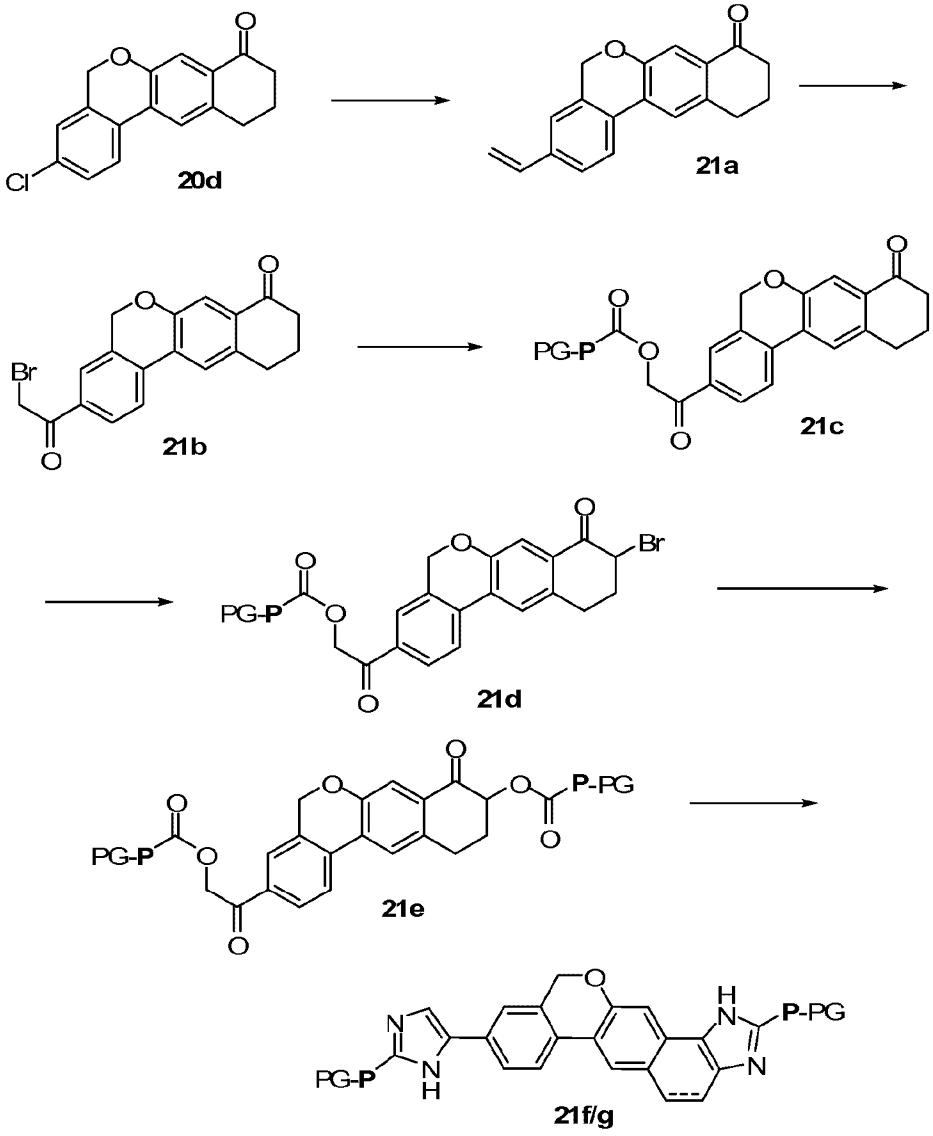
The formation of multiple benzimidazoles is performed in the same manner, starting with a bis-diamine to provide the corresponding bis-benzamidazole.

**Scheme 20. Representative synthesis of R$^1$-P-W-P-R$^2$**



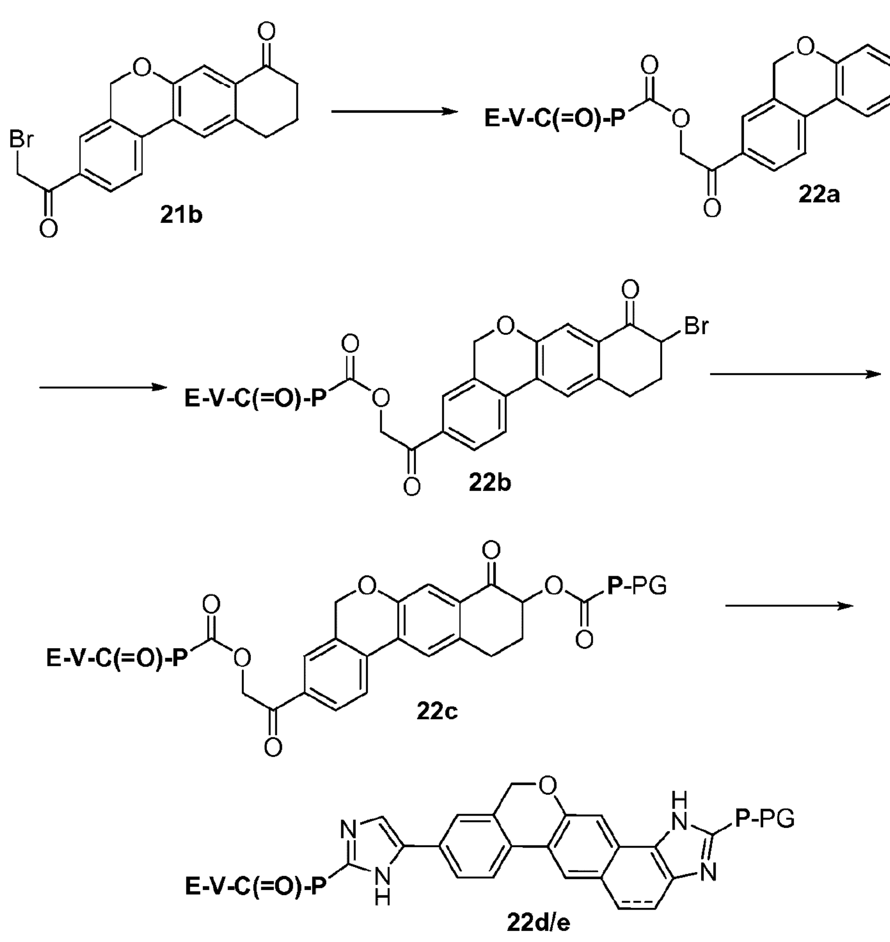
Scheme 20 shows a general synthesis of an R$^1$-**P-W-P**-R$^2$ intermediate of the invention wherein, for illustrative purposes, R$^1$ and R$^2$ are independent protecting groups and **W** is a two aromatic ring unit constructed via a transition metal mediated cyclization. Alkylation of phenol **20b** with an alkyl bromide, such as **20a**, provides the ether **20c**. Cyclization of the aromatic rings in the presence of a palladium catalyst provides the compound **20d**. Treatment of **20d** with $CuBr_2$ provides the α-haloketone **20e**, which provides **20f** upon addition of an acid under basic conditions (e.g. $Et_3N$). Reaction of **20f** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **20g**. Oxidation of **20g**, **20i**, or **20l** can be accomplished by heating in the presence of $MnO_2$ to provide **20h**, **20j**, or **20m**, respectively. Conversion of **20g** or **20h** with a palladium catalyst, such as $Pd_2dba_3$ and X-Phos, and a boron source such as bis(pinacolato)diboron provides the boronic ester **20i** or **20j**. The boronic ester is coupled with an appropriate coupling partner (e.g. **20k**) using a palladium catalyst, such as $Pd(PPh_3)_4$ or $PdCl_2(dppf)$, to afford **20l** or **20m**. For each transition metal mediated cross-coupling reaction, the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Other transition metal mediated cross couplings that enable the construction of **W**, but employ alternative coupling partners and reagents, include, but are not limited to, the Negishi, Kumada, Stille, and Ullman couplings. For the preparation of alternate two aromatic ring containing **W** groups, this general scheme can be applied through the appropriate choice of the starting reagents.

**Scheme 21. Representative synthesis of $R^1$-P-W-P-$R^2$**



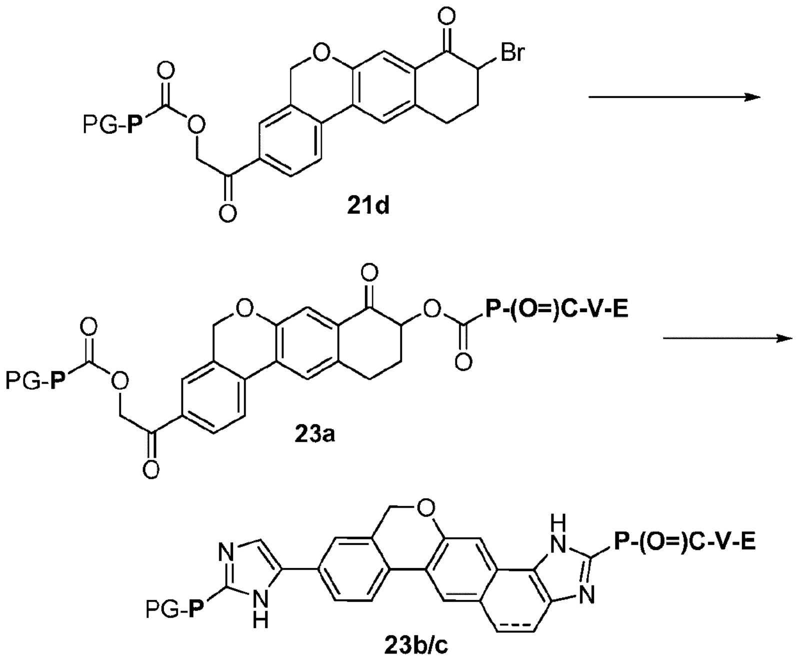
Scheme 21 shows a general synthesis of an $R^1$-**P-W-P**-$R^2$ intermediate of the invention wherein, for illustrative purposes, $R^1$ and $R^2$ are independent protecting groups and **W** is a two aromatic ring unit constructed via a transition metal mediated cyclization. Treatment of **20d** with an activated vinyl reagent (e.g. potassium vinyltrifluoroborate) in the presence of a palladium catalyst (e.g. palladium acetate and S-Phos) provides the vinyl compound **21a**. Conversion to the corresponding α-halo ketone can be accomplished by bromination with N-bromosuccinimide, followed by oxidation with $MnO_2$. Displacement of the α-halo ketone proceeds by the addition of an acid under basic conditions (e.g. $Et_3N$). Bromination of **21d** proceeds upon treatment with pyridinium tribromide, and is followed by the addition of a second acid under basic conditions to provide the diester **21e**. Reaction of **21e** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **21f**. Oxidation of **21f** can be accomplished in the presence of $MnO_2$ to provide **21g**.

**Scheme 22. Representative synthesis of E-V-C(=O)-P-W-P-R**



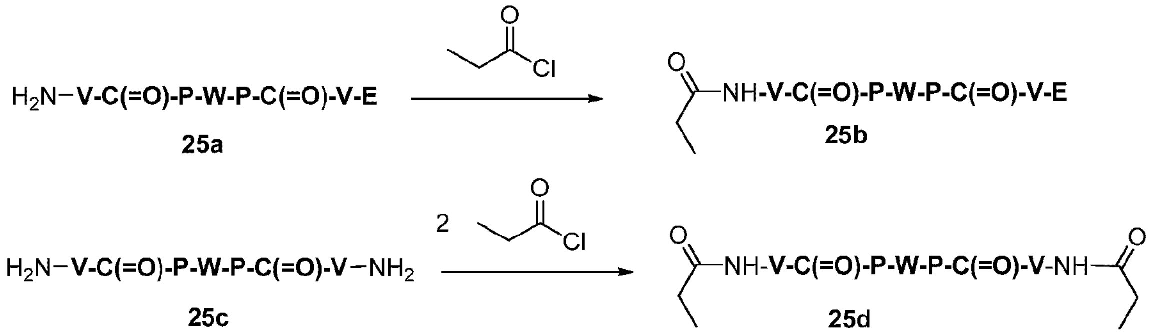
Scheme 22 shows a general synthesis of an **E-V-C(=O)-P-W-P-**R intermediate of the invention wherein, for illustrative purposes, R is a protecting group and **W** is a two aromatic ring unit. Displacement of the α-halo ketone **21b** proceeds by the addition of an acid under basic conditions (e.g. $Et_3N$). Bromination of **22b** proceeds upon treatment with pyridinium tribromide, and is followed by the addition of a second acid under basic conditions to provide the diester **22c**. Reaction of **22c** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **22d**. Oxidation of **22d** can be accomplished in the presence of $MnO_2$ to provide **22e**.

**Scheme 23. Representative synthesis of R-P-W-P-C(=O)-V-E**



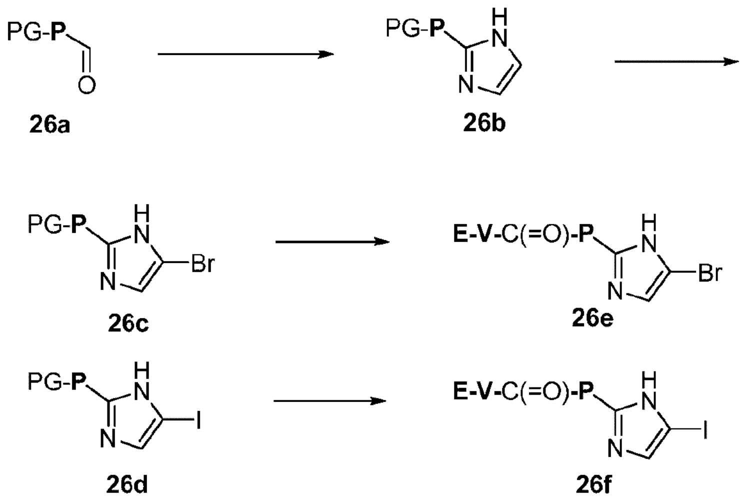
Scheme 23 shows a general synthesis of an **E-V-C(=O)-P-W-P-**R intermediate of the invention wherein, for illustrative purposes, R is a protecting group and **W** is a two aromatic ring unit. Displacement of the α-halo ketone **21d** proceeds by the addition of an acid under basic conditions (e.g. $Et_3N$). Reaction of **23a** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **23b**. Oxidation of **23b** can be accomplished in the presence of $MnO_2$ to provide **23c**.

### Scheme 25. Representative synthesis of E-V-C(=O)-P-W-P-C(=O)-V-E



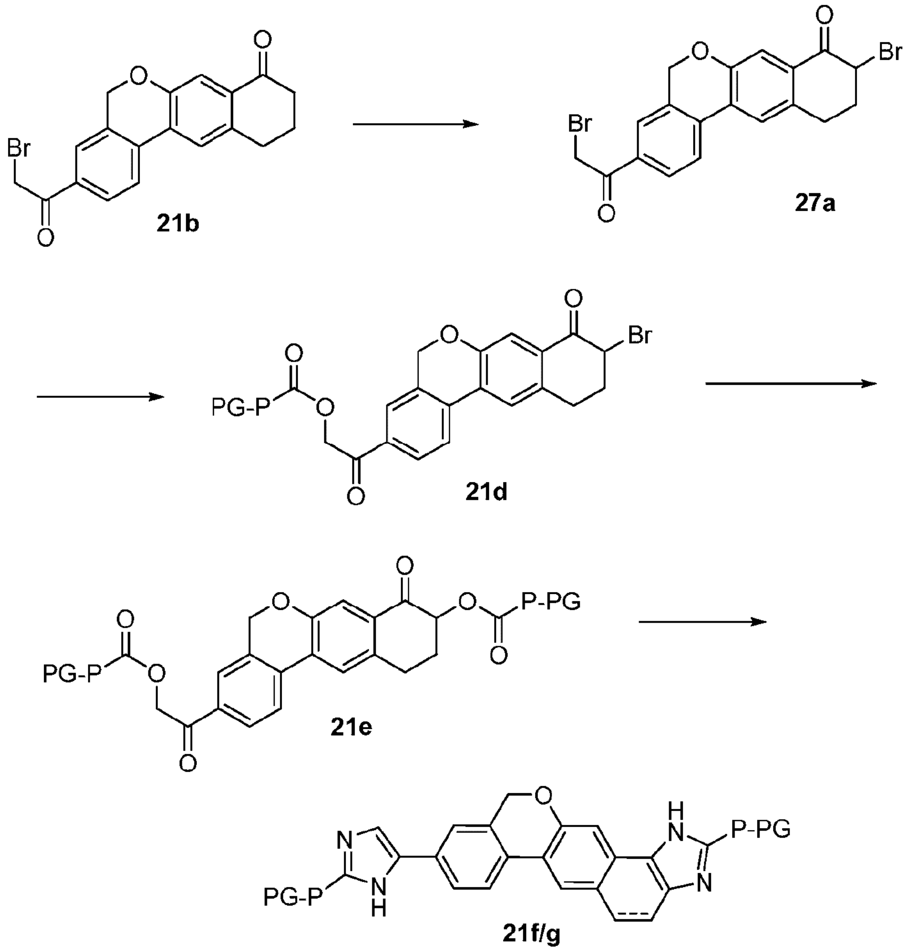
Scheme 25 shows a general synthesis of an **E-V-C(=O)-P-W-P-C(=O)-V-E** molecule of the invention wherein, for illustrative purposes, **E** is ethylcarbonylamino. The treatment of either **25a** or **25c** with one or two equivalents respectively of propionyl chloride under basic conditions (e.g. sodium hydroxide) provides the molecule **25b** or **25d**.

### Scheme 26. Representative syntheses of E-V-C(=O)-P-R and R$^1$-P-R



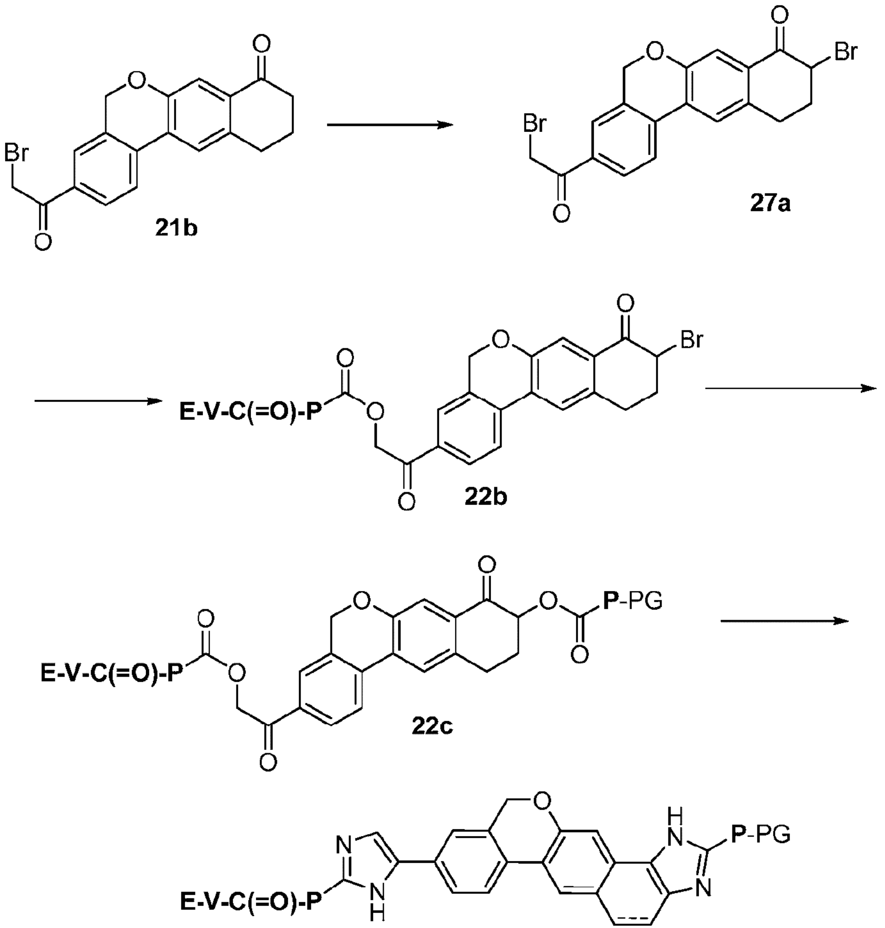
Scheme 26 shows a general synthesis of an **E-V-C(=O)-P**-R and an R$^1$-**P**-R molecule of the invention wherein, for illustrative purposes R is a haloimidazole. Treatment of the aldehyde **26a** with glyoxal, in the presence of ammonium hydroxide provides the imidazole **26b**. Treatment with either N-bromosuccinamide or iodine provides the corresponding haloimidazole **26c** and **26d** respectively. Separation from the corresponding bis-halogenated compound can be accomplished by preparative HPLC chromatography. The conversion of the bis-haloimidazole to the mono-haloimidazole can also be accomplished upon heating in the presence of sodium sulfite. Further functionalization of the **P** group can be accomplished upon removal of the protecting group and coupling with an appropriate acid (**E-V-**C(=O)-OH).

**Scheme 27. Representative synthesis of R$^1$-P-W-P-R$^2$**



Scheme 27 shows an alternate general synthesis of an R$^1$-**P-W-P**-R$^2$ intermediate of the invention wherein, for illustrative purposes, R$^1$ and R$^2$ are independent protecting groups and **W** is a two aromatic ring unit constructed via a transition metal mediated cyclization. Bromination of **21b** with a brominating agent (i.e. pyridinium tribromide) provides the dibromide **27a**. Displacement of the primary bromide then proceeds by the addition of an acid under basic conditions (e.g. $K_2CO_3$) to provide **21d**. Conversion to **21f** or **21g** can be accomplished following methods described in Scheme 21.

**Scheme 28. Representative synthesis of E-V-C(=O)-P-W-P-R**



Scheme 28 shows an alternate general synthesis of an **E-V-C(=O)-P-W-P-**R intermediate of the invention wherein, for illustrative purposes, R is a protecting group and **W** is a two aromatic ring unit. Bromination of **21b** with a brominating agent (i.e. pyridinium tribromide) provides the dibromide **27a**. Displacement of the primary bromide then proceeds by the addition of an acid under basic conditions (e.g. $K_2CO_3$) to provide **22d**. Conversion to **22d** or **22e** can be accomplished following methods described in Scheme 22.

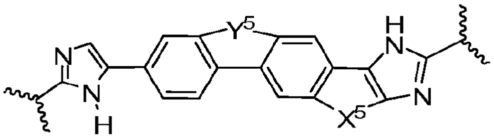
## Specific Embodiments

In one embodiment, provided is a compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{-}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b}\ (I)$$

wherein:

$W^{1a}$ is



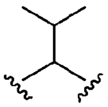
and $W^{1a}$ is optionally substituted with one or more groups independently selected from halo, alkyl, haloalkyl, optionally substituted aryl, optionally substituted heterocycle, and cyano;

$Y^5$ is -O-CH$_2$-, -CH$_2$-O-, -O-C(=O)-, or -C(=O)-O-; $X^5$ is -CH$_2$-CH$_2$- or -CH=CH-;

$E^{1a}$ is -N(H)(alkoxycarbonyl), -N(H)(cycloalkylcarbonyl) or -N(H)(cycloalkyloxycarbonyl); or $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$;

$E^{1b}$ is -N(H)(alkoxycarbonyl), -N(H)(cycloalkylcarbonyl) or -N(H)(cycloalkyloxycarbonyl); or $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$;

$V^{1a}$ and $V^{1b}$ are each independently selected from: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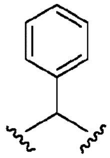
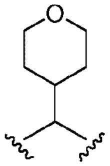
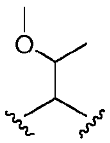

(ab)


(ac)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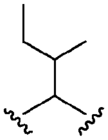
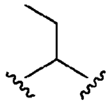

(ae)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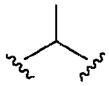
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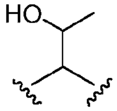
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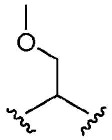
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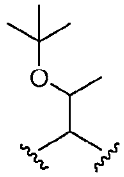
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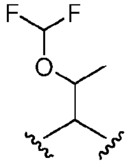
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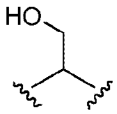
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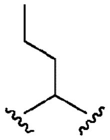
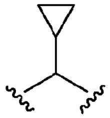
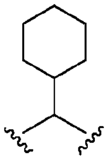
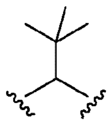
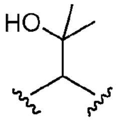

(am)


(an)


(ao)

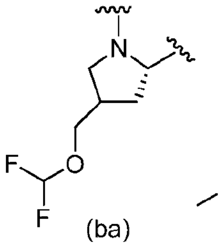

(ap)

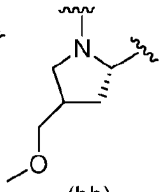
or

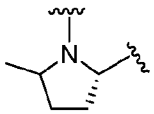

(aq)

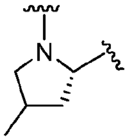
;

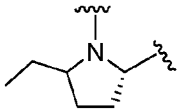
$P^{1a}$ is selected from:

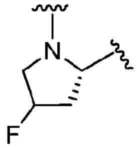

(ba)

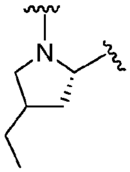

(bb)

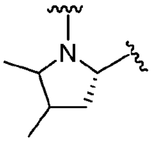

(bc)

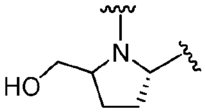

(bd)

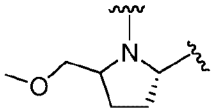

(be)


(bf)


(bg)


(bh)


(bi)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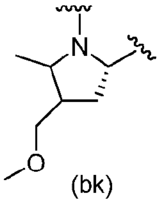
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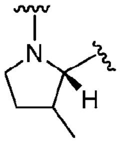
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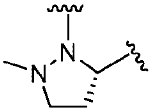
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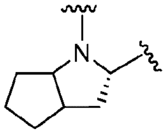
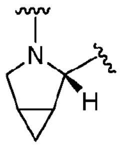
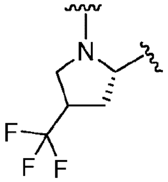
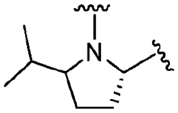

(bn)


(bo)


(bp)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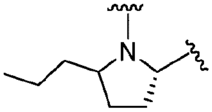
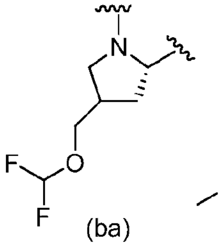
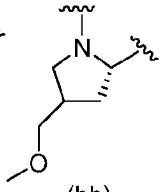
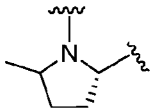


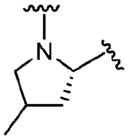
(bq) (br)

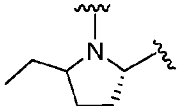
$P^{1b}$ is selected from:

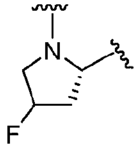

(ba)


(bb)


(bc)


(bd)


(be)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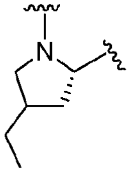
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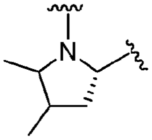
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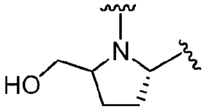
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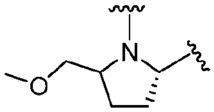
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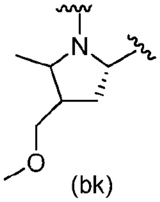
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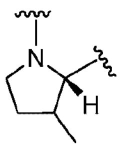
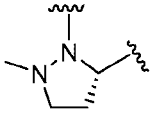
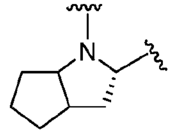
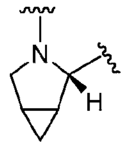

(bl)


(bm)


(bn)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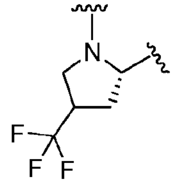
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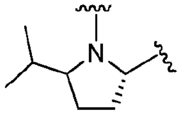
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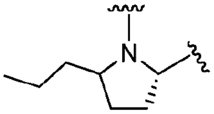
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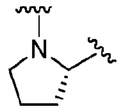
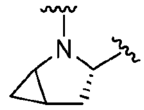
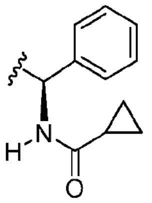

(bs)

or

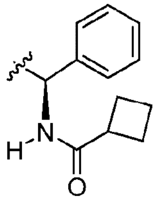

(bt)

and

$R^{9a}$ and $R^{9b}$ are each independently selected from:



or



;

or a pharmaceutically acceptable salt or prodrug thereof;

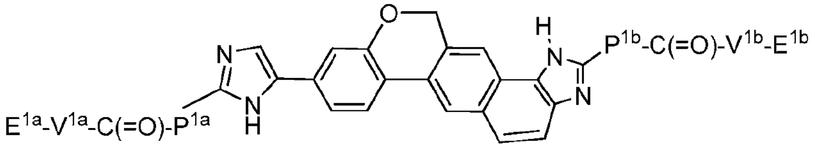
provided that when $Y^5$ is -O-CH$_2$-, or -CH$_2$-O-, then at least one of the following occurs:

(1) at least one of $V^{1a}$ and $V^{1b}$ is selected from (af), (ag), (ah), (ai), (aj), (ak), (al), (am), (an), (ao), (ap) or (aq); or

(2) $P^{1a}$ is selected from (be), (bf), (bg), (bh), (bi), (bj), (bk), (bl), (bm), (bn), (bo), (bq) or (br); or

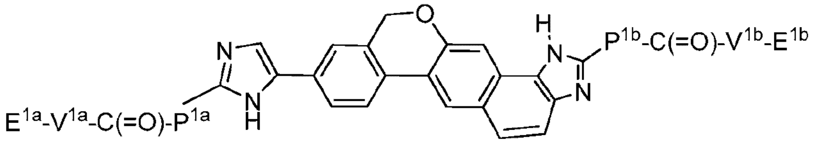
(3) $P^{1b}$ is selected from (be), (bf), (bg), (bh), (bi), (bj), (bk), (bl), (bm), (bn), (bo), (bp), (bq) or (br).

In one embodiment, he compound of formula (I) is represented by formula:

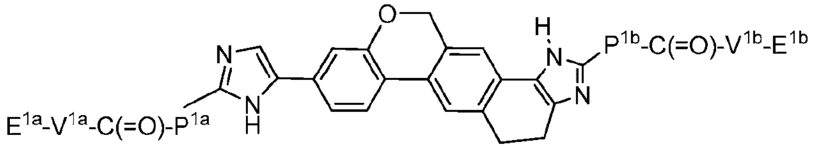


**(A1)**

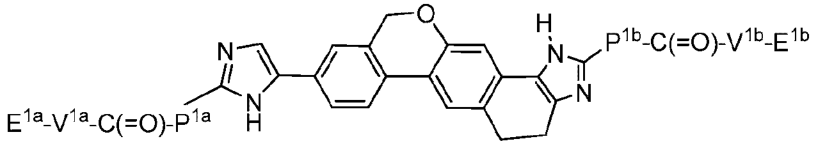
;



**(A2)** ;



**(A3)** ; or

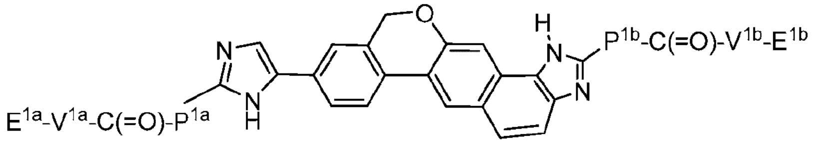


**(A4)**

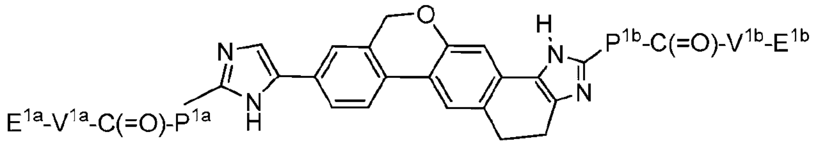
wherein the imidazole ring shown in formula **(A1)**, **(A2)**, **(A3)** and **(A4)** is optionally substituted with one or more groups independently selected from halo, haloalkyl, cyano, and alkyl;

or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of formula (I) is represented by formula:



**(A2)** ; or



**(A4)**

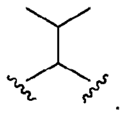
wherein the imidazole ring shown in formula **(A2)** and **(A4)** is optionally substituted with one or more groups independently selected from halo, haloalkyl, cyano, and alkyl;

or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, at least one of $E^{1a}$ and $E^{1b}$ is -N(H)(alkoxycarbonyl). In one embodiment, at least one of $E^{1a}$ and $E^{1b}$ is -N(H)C(=O)OMe. In another embodiment, both of $E^{1a}$ and $E^{1b}$ are -N(H)C(=O)OMe.

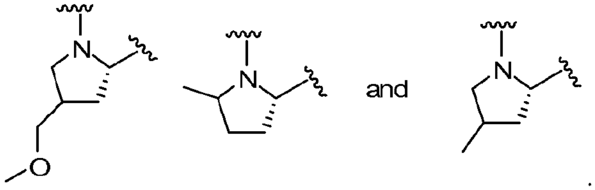
In one embodiment, at least one of $E^{1a}$ and $E^{1b}$ is -N(H)(cycloalkylcarbonyl) or -N(H)(cycloalkyloxycarbonyl). In one embodiment, at least one of $E^{1a}$ and $E^{1b}$ is cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopropyloxycarbonylamino or cyclobutyloxycarbonylamino. In another embodiment, $E^{1a}$ and $E^{1b}$ are each independently selected from cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopropyloxycarbonylamino and methoxycarbonylamino.

In one embodiment, at least one of $V^{1a}$ and $V^{1b}$ is:

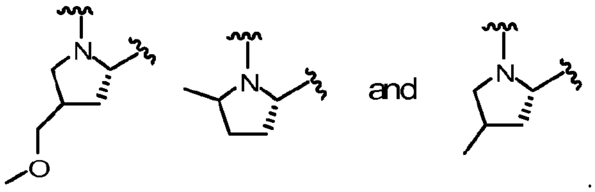


In one embodiment, $E^{1a}$-$V^{1a}$ taken together are $R^{9a}$ or wherein $E^{1b}$-$V^{1b}$ taken together are $R^{9b}$.

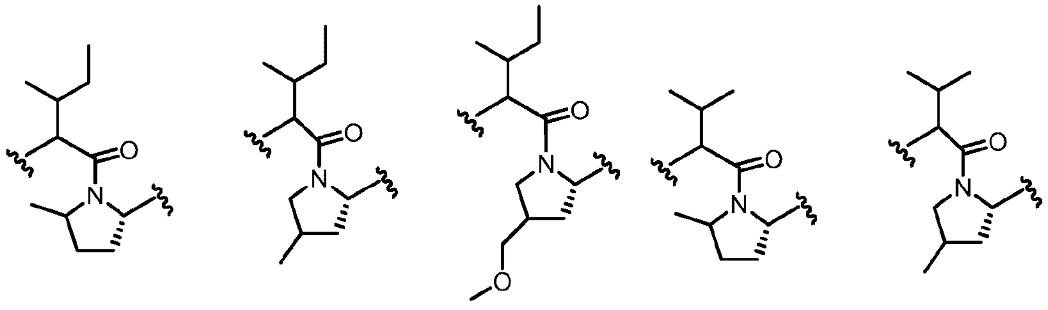
In one embodiment, at least one of $P^{1a}$ and $P^{1b}$ is selected from:

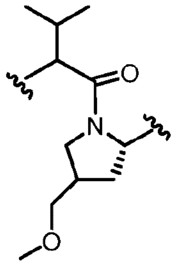
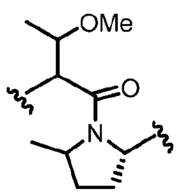
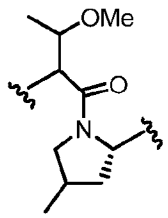
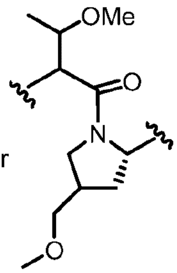


In one embodiment, $P^{1a}$ and $P^{1b}$ are each independently selected from:



In one embodiment, at least one of -$V^{1a}$ –C(=O)-$P^{1a}$ – and -$P^{1b}$-C(=O)-$V^{1b}$- is:






or

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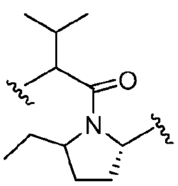
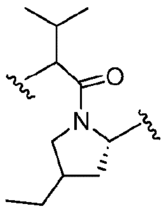
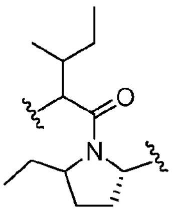
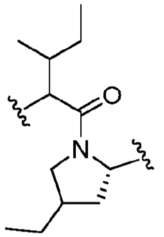
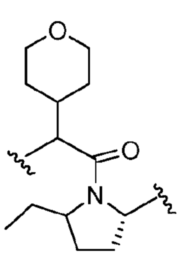
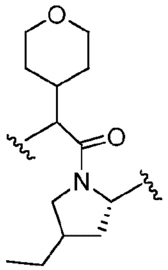
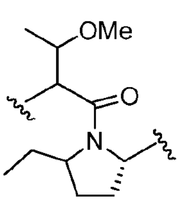
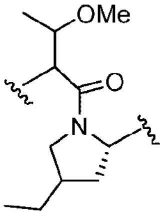
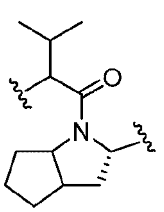
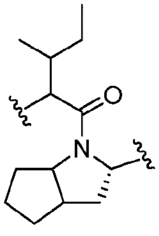
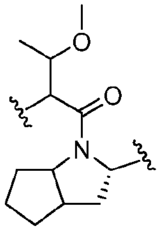
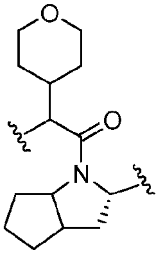
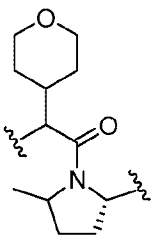
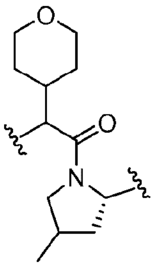
In another embodiment, at least one of -$V^{1a}$ –C(=O)-$P^{1a}$ – and -$P^{1b}$-C(=O)-$V^{1b}$- is: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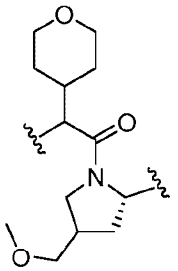
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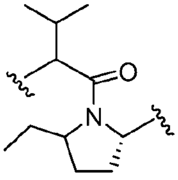
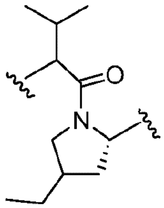
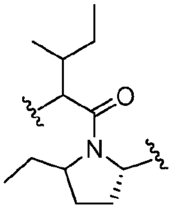
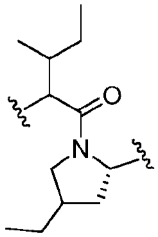
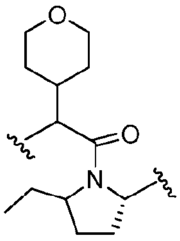
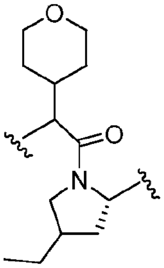
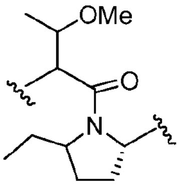
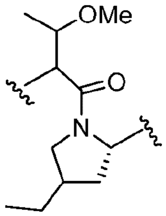
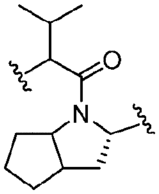
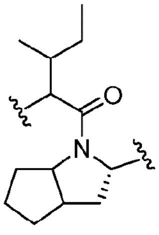
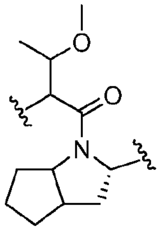
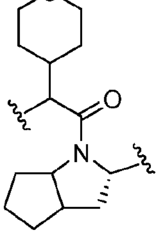
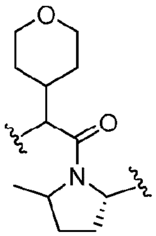
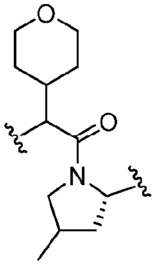
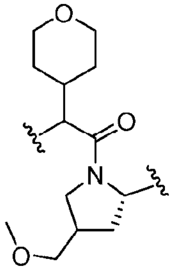
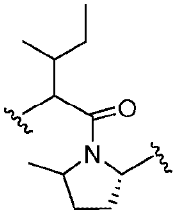
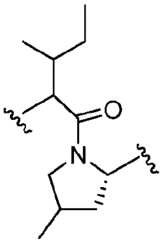
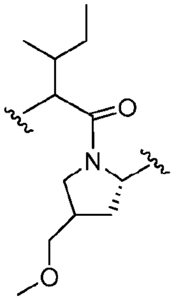
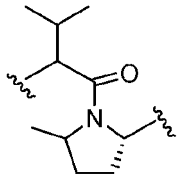
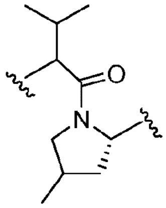
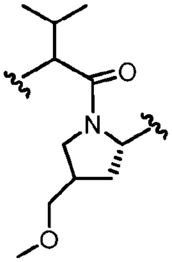
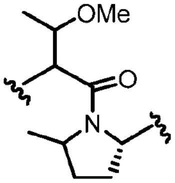
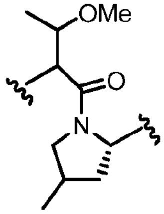
In yet another embodiment, -$V^{1a}$ –C(=O)-$P^{1a}$ – and -$P^{1b}$-C(=O)-$V^{1b}$- are each independently:

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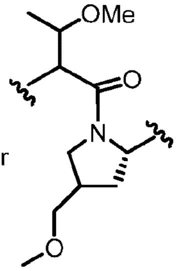
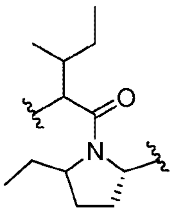
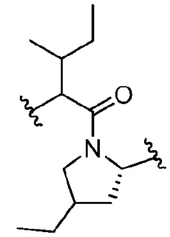
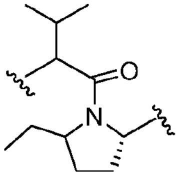
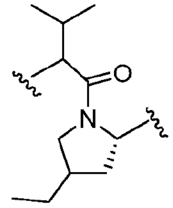
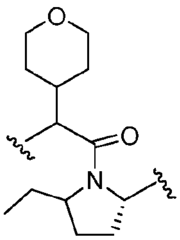
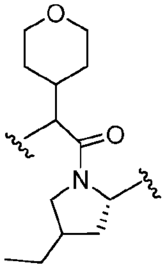
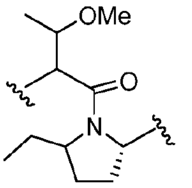
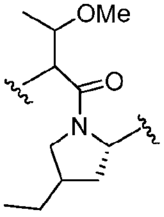
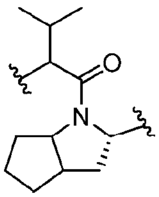
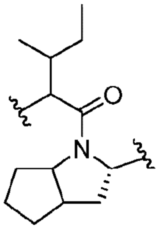
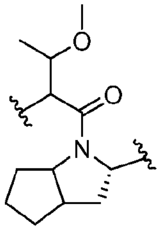
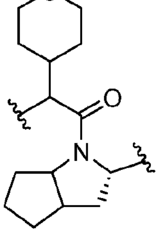
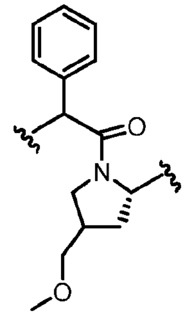
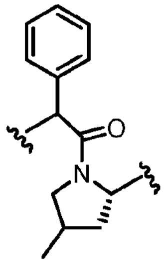
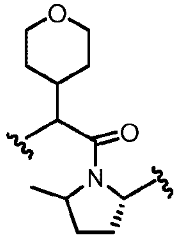
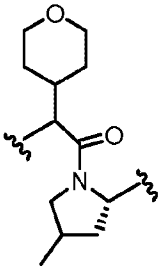
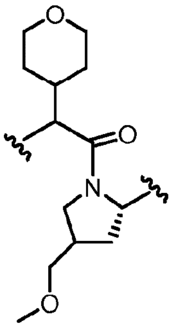
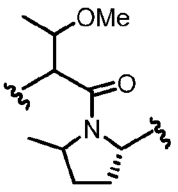
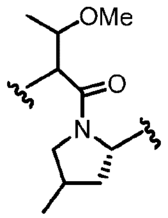


.

In one embodiment, one of $-V^{1a}-C(=O)-P^{1a}-$ and $-P^{1b}-C(=O)-V^{1b}-$ is:

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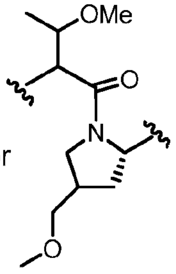
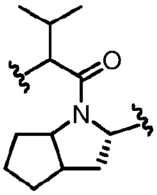
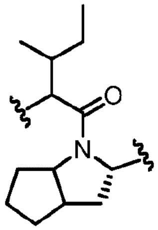
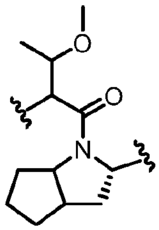


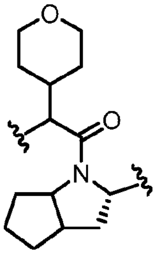
;

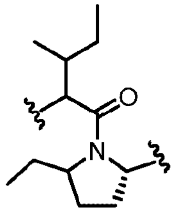
and the other of -$V^{1a}$ –C(=O)-$P^{1a}$ – and -$P^{1b}$-C(=O)-$V^{1b}$- is:

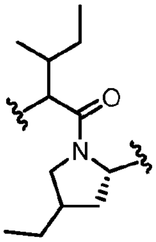


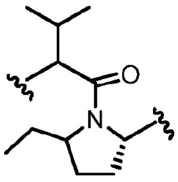


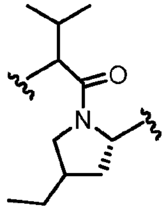


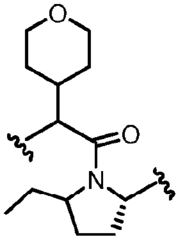


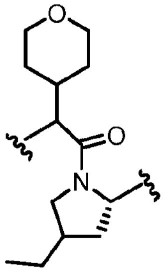


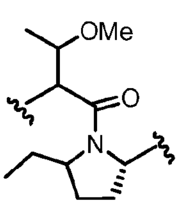


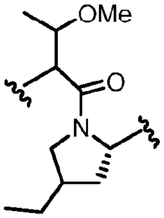


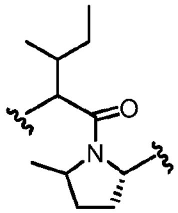


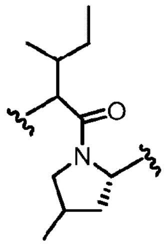


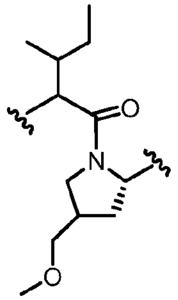


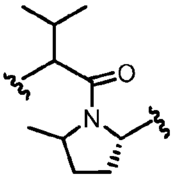


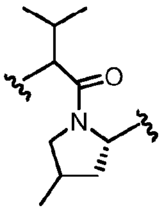


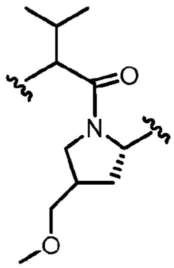


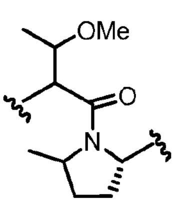


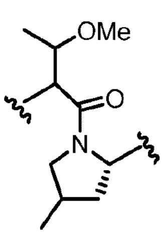












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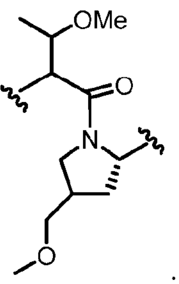

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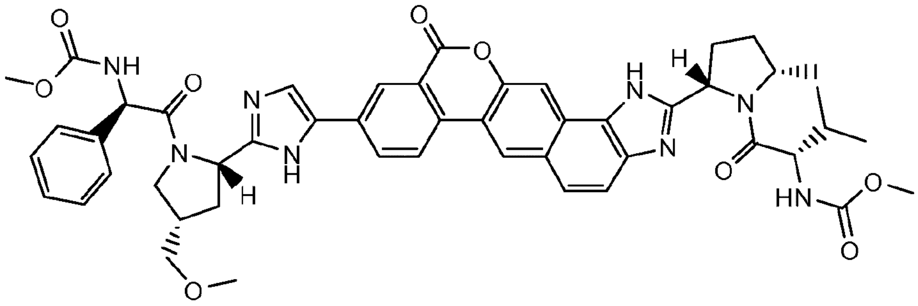
In one embodiment, the disclosure provides a compound of formula:

97



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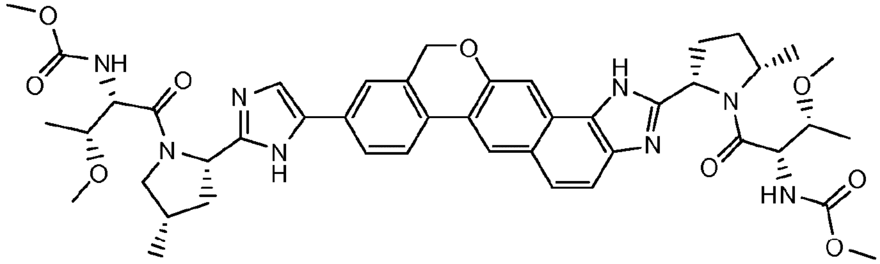

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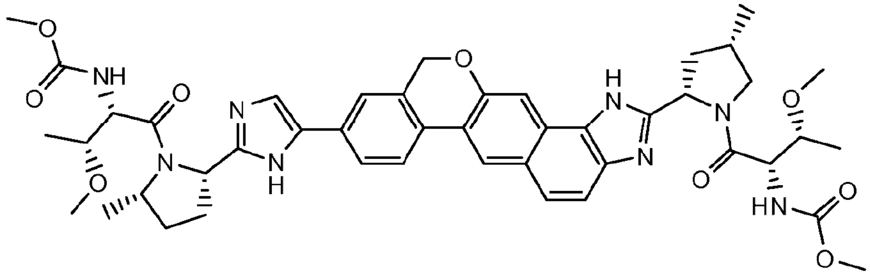

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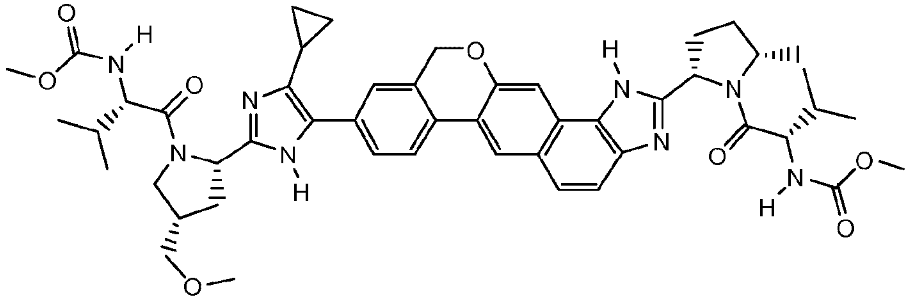

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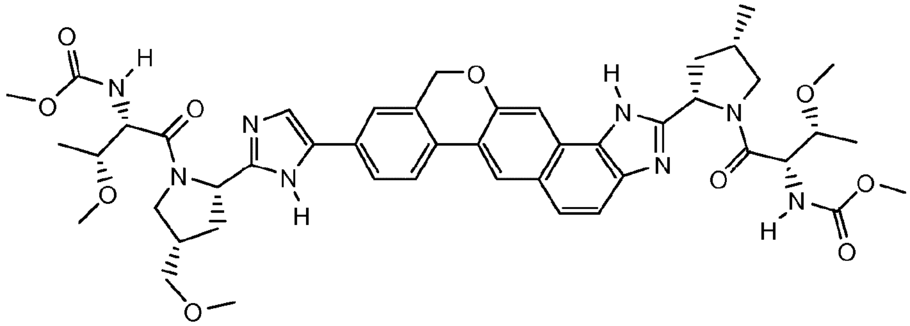

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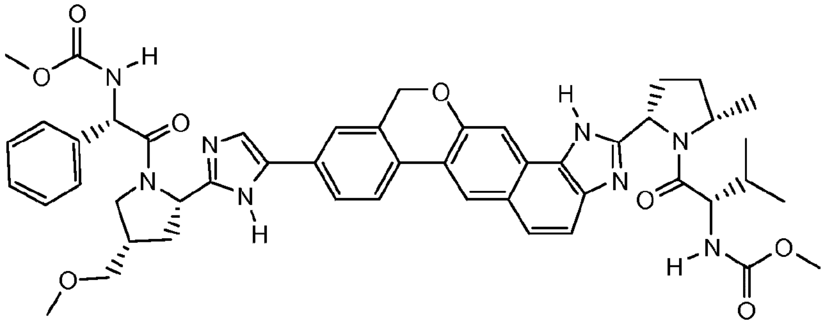

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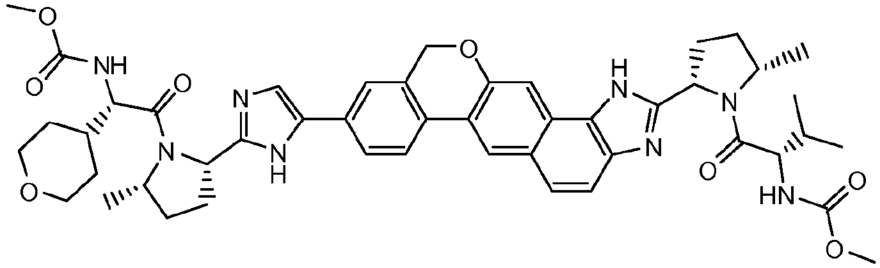

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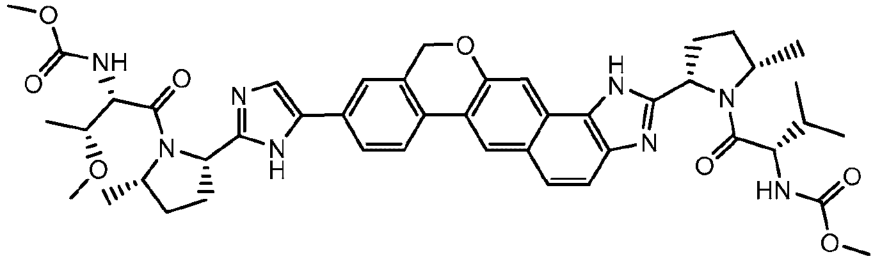

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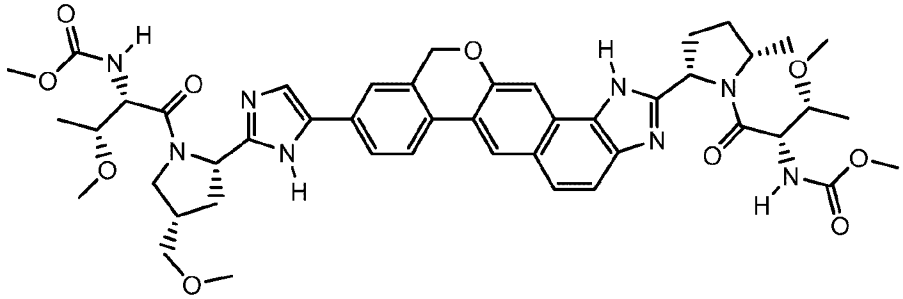

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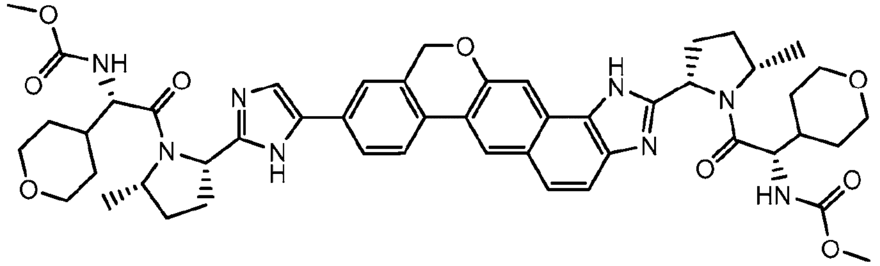

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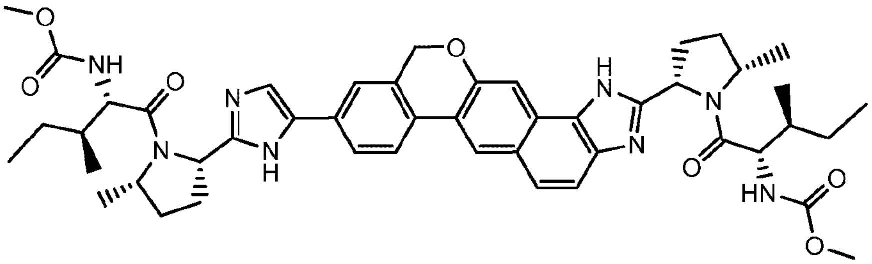

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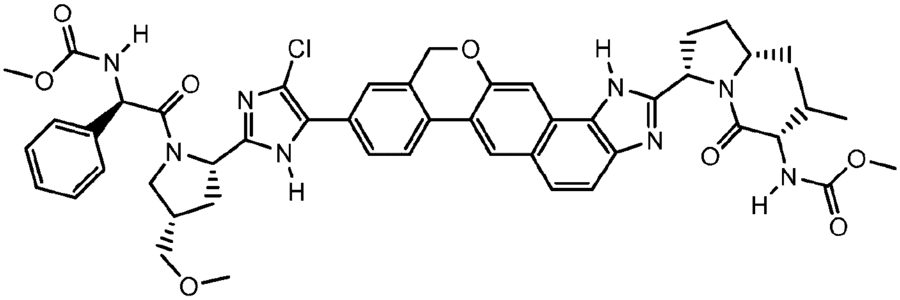

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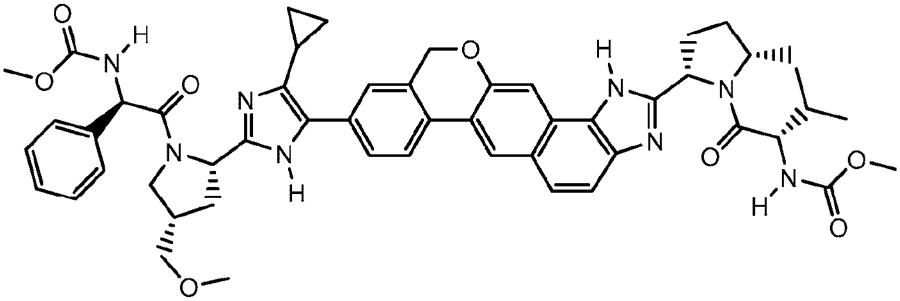

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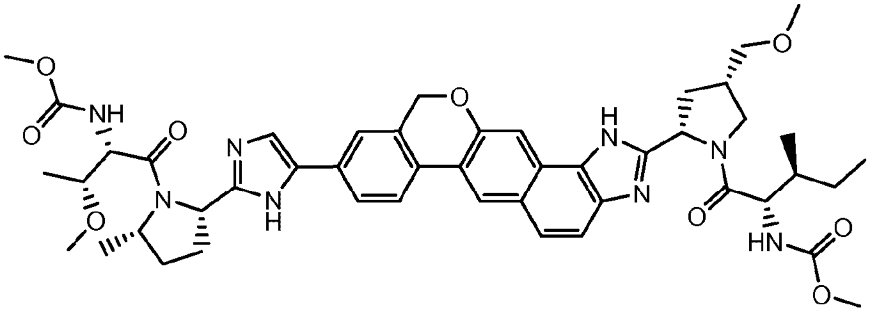

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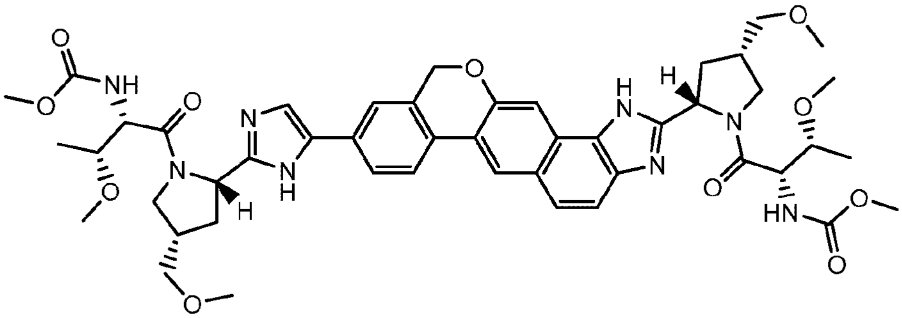

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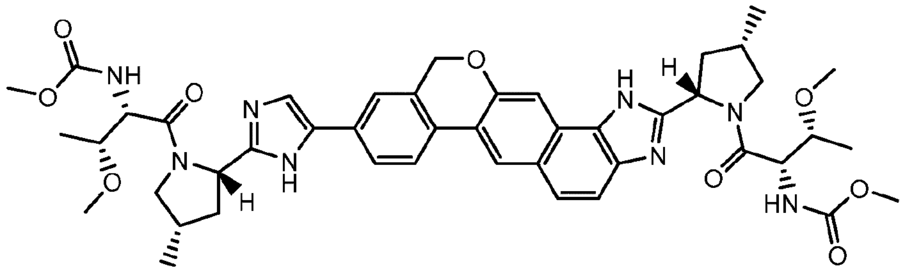

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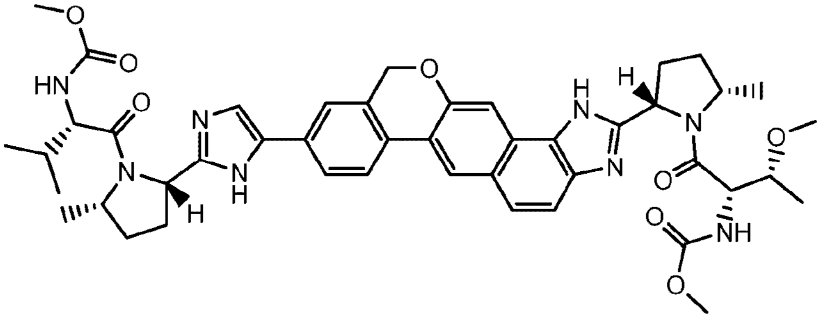

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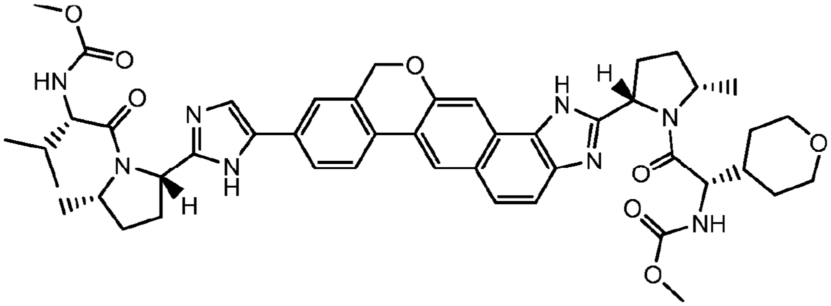

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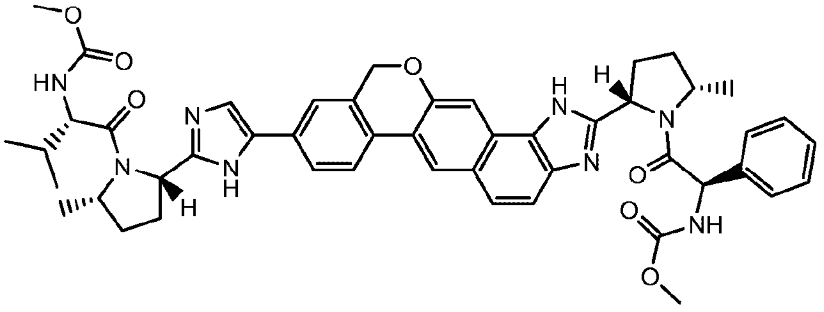

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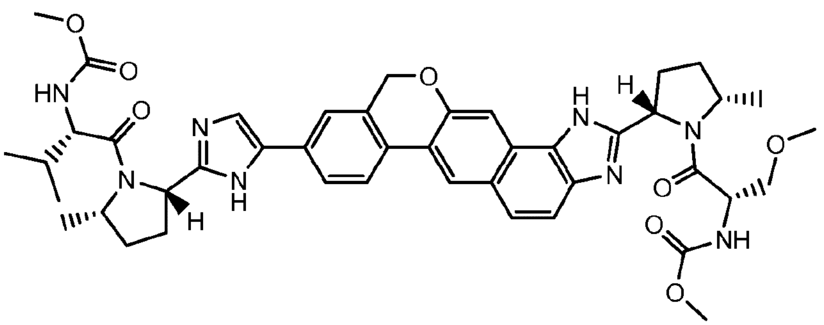

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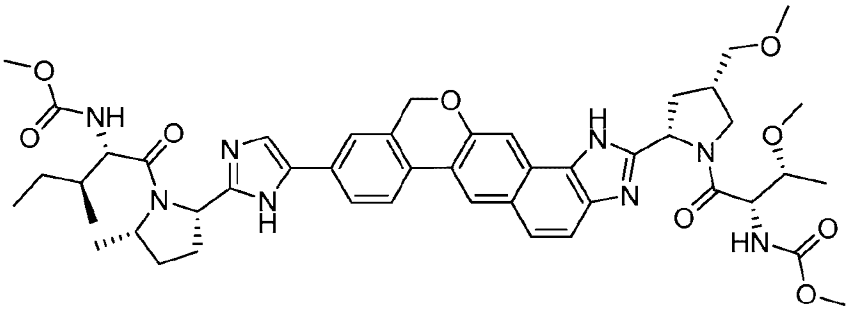

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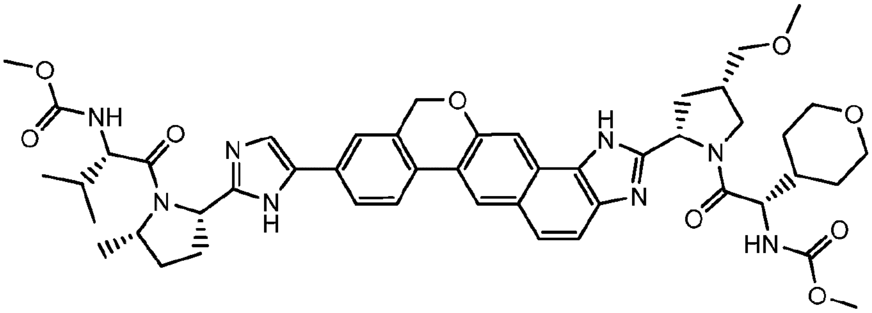

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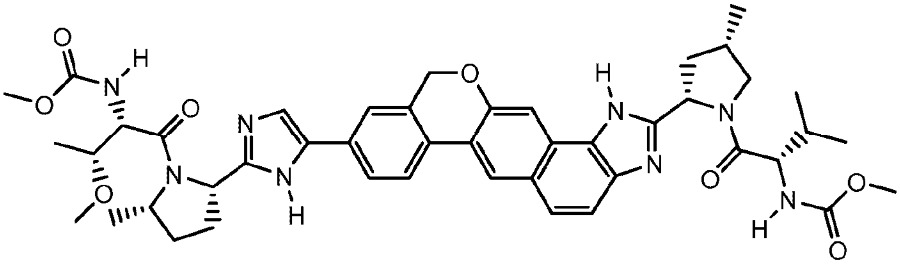

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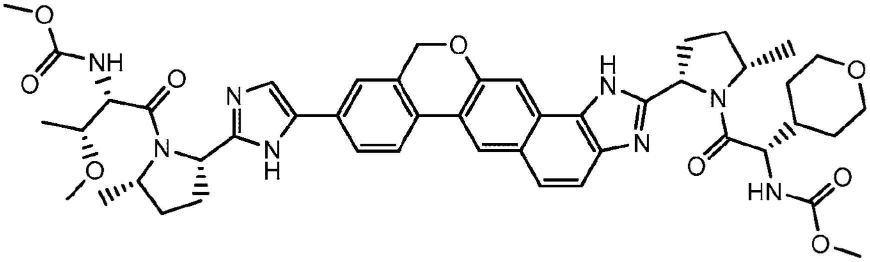

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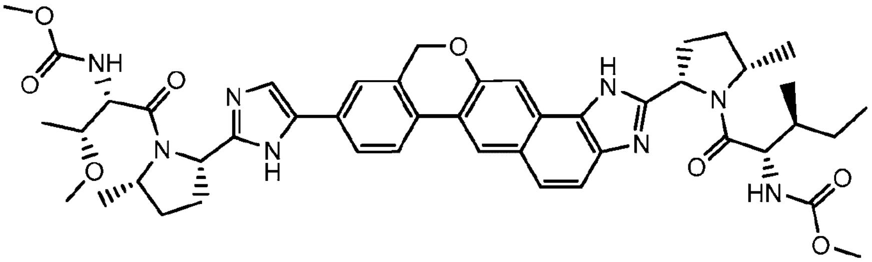

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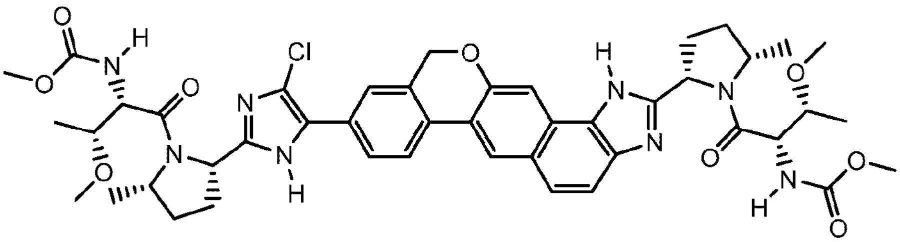

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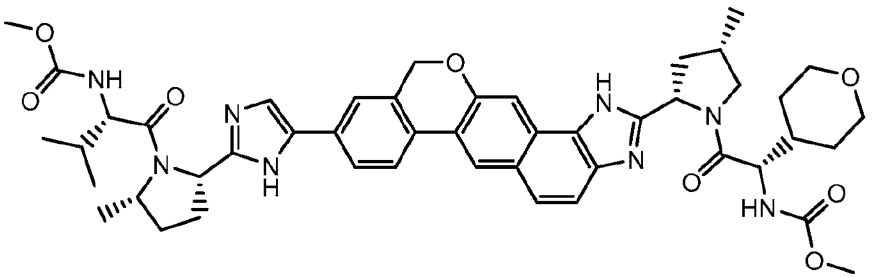

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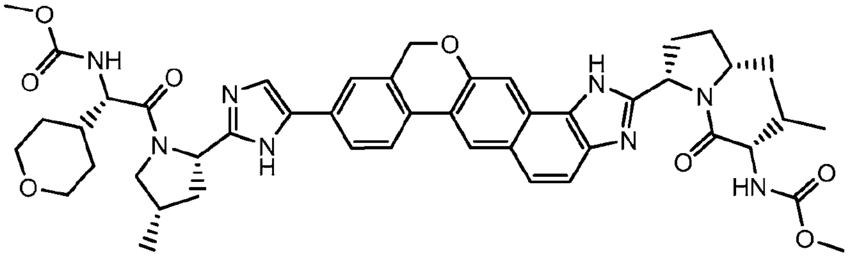

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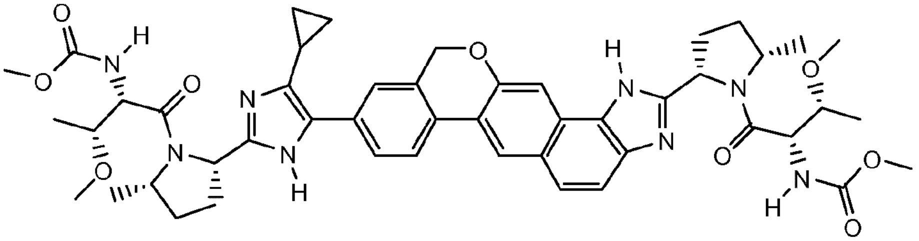

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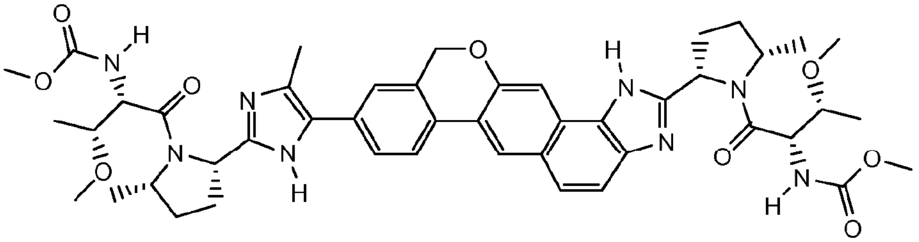

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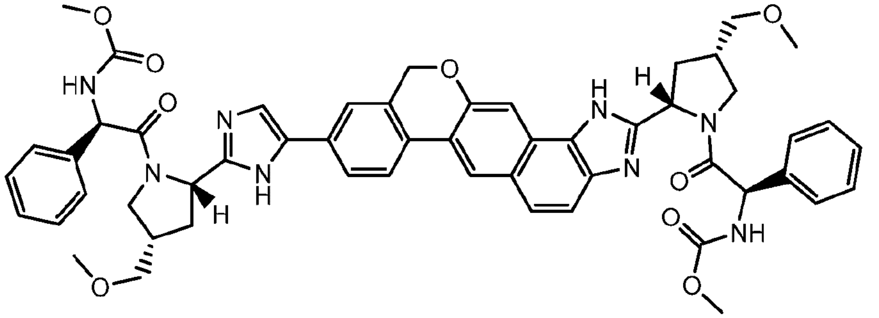

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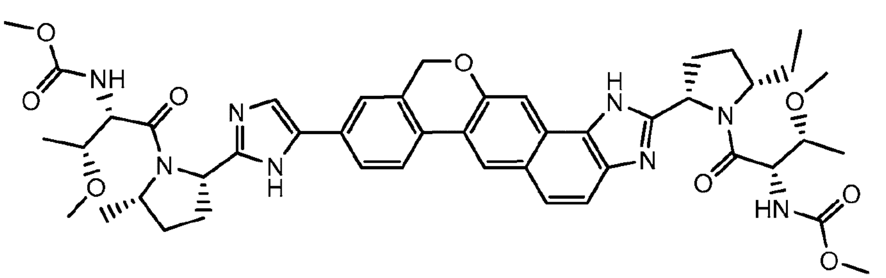

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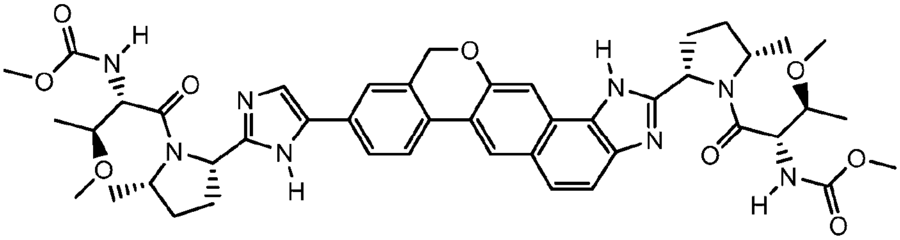

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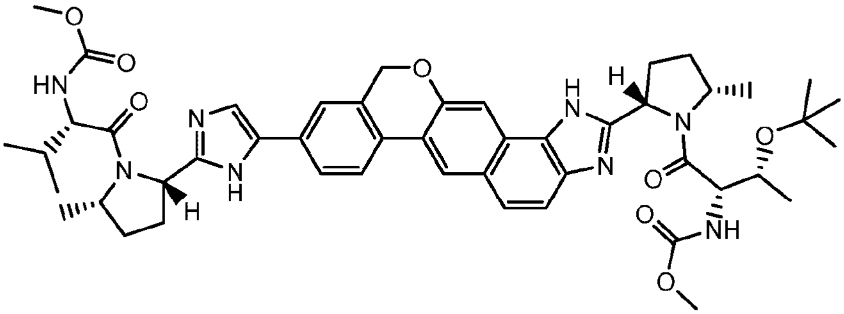

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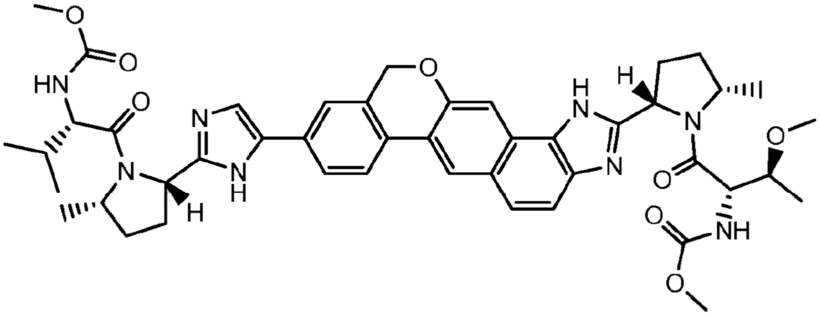

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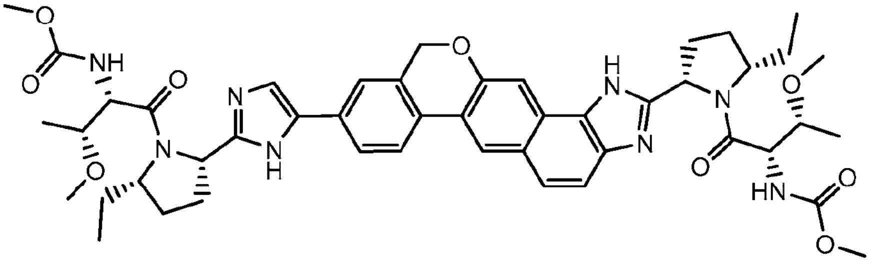

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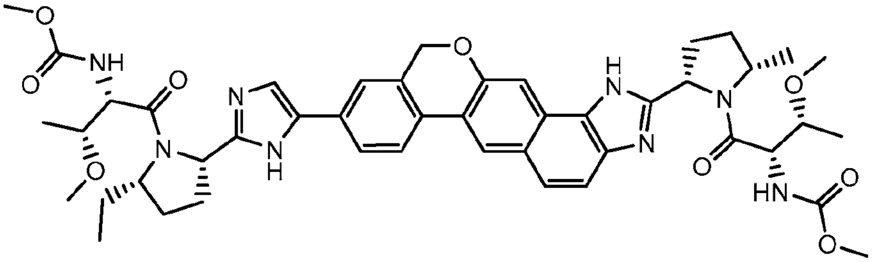

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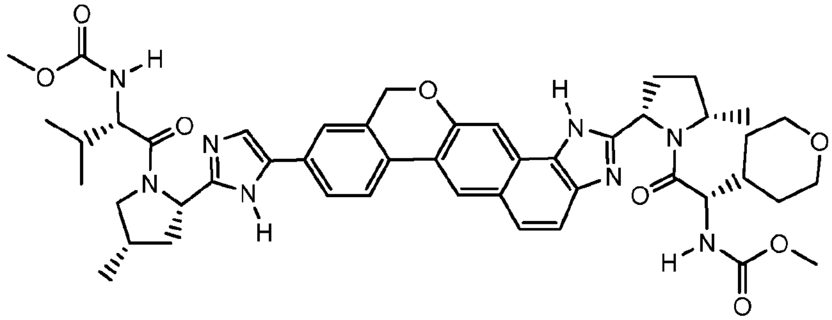

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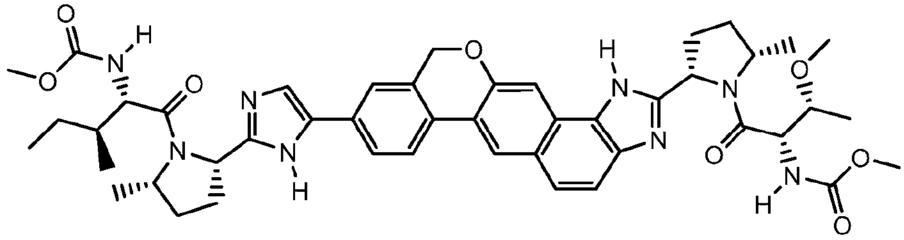

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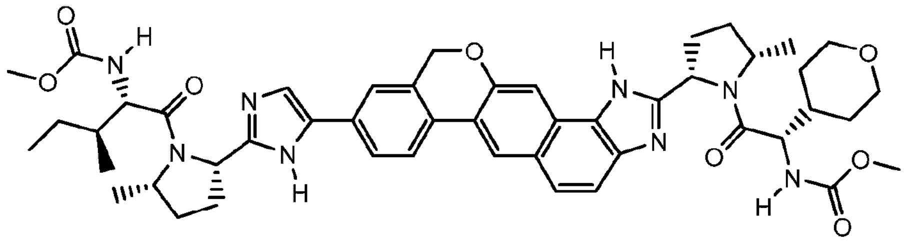

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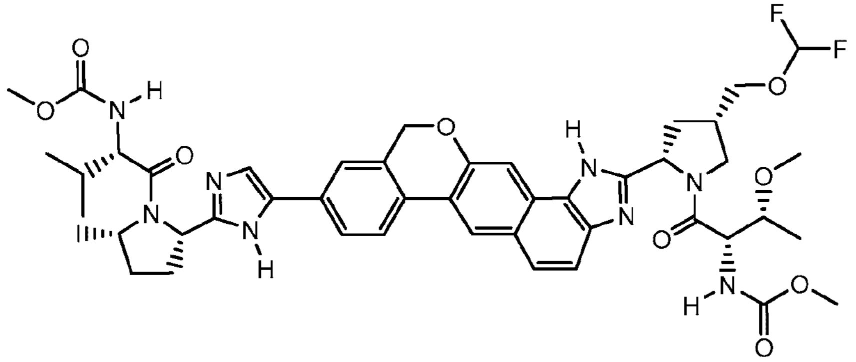

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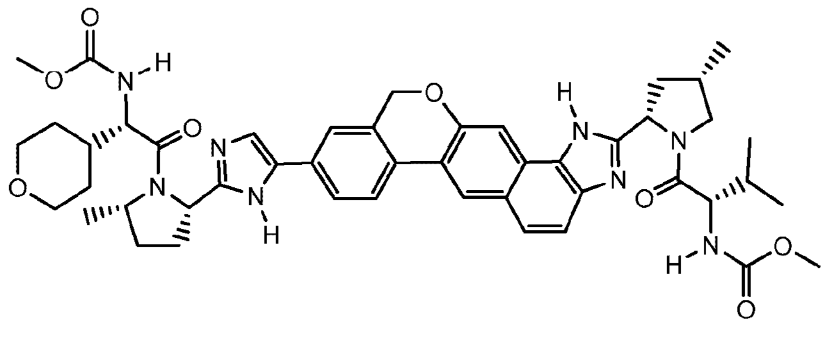

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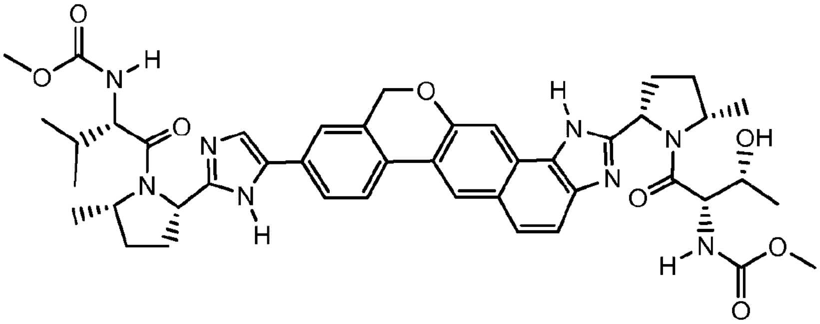

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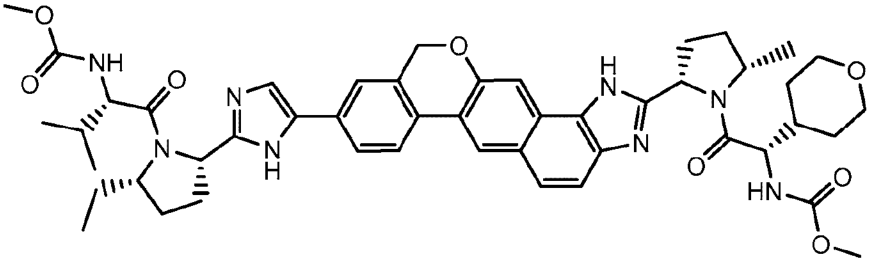

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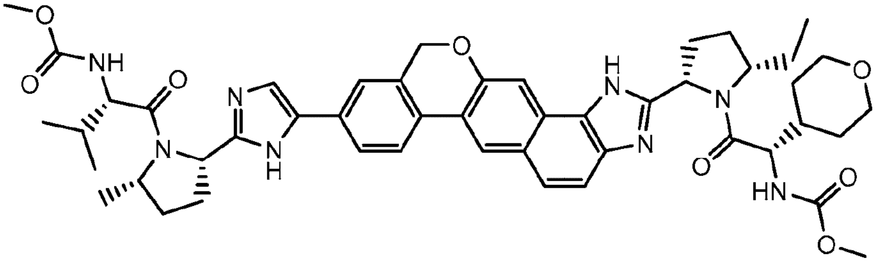

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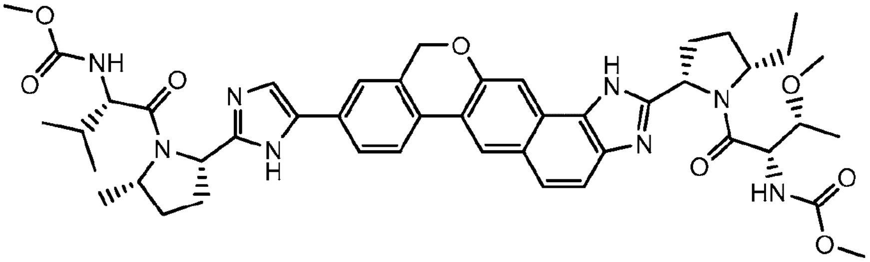

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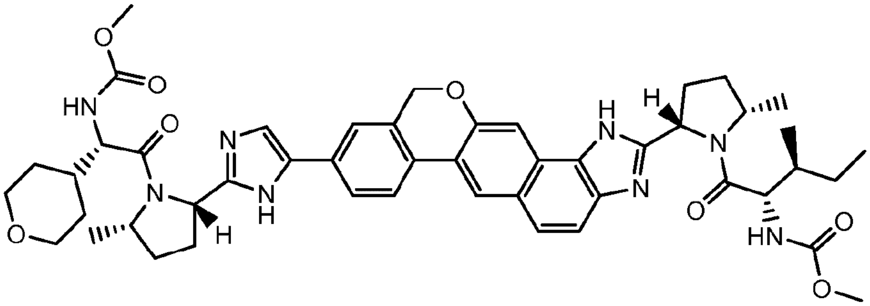

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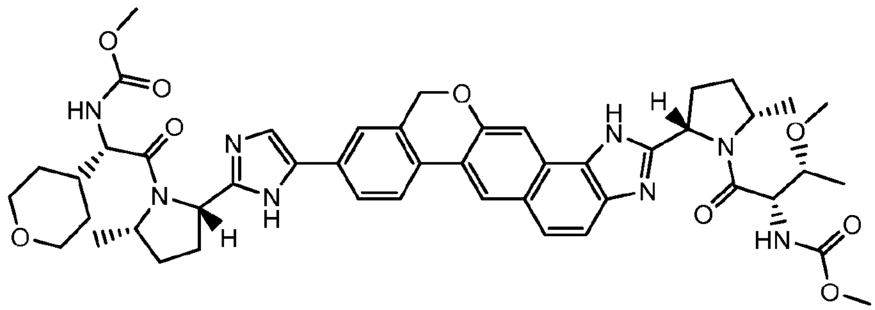

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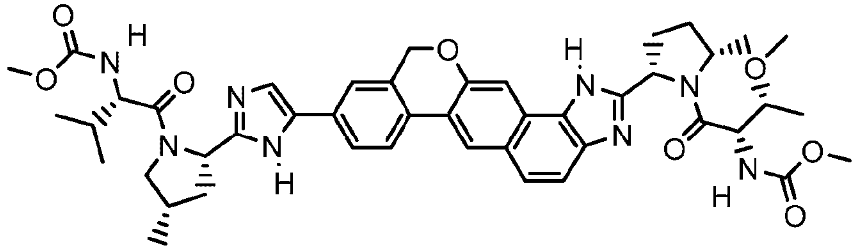

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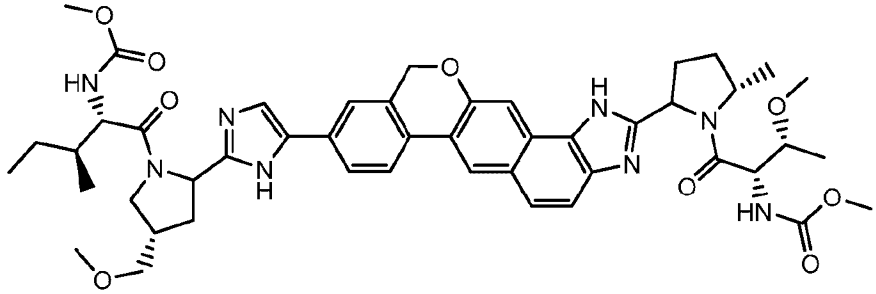

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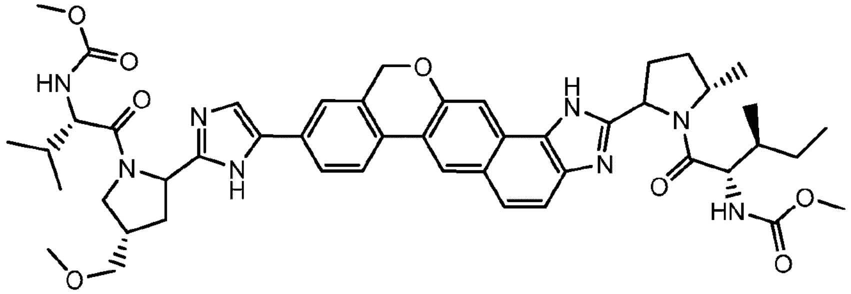

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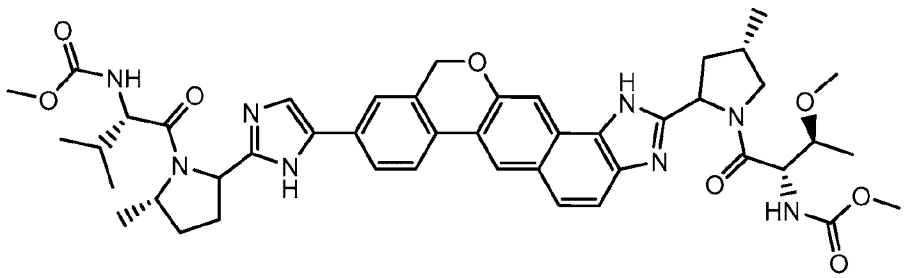

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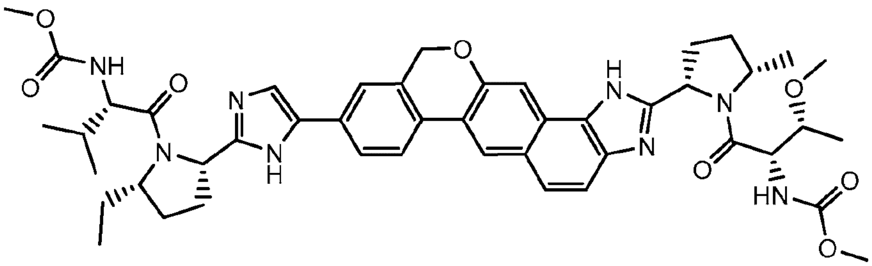

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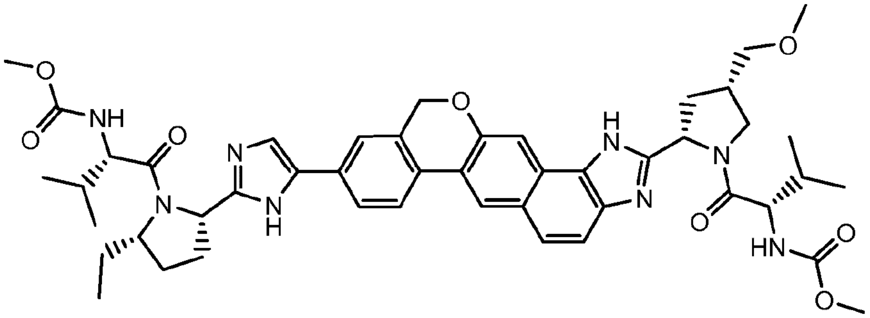

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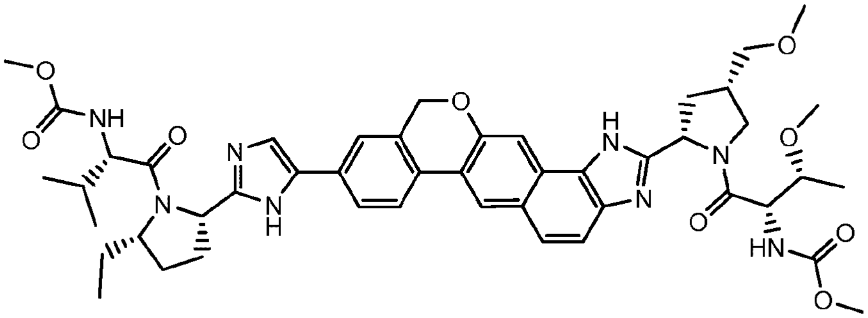

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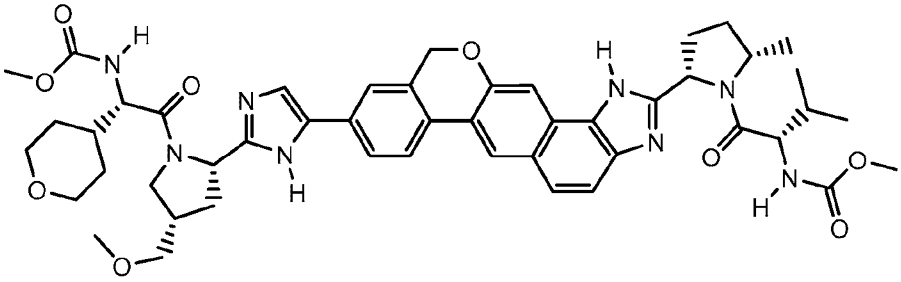

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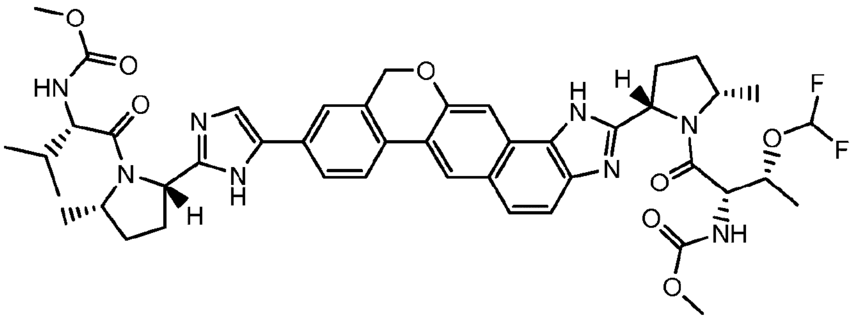

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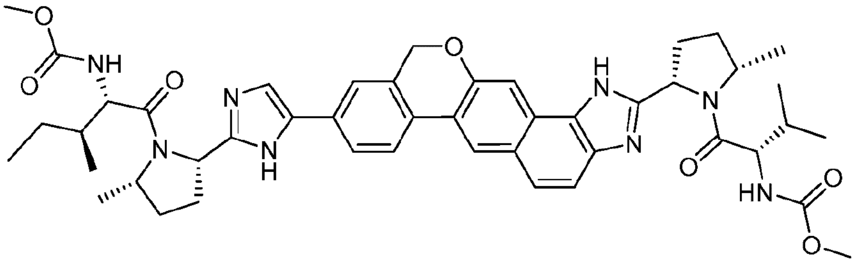

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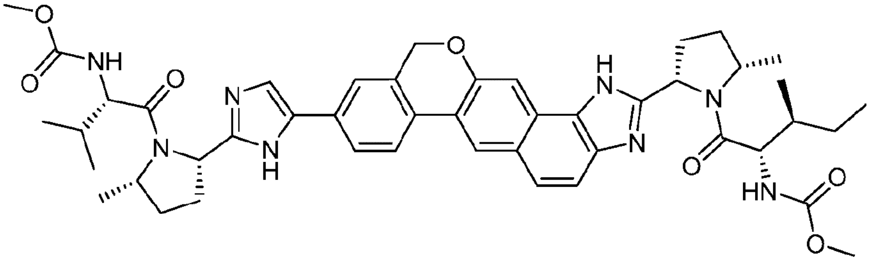

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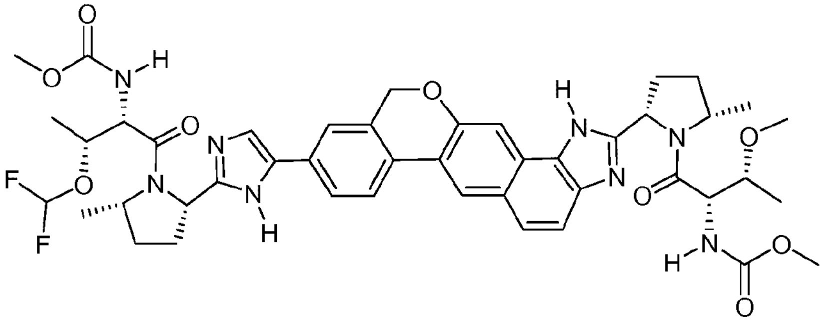

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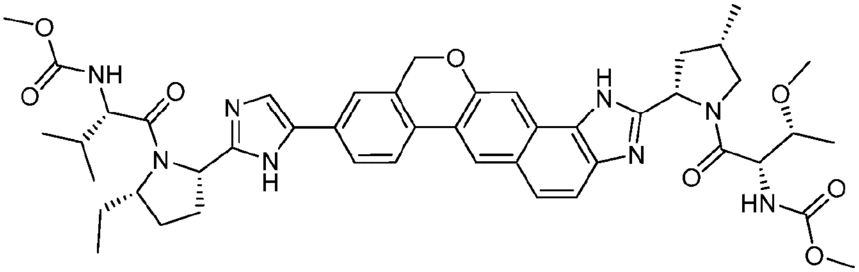

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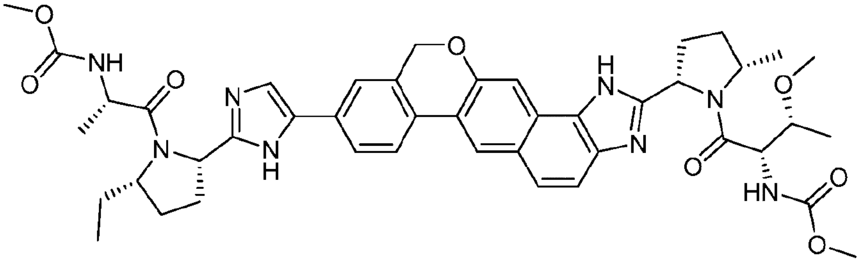

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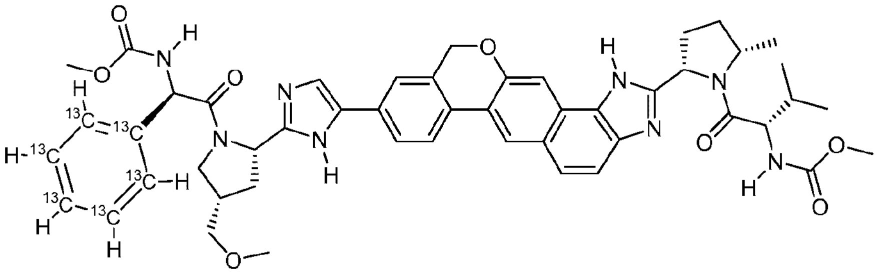
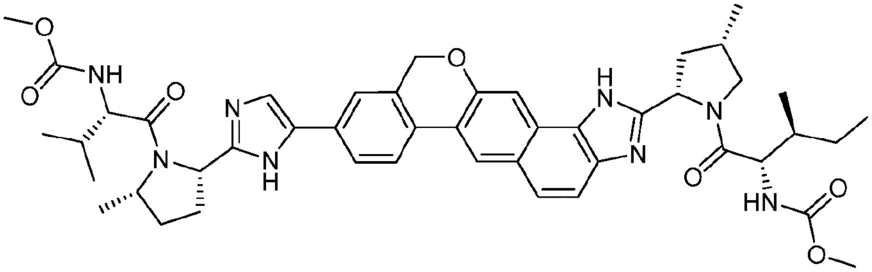
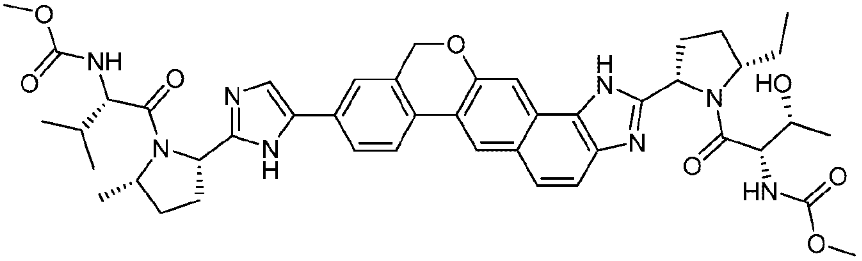
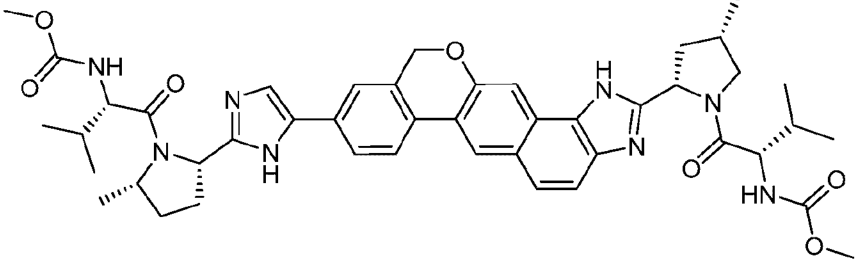
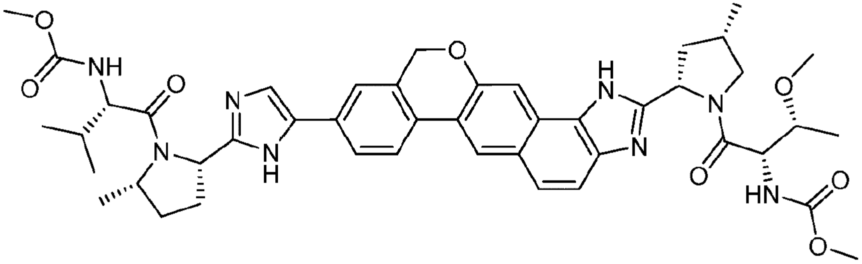
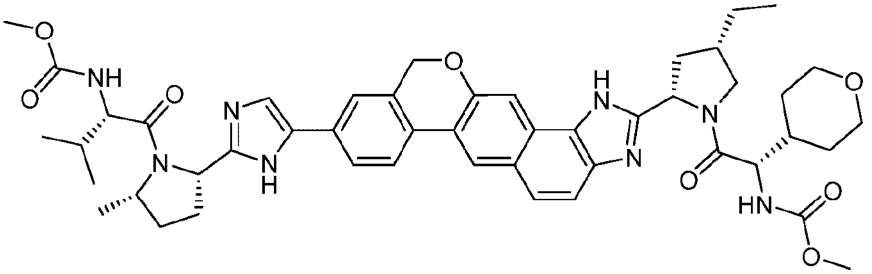


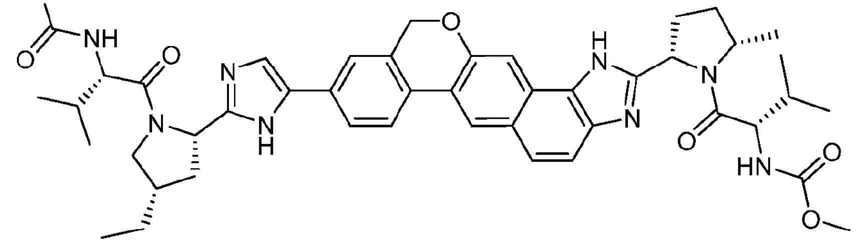
160 

161 

162 

163 

164 

165 

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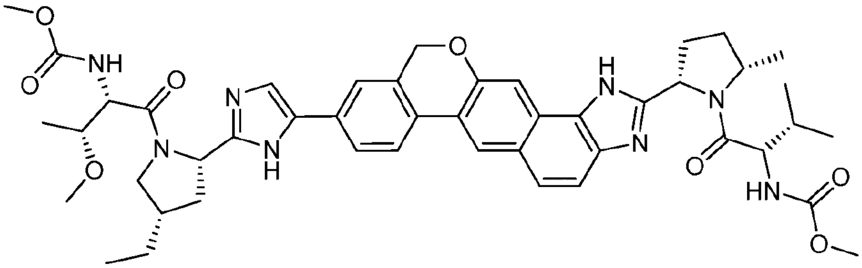

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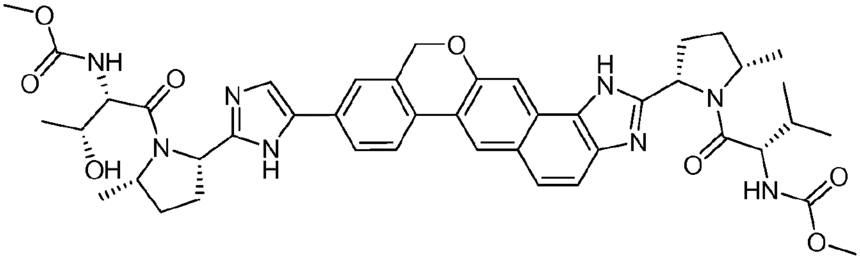

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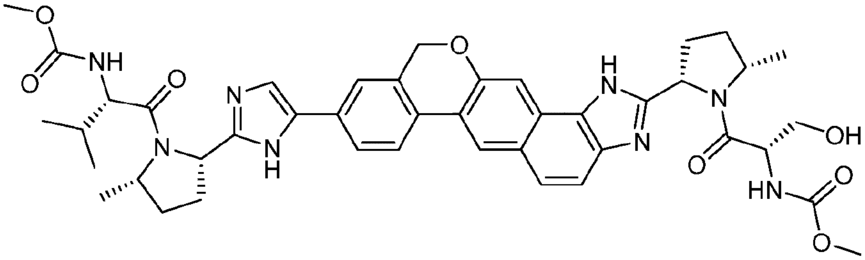

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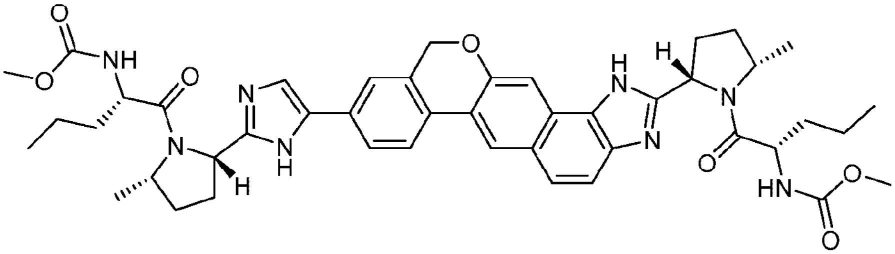

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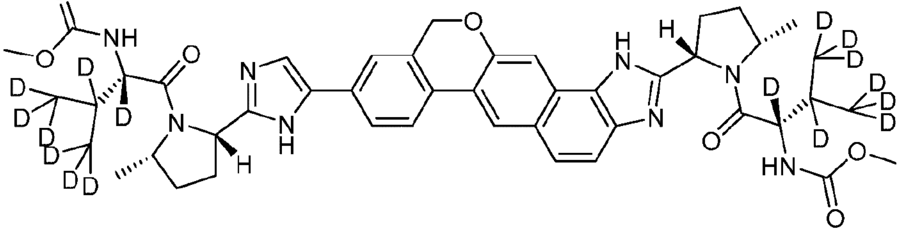

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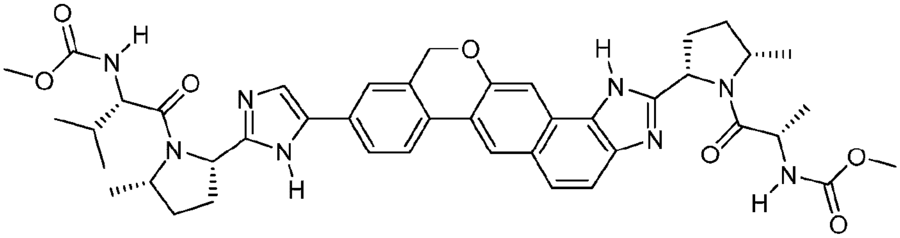

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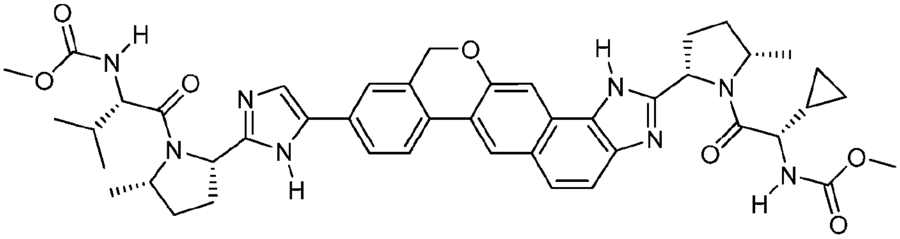

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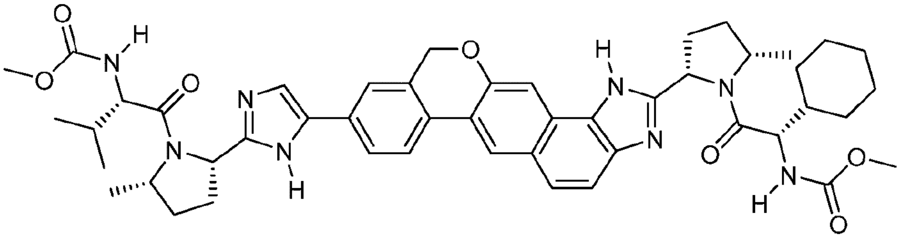

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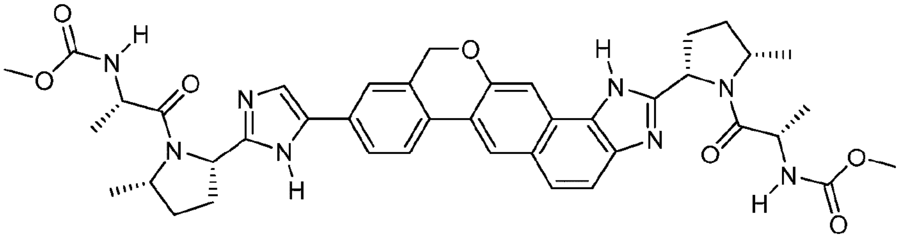

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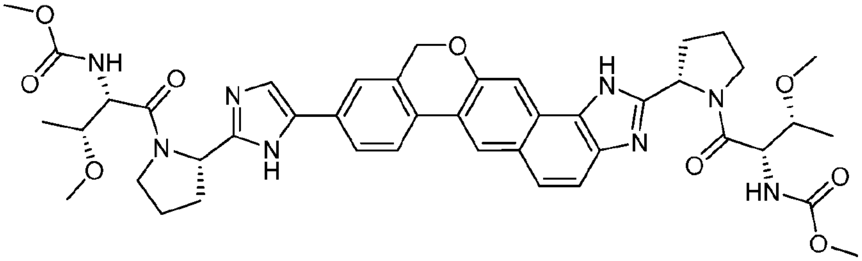

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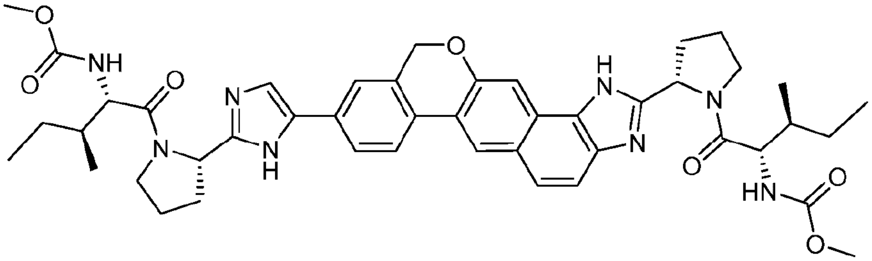

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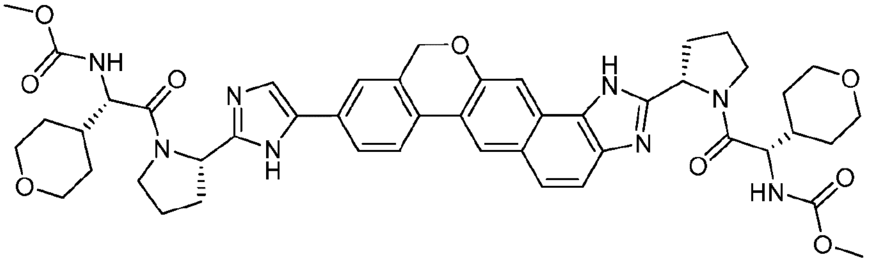

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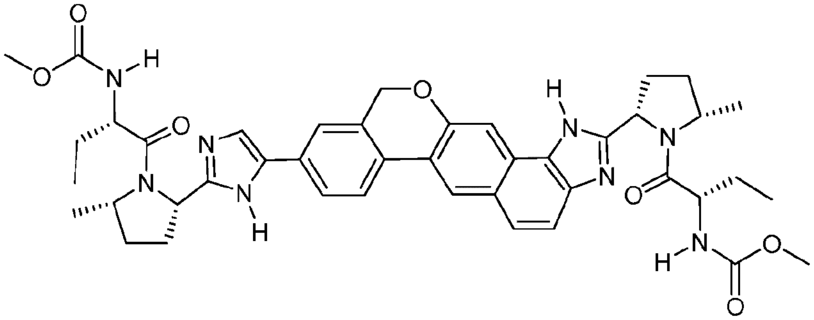

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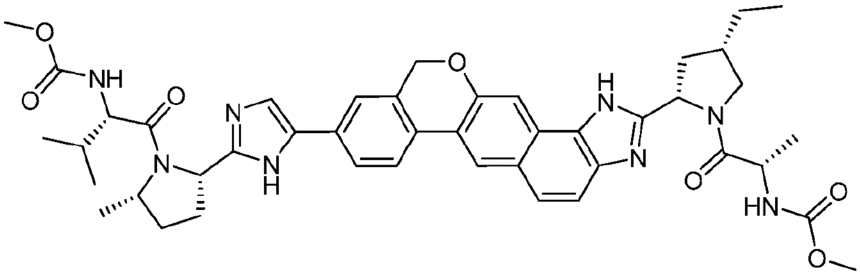

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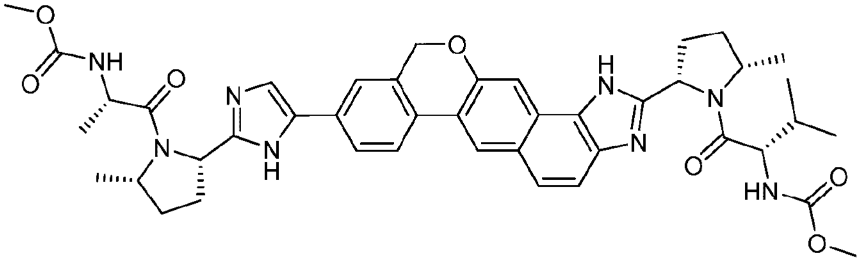

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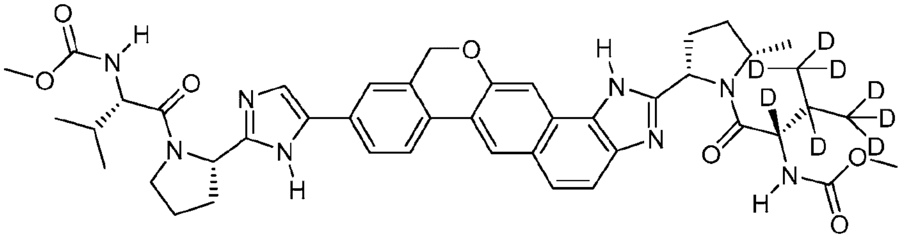

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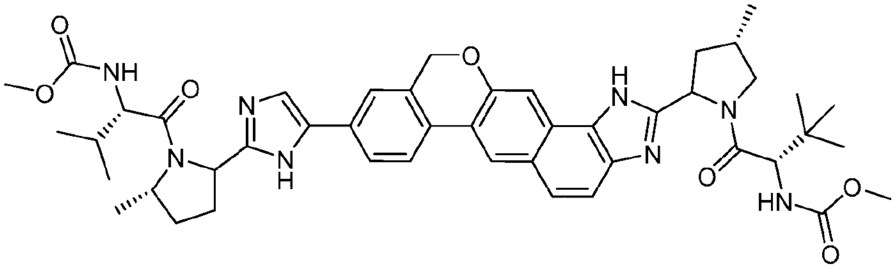

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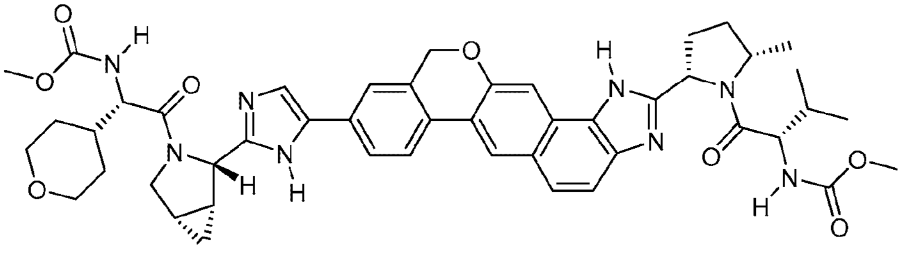

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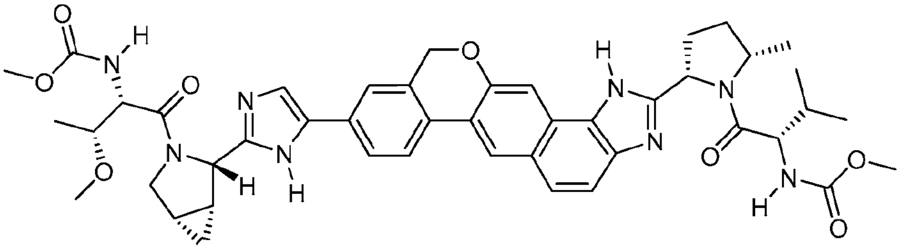

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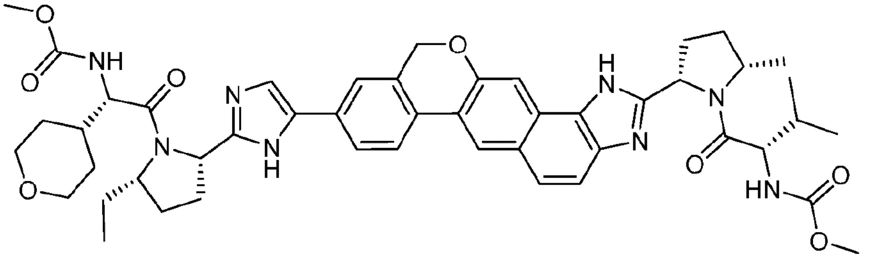

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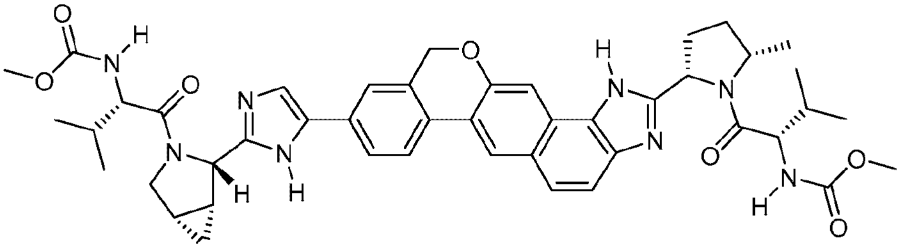

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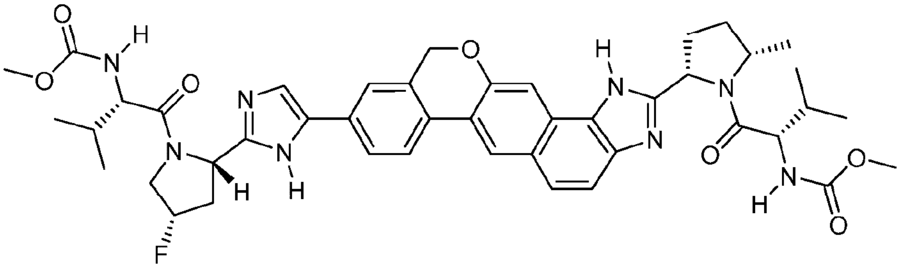

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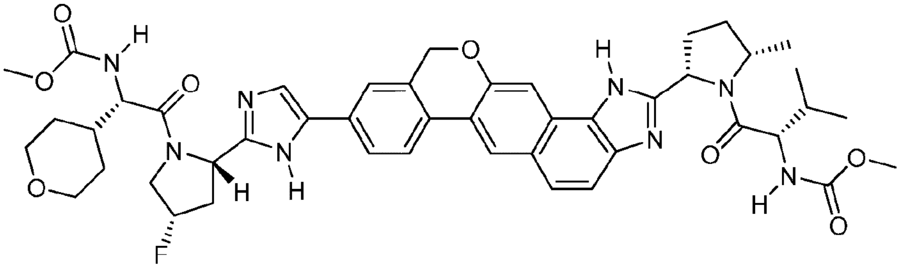

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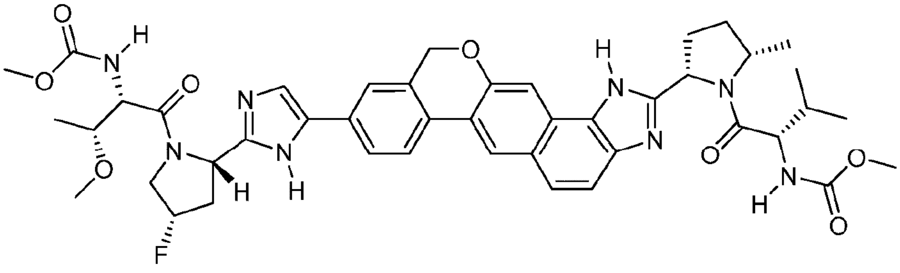

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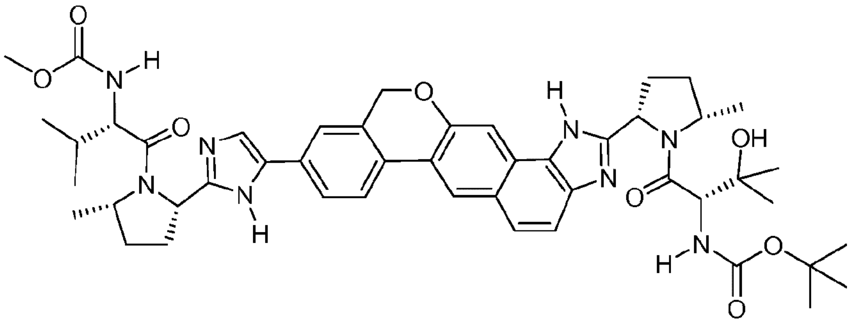

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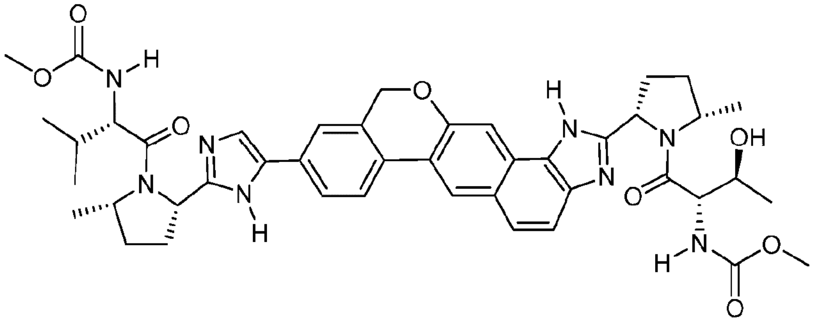

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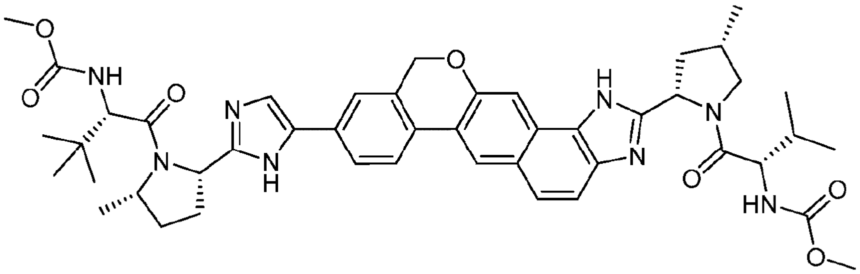

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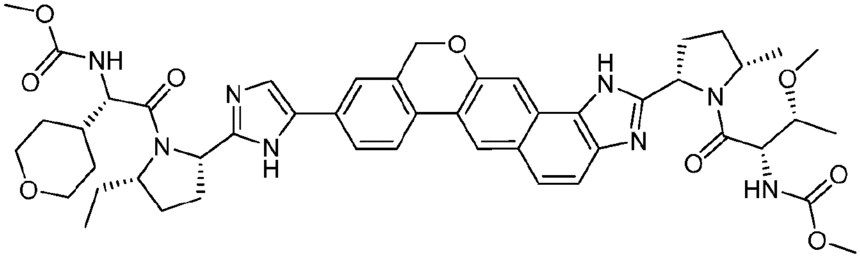

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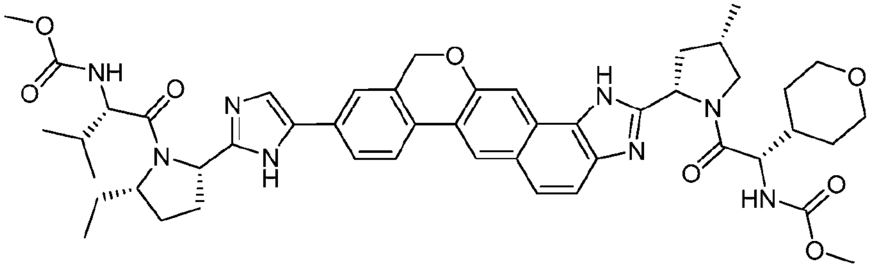

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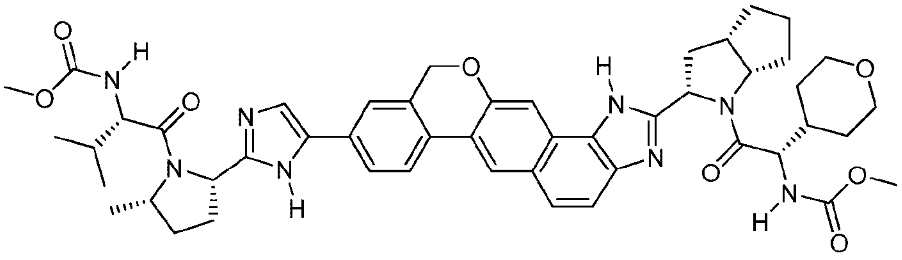

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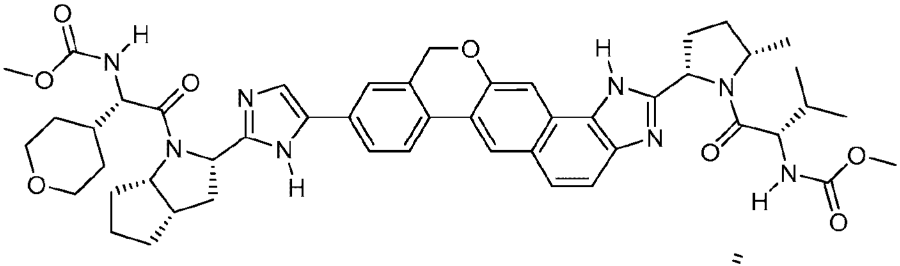

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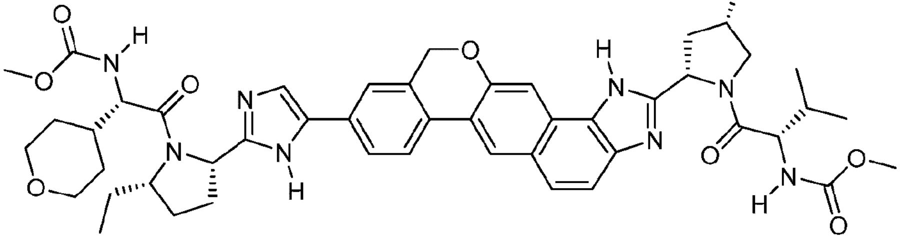

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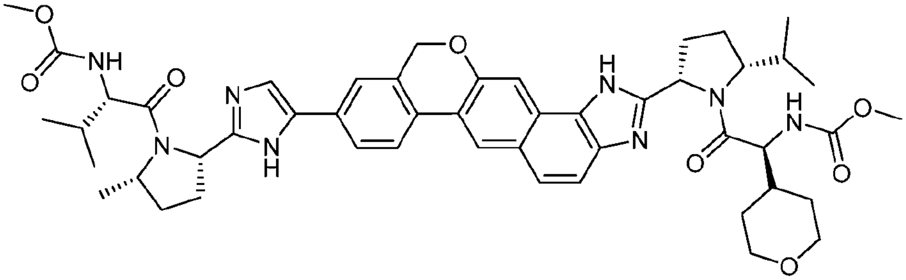

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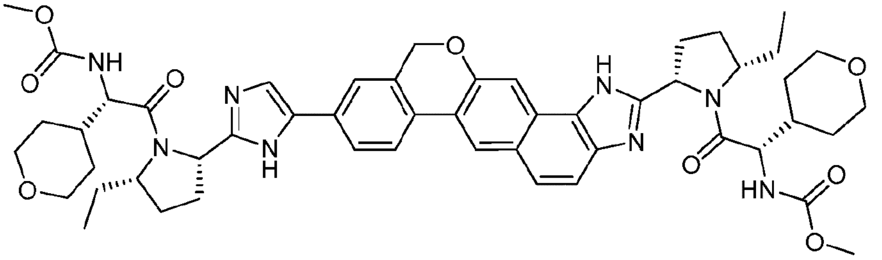

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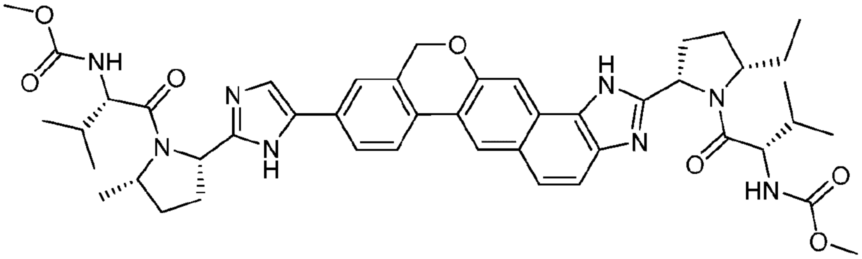

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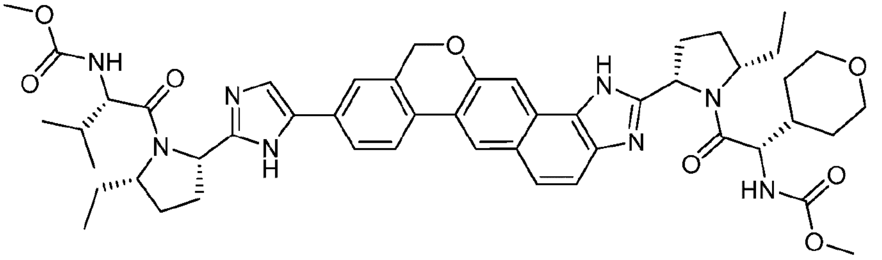

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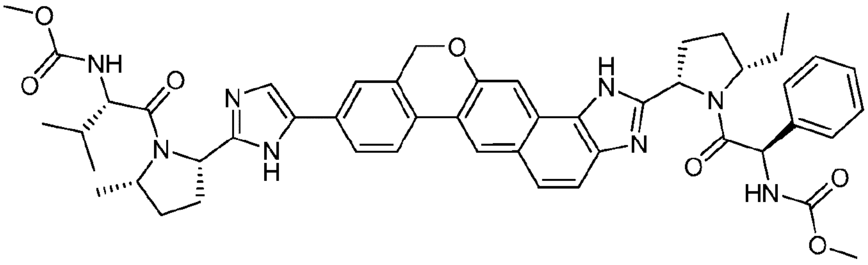

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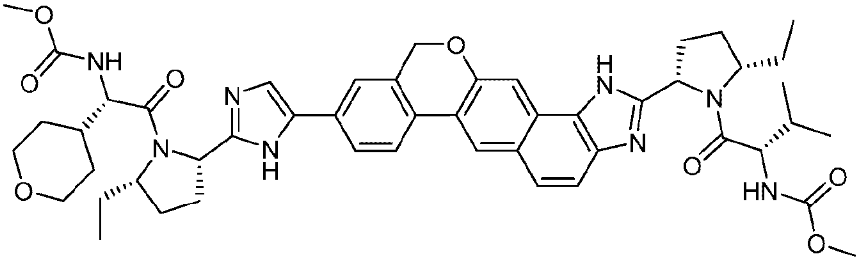

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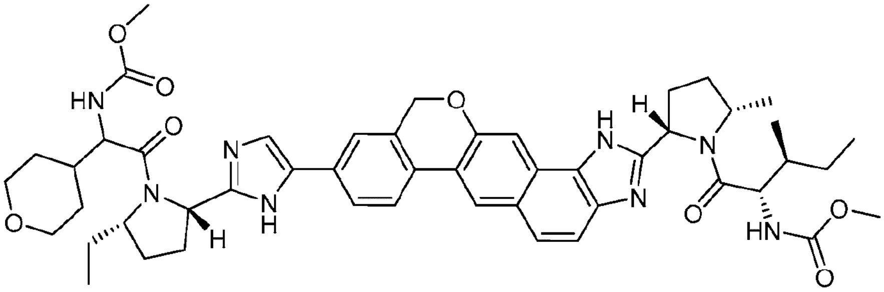

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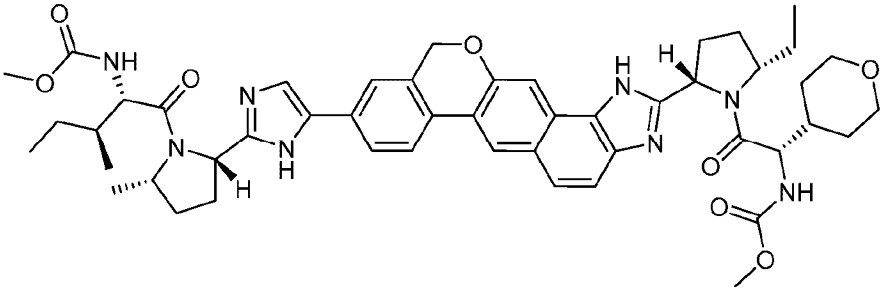

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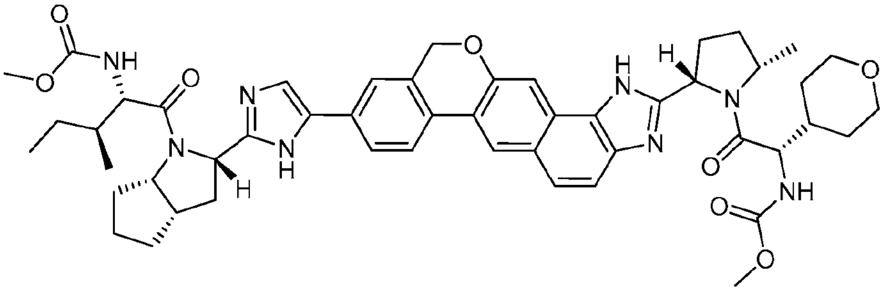

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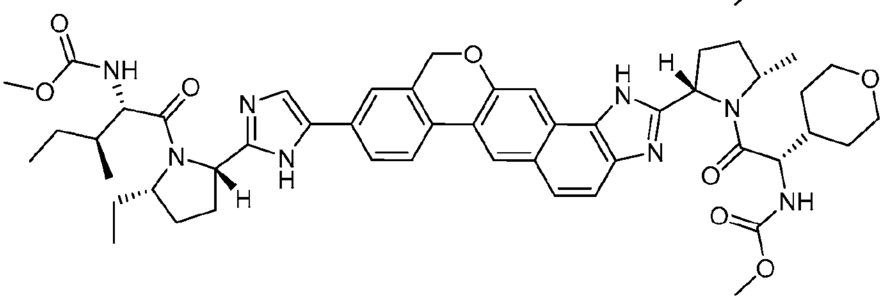

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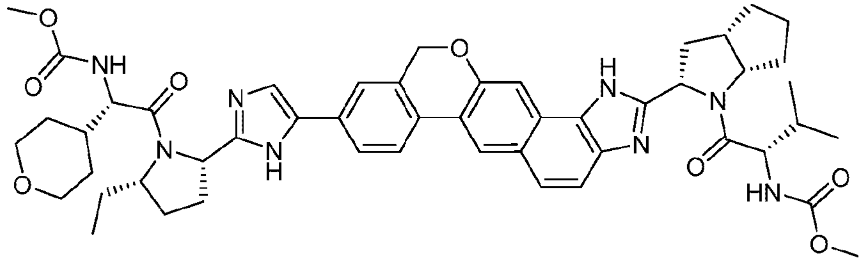

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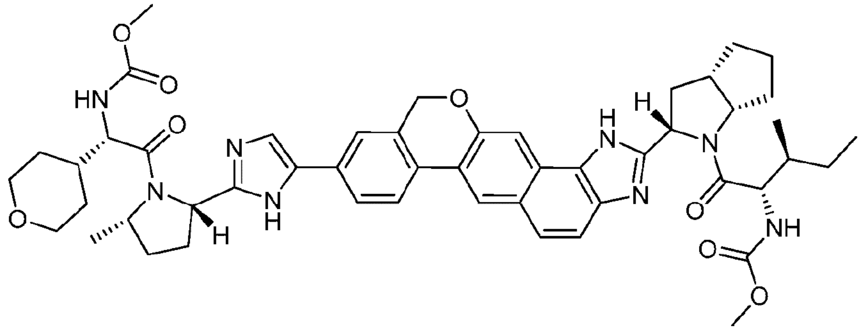

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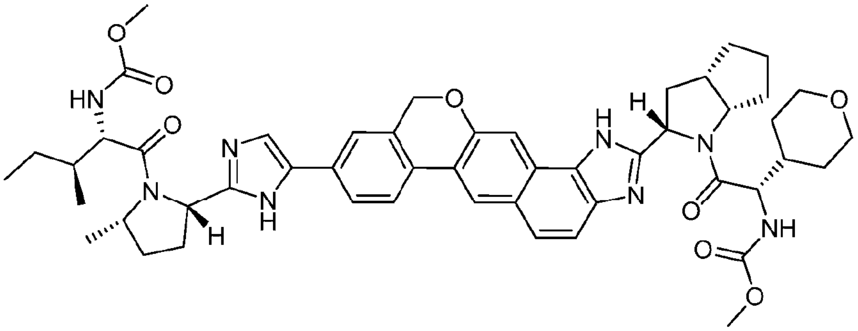

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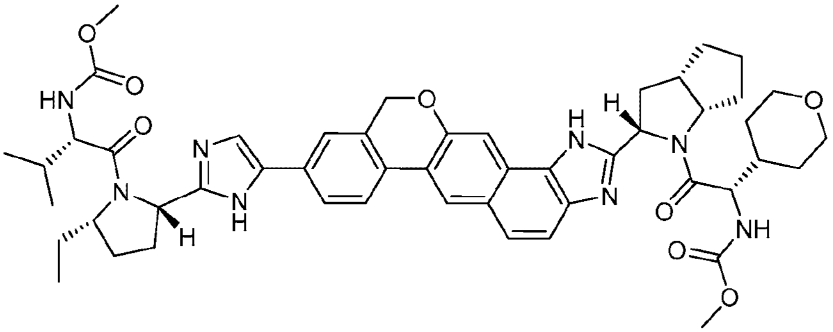

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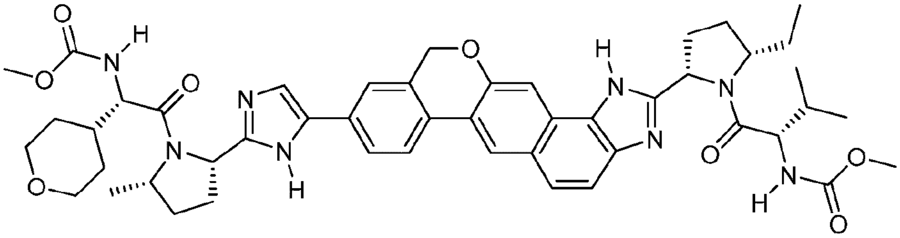

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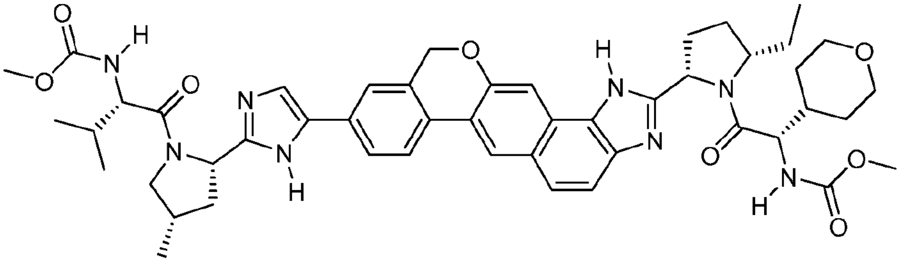

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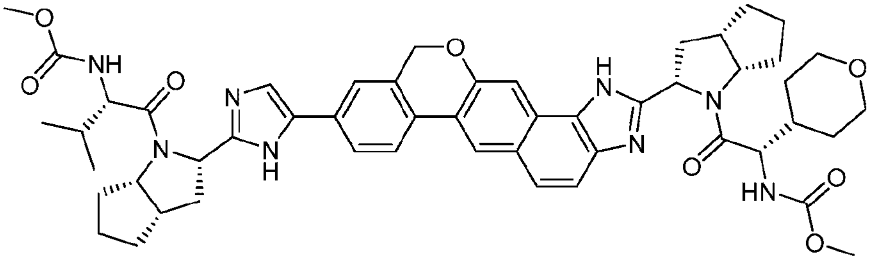

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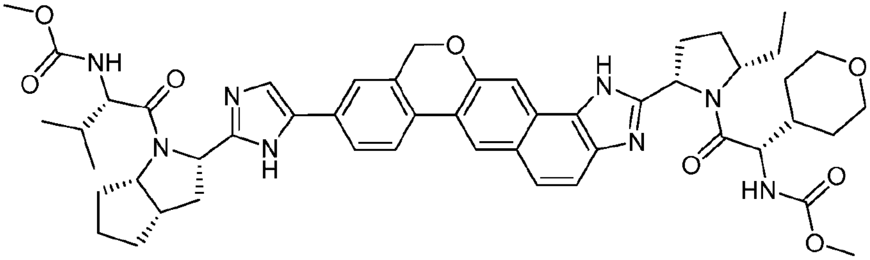

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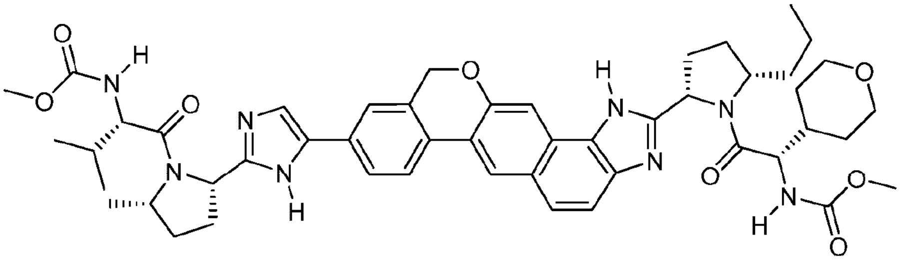

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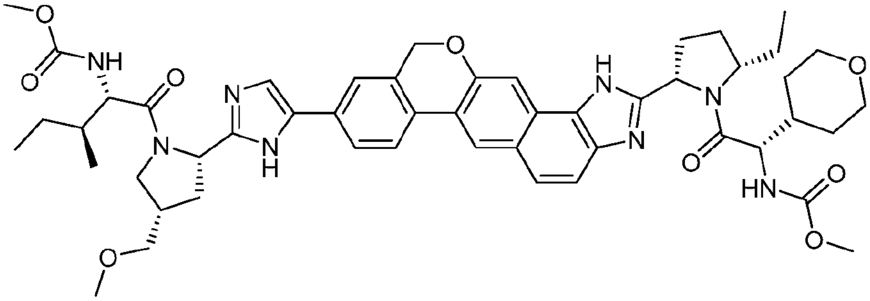

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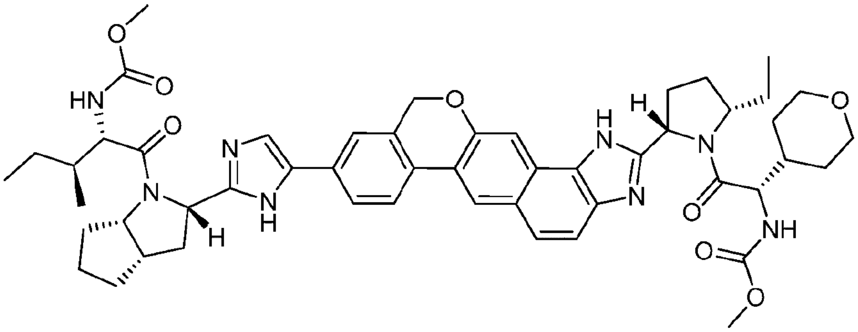
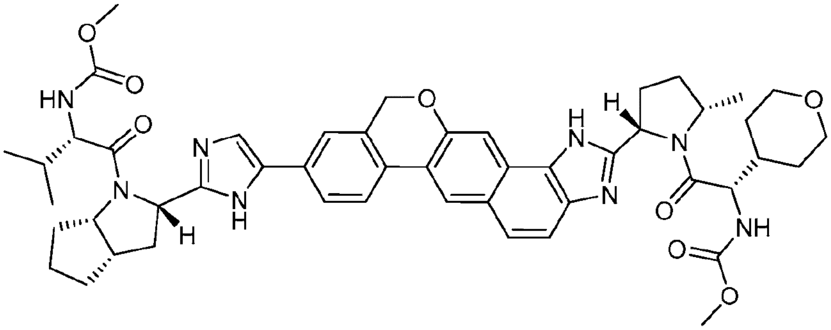


219 

or a pharmaceutically acceptable salt or prodrug thereof.

The disclosure will now be illustrated by the following non-limiting Examples. The following abbreviations are used throughout the specification, including the Examples.

| | |
|---|---|
| (aq) | Aqueous |
| (g) | Gas |
| (s) | Solid |
| °C | Degree Celsius |
| Ac | Acetate |
| ACN | Acetonitrile |
| apprx | Approximate |
| Bis-pinB/(Bpin)$_2$/(pinB)$_2$ | Bis(pinacolato)diboron |
| BOC/Boc | tert-Butoxycarbonyl |
| calc'd | Calculated |
| CC$_{50}$ | 50% Cytotoxicity concentration |
| COMU | 1-[(1-(Cyano-2-ethoxy-2-oxoethylideneaminooxy)dimethylaminomorpholino)] uronium hexafluorophosphate |
| d | Doublet |
| dba | dibenzalacetone |
| DCM | Dichloromethane |
| dd | Doublet of doublets |
| ddd | Doublet of doublet of doublets |
| DIPEA/DIEA | N,N-Diisopropylethylamine |

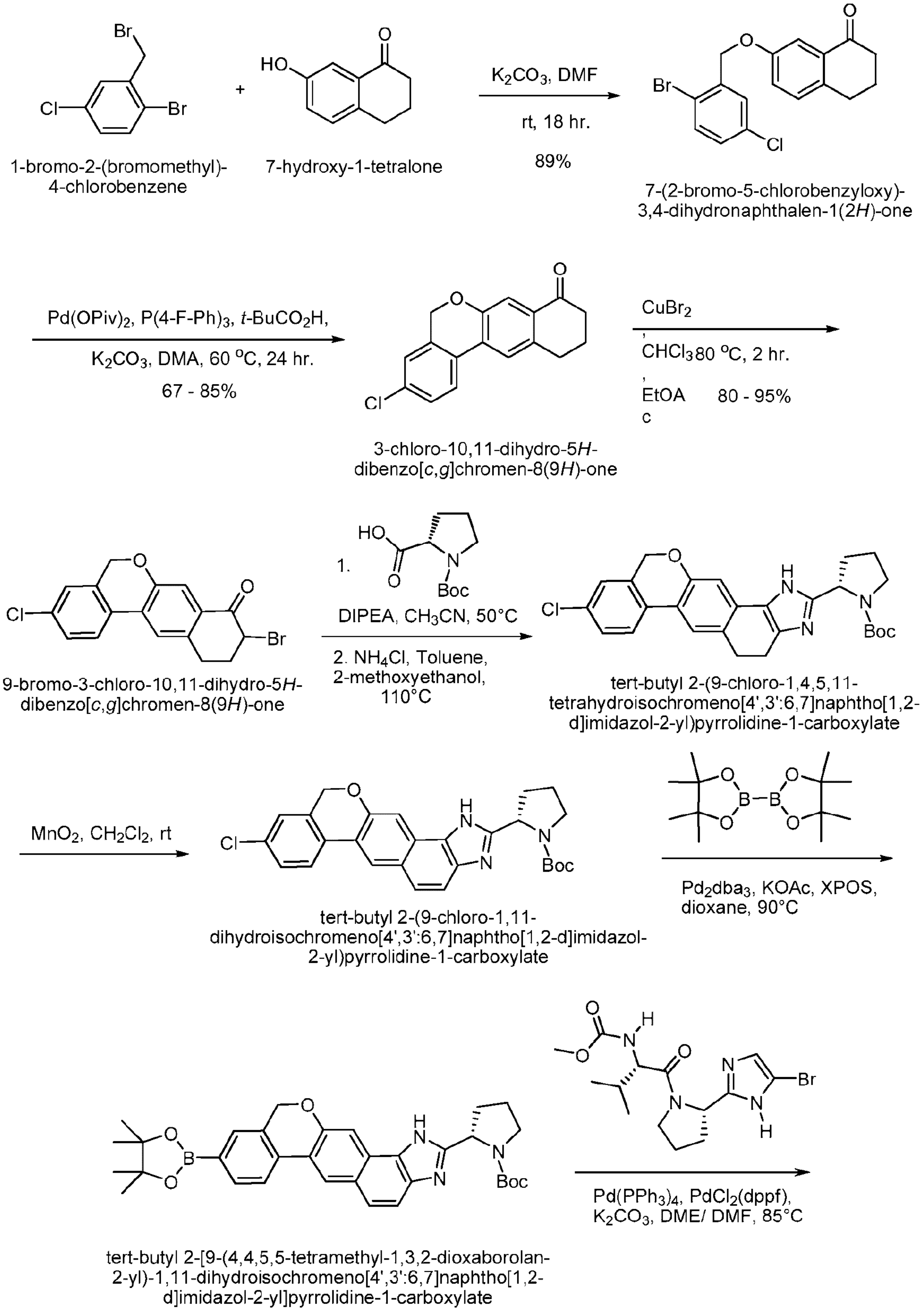
| | |
|---|---|
| DMA | N,N-Dimethylacetamide |
| DMAP | 4-Dimethylaminopyridine |
| DME | Dimethoxyethane |
| DMEM | Eagle's minimal essential medium |
| DMF | Dimethylformamide |
| DMSO/dmso | Dimethylsulfoxide |
| dppf | 1,1'-bis( diphenylphosphanyl) ferrocene |
| dt | Doublet of triplets |
| $EC_{50}$ | Half maximal effective concentration |
| ESI | Electrospray ionization |
| Et | Ethyl |
| ext. | External |
| FBS | Fetal bovine serum |
| g | Gram |
| HATU | 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium |
| HPLC | High performance liquid chromatography |
| hr/h | Hour |
| Hz | Hertz |
| J | Coupling constant |
| LCMS | Liquid chromatography mass spectrometry |
| M | Molar |
| m | Multiplet |
| m/z | Mass to charge |
| M+ | Mass peak |
| Me | Methyl |
| mg | Milligram |
| MHz | Megahertz |

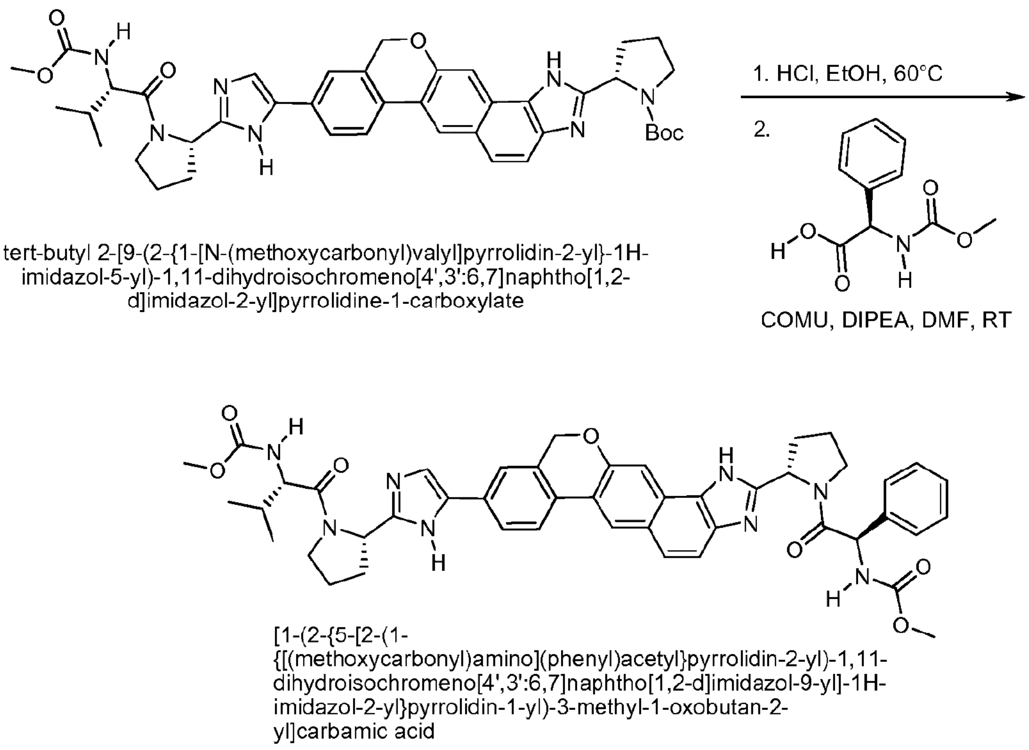
| | |
|---|---|
| min | Minute |
| mL | Milliliter |
| mmol | Millimole |
| Moc | Methoxycarbonyl |
| MS | Mass spectrometry |
| MTBE | Methyl tert-butyl ether |
| N | Normal |
| NADPH | Nicotinamide adenine dinucleotide phosphate |
| NBS | N-Bromosuccinimide |
| NMM | N-Methylmorpholine |
| NMR | Nuclear magnetic resonance |
| o/n | Over night |
| Papp | Apparent permeability |
| PBS | Phosphate buffer system |
| Pd/C | Palladium on carbon |
| Ph | Phenyl |
| Phg/PhGly | Phenyl glycine |
| Piv | Pivalate |
| Pro | Proline |
| pyr | Pyridine |
| q | Quartet |
| qd | Quartet of doublets |
| quant | Quantitative |
| quint | Quintet |
| rt/RT | Room temperature |
| s | Singlet |
| SPhos | 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl |
| t | Triplet |

| | |
|---|---|
| t-Bu | tert-Butyl |
| TEMPO | (2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl |
| Tf | Trifluoromethanesulfonate |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| Thr | Threonine |
| TLC | Thin layer chromatography |
| tol. | Toluene |
| UV | Ultraviolet |
| Val | Valine |
| w/v | Weight to volume |
| w/w | Weight to weight |
| X-Phos/XPOS/Xphos | 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl |
| δ | Chemical shift |
| µg | Microgram |
| µL | Microliter |

# Examples

## Example AA





tert-butyl 2-[9-(2-{1-[N-(methoxycarbonyl)valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate

[1-(2-{5-[2-(1-{[(methoxycarbonyl)amino](phenyl)acetyl}pyrrolidin-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl]carbamic acid

**3,4-dihydronaphthalen-1(2H)-one:** To a stirred solution of 7-hydroxy-1-tetralone (13.9 g, 85.7 mmol) and 1-bromo-2-(bromomethyl)-4-chlorobenzene (25.6 g, 90.0 mmol) in dimethylformamide (850 mL) was added potassium carbonate (24 g, 172 mmol). The reaction was stirred under argon for 18 hours then diluted with ethyl acetate (1 L). The organics were washed three times with water and once with brine. The organic layer was then dried with magnesium sulfate, filtered and concentrated. To the resulting oil was added methanol (500 mL) and the suspension was agitated for thirty minutes. 7-(2-bromo-5-chlorobenzyloxy)- (27.8 g, 89% yield) was isolated by filtration.

**3-chloro-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one:** To a 1 L flask containing palladium(II) pivalate (1.18 g, 3.8 mmol), tri(4-fluorophenyl)phosphine (1.20 g, 3.8 mmol), pivalic acid (2.33 g, 22.8 mmol) and potassium carbonate (31.8 g, 228 mmol) was added a solution of 7-(2-bromo-5-chlorobenzyloxy)-3,4-dihydronaphthalen-1(2H)-one (27.8 g, 76.2 mmol) in dimethyacetamide (380 mL). The flask was evacuated and backfilled with argon 5 times and then stirred under argon at 60 °C for 24 hours. The reaction was cooled to room temperature and diluted with MTBE and water. The resulting biphasic mixture was stirred for 3 hours and filtered through Celite, rinsing with MTBE. The organic layer of the filtrate was separated and then washed twice with water and once with brine. The organics were then dried with magnesium sulfate, filtered, concentrated and purified by flash column chromatography (Hexanes/DCM) to yield 3-chloro-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (14.4 g, 67% yield) as an off-white solid.

**9-bromo-3-chloro-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one:** To a mixture of 3-chloro-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (14.8 g, 52 mmol) in chloroform (50 mL) and ethyl acetate (50 mL) was added copper(II) bromide (24.3 g, 104 mmol). The reaction was heated to 80 °C for 2 hours and then cooled to room temperature. The mixture was diluted with dichloromethane and washed twice with a 5:1 solution of saturated aqueous ammonium chloride and aqueous ammonium hydroxide (~38%), and washed once with water. The organic layer was dried with magnesium sulfate, filtered and concentrated to yield 9-bromo-3-chloro-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (18.5 g, >95% yield) with >95% purity. Note: This reaction is not always this clean. Sometimes there is over-bromination and sometimes there is significant starting material. These impurities can be removed by flash column chromatography.

**tert-butyl 2-(9-chloro-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate**: To a solution of (1R)-2-(tert-butoxycarbonyl)cyclopentanecarboxylic acid (10.17 g, 47.25 mmol) and 9-bromo-3-chloro-10,11-dihydro-6H-naphtho[2,3-c]chromen-8(9H)-one (5.7 mg, 15.7 mmol) in acetonitrile (50 mL) was added diisopropylethylamine (11.11 mL, 64 mmol). The reaction was stirred at 50 °C for 4 hours and was then diluted with ethyl acetate. The organics were washed with water and brine, dried ($MgSO_4$) and concentrated. The resulting crude residue was purified by flash chromatography to yield (2S)-1-tert-butyl 2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-5H-naphtho[c,g]chromen-9-yl) pyrrolidine-1,2-dicarboxylate (4.52 g, 58%). To a solution of (2S)-1-tert-butyl 2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-6H-naphtho[2,3-c]chromen-9-yl) pyrrolidine-1,2-dicarboxylate (3.27 mg, 6.56 mmol) in a mixture of toluene (11 mL) and 2-methoxyethanol (0.7 mL) was added ammonium acetate (5.06 g, 65.6 mmol). The reaction mixture was heated to 110 °C for 3 hours, cooled to room temperature and diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield tert-butyl 2-(9-chloro-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (1.95 g, 61%). LCMS-ESI$^+$: calculated for $C27H28ClN_3O34_2$: 477.98; observed $[M+1]^+$: 478.47

**tert-butyl 2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate.** To a solution of tert-butyl 2-(9-chloro-1,4,5,11-

tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (1.9 g, 3.96 mmol) in dichloromethane (35 mL) was added manganese(IV) oxide (17 g, 198 mmol). The reaction mixture was stirred at room temperature for 18 hours, diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield tert-butyl 2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (1.52 g, 81%). LCMS-ESI$^+$: calculated for C27H26ClN3O3 $_{42}$: 475.9; observed [M+1]$^+$: 476.45.

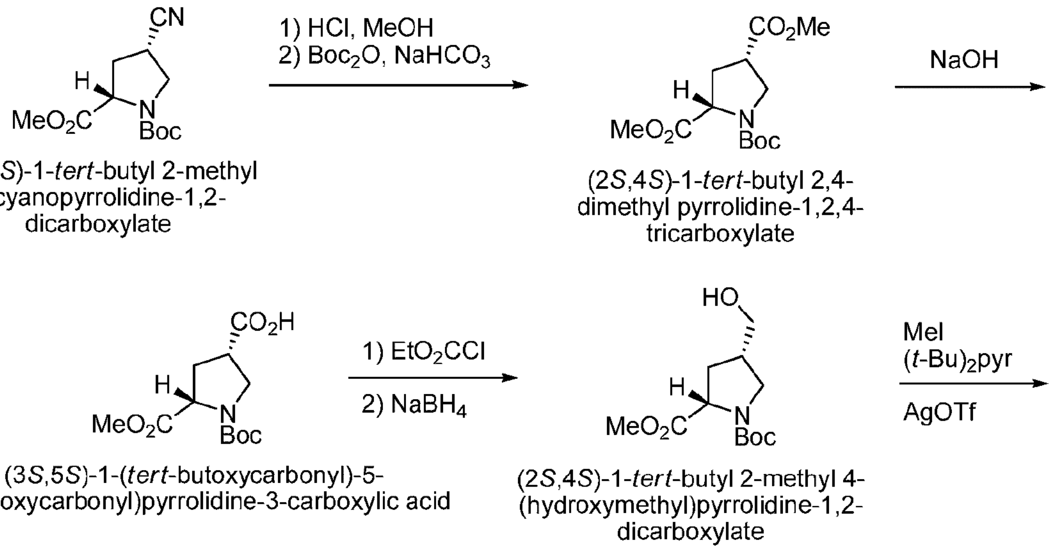
**tert-butyl 2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate**: A degassed mixture of tert-butyl 2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (1.52 g, 3.17 mmol), bis(pinacolato)diboron (1.21 g, 4.75 mmol), potassium acetate (934 mg, 9.52 mmol), tris(dibenzylideneacetone)palladium (116 mg, 0.13 mmol) and 2-dicyclohexylphosphino-2', 4', 6'-tri-i-propyl-1, 1'-biphenyl (121 mg, 0.08 mmol) in 1,4-dioxane (16 mL) was heated to 90 °C for 1.5 hours, cooled to room temperature and diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield tert-butyl 2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate (1.7 g, 94%)

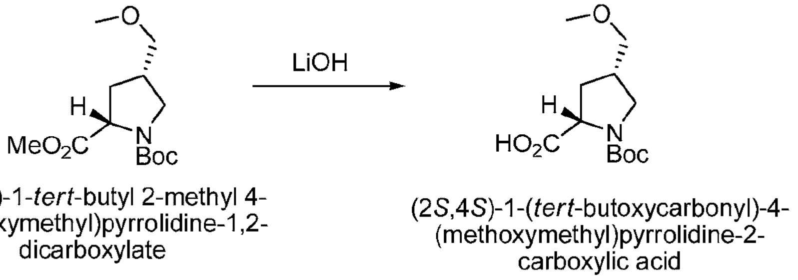
**tert-butyl 2-[9-(2-{1-[N-(methoxycarbonyl)valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate**: To a solution of methyl (S)-1-((S)-2-(5-bromo-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (1.48 g, 3.97 mmol), tert-butyl 2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate (1.88 g, 1.48 mmol), tetrakis(triphenyl phosphine)palladium(0) (191 mg, 0.16 mmol) and dichloro[1,1'-bis(diphenylphosphino) ferrocene]palladium(II) (242 mg, 0.33 mmol) in a mixture of 1,2-dimethoxyethane (37.0 mL) and dimethylformamide (6 mL) was added a solution of potassium carbonate (2M in water, 5 mL, 9.93 mmol). The resulting mixture was degassed and then heated to 85 °C under argon for 18 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield tert-butyl 2-[9-(2-{1-[N-(methoxycarbonyl)valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-

dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate (1.45 mg, 59%). LCMS-ESI$^+$: calculated for C41H47N7O6 $_{73}$ 733.86; observed [M+1]$^+$: 734.87.

**[1-(2-{5-[2-(1-{[(methoxycarbonyl)amino](phenyl)acetyl}pyrrolidin-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl]carbamic acid**: A solution of tert-butyl 2-[9-(2-{1-[N-(methoxycarbonyl)valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate (462 mg, 0.63 mmol), ethanol (6 mL) and concentrated HCl (2 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and the crude material dissolved in DCM (6 mL). This solution was concentrated and to this material was added a solution of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (172 mg, 0.82 mmol) and COMU (311 mg, 073 mmol) in DMF (6 mL). To the resulting solution was added diisopropylethylamine (330 µL, 1.89 mmol). After stirring for 18 hours at room temperature, the reaction was diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 45% ACN/$H_2O$ + 0.1% TFA). The product fractions were lyophilized to give [1-(2-{5-[2-(1-{[(methoxycarbonyl)amino](phenyl)acetyl}pyrrolidin-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl]carbamic acid (231 mg, 45%). LCMS-ESI$^+$: calculated for C46H48N8O7$_8$: 824.92; observed [M+1]$^+$: 826.00

## Example AB





**(2S,4S)-1-tert-butyl 2,4-dimethyl pyrrolidine-1,2,4-tricarboxylate.** To a solution of (2S,4S)-1-tert-butyl 2-methyl 4-cyanopyrrolidine-1,2-dicarboxylate (9.0 g, 35.4 mmol) in MeOH (196 mL) was added HCl (4M in 1,4-dioxane, 100 mL, 403 mmol). The solution was stirred at room temperature for 16h and concentrated *in vacuo*. The crude intermediate was dissolved in EtOAc (180 mL) and basified with aqueous bicarbonate (sat.). Di-tert-butyl dicarbonate (8.5 g, 38.9 mmol) was added and the biphsic solution was stirred at room temperature for 12h. The layers were then separated and the aqueous layer was backextracted with EtOAc. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated. The crude oil was purified by silica gel chromatography (15% to 40% to 100% EtOAc/Hexanes) to provide (2S,4S)-1-tert-butyl 2,4-dimethyl pyrrolidine-1,2,4-tricarboxylate (9.56 g, 94%).

**(3S,5S)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)pyrrolidine-3-carboxylic acid.** To a solution of (2S,4S)-1-tert-butyl 2,4-dimethyl pyrrolidine-1,2,4-tricarboxylate (9.56 g, 33.3 mmol) in THF (70 mL) at 0 °C (external temperature, ice bath) was added NaOH (1N aqueous, 33 mL, 33.3 mmol) dropwise over 15 min. The solution was stirred at 0 °C for 5h before acidification with HCl (1N). The solution was extracted with EtOAc (3x). The combined organic layers were dried over $Na_2SO_4$ and concentrated. The crude oil was purified by silica gel chromatography (2% to 5% to 10% MeOH/$CH_2Cl_2$) to provide (3S,5S)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)pyrrolidine-3-carboxylic acid (6.38g, 70%).

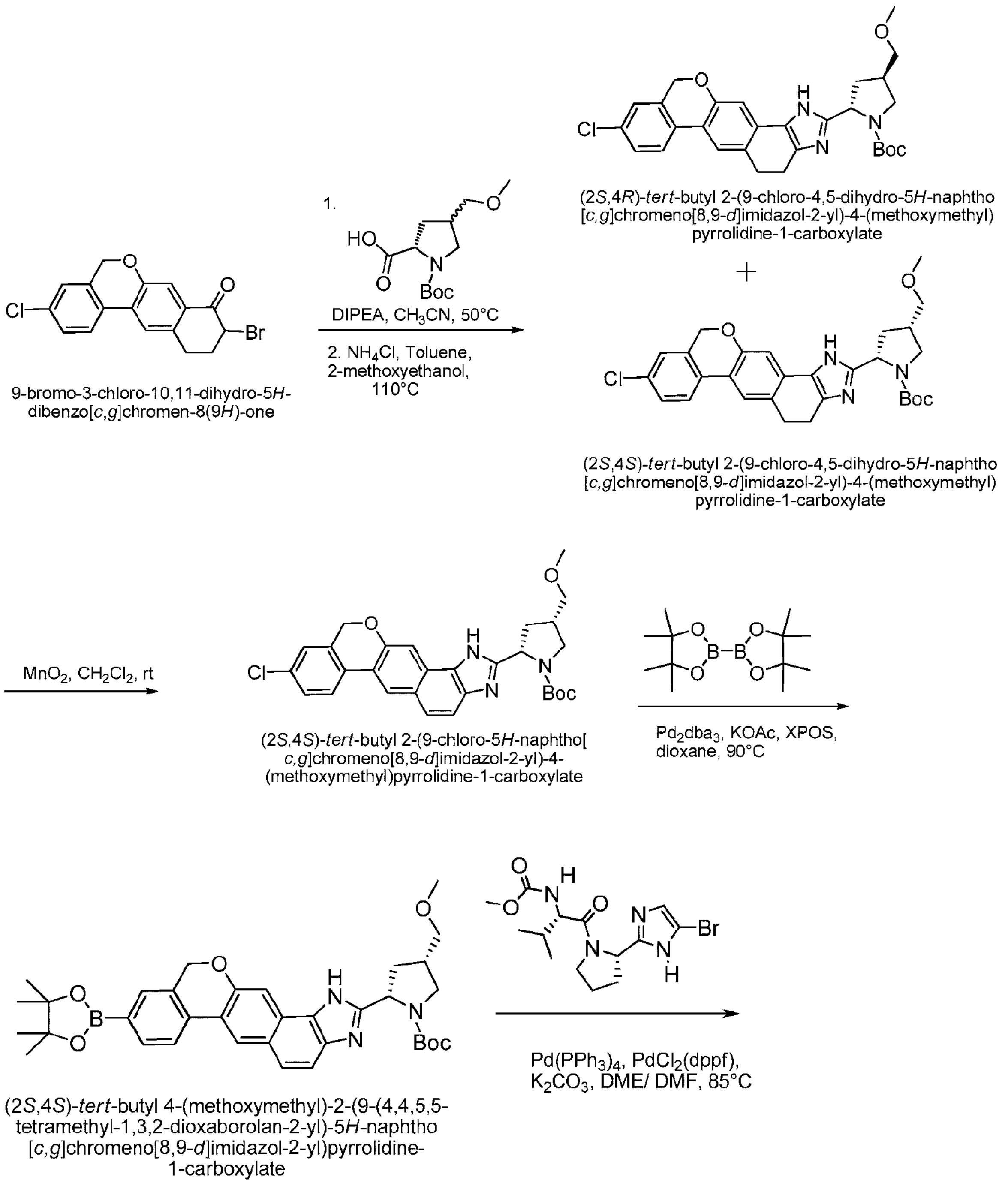
**(2S,4S)-1-tert-butyl 2-methyl 4-(hydroxymethyl)pyrrolidine-1,2-dicarboxylate.** To a solution of (3S,5S)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)pyrrolidine-3-carboxylic acid (6.38 g, 23.3 mmol) in THF (116 mL) at 0 °C (external temperature, ice bath) was added $Et_3N$ (4.9 mL, 35.0 mmol) and ethyl chloroformate (2.7 mL, 28.0 mmol). The resulting solution was stirred at 0 °C for 45 min, during which time a white precipitate forms. The reaction mixture was filtered through celite and concentrated.

The crude intermediate was dissolved in THF (59 mL) and cooled to 0 °C (external temperature, ice bath). $NaBH_4$ (4.41 g, 116.7 mmol) in $H_2O$ (59 mL) was slowly added and the resulting solution was stirred at 0 °C for 2 h. The reaction mixture was diluted with EtOAc and washed with $H_2O$. The aqueous layer was backextracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$ and concentrated. The crude oil was purified by silica gel chromatography (42% to 69% to 100% EtOAc/Hexanes) to provide (2S,4S)-1-tert-butyl 2-methyl 4-(hydroxymethyl)pyrrolidine-1,2-dicarboxylate (3.63 g, 60%).

**(2S,4S)-1-tert-butyl 2-methyl 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate.** To a solution of (2S,4S)-1-tert-butyl 2-methyl 4-(hydroxymethyl)pyrrolidine-1,2-dicarboxylate (2.57 g, 9.9 mmol) in $CH_2Cl_2$ (50 mL) was added AgOTf (4.07 g, 15.8 mmol) and 2,6-di-*tert*-butylpyridine (4.4 mL, 19.8 mmol). The reaction mixture was cooled to 0 °C (external temperature, ice bath) and MeI (0.98 mL, 15.8 mmol) was slowly added. The resulting slurry was stirred at 0 °C for 1.5 h and at room temperature for 1.5 h. The slurry was diluted with $CH_2Cl_2$ and filtered through celite. The filtrate was concentrated to dryness, dissolved in $Et_2O$, and washed with HCl (1N) and brine. The aqueous layers were backextracted with $Et_2O$ and the combined organic layers were dried over $Na_2SO_4$ and concentrated. The crude oil was purified by silica gel chromatography (10% to 75% to 100% EtOAc/Hexanes) to provide (2S,4S)-1-tert-butyl 2-methyl 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate (2.11 g, 78%). $^1H$-NMR: 400 MHz, ($CDCl_3$) $\delta$: (mixture of rotomers, major reported) 4.20 (t, 1H), 3.71 (s, 3H), 3.67 (m, 1H), 3.34 (m, 2H), 3.30 (s, 3H), 3.16 (t, 1H), 2.43 (m, 2H), 1.74 (m, 1H), 1.38 (s, 9H).

**(2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid.** To a solution of (2S,4S)-1-tert-butyl 2-methyl 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate (2.11 g, 7.7 mmol) in a miture of THF (38 mL) and MeOH (15 mL) was added LiOH (2.5 M aqueous, 15 mL, 38.6 mmol). The resulting solution was stirred at room temperature for 2h, and acidified with aqueous HCl (1N). The desired product was extracted with $CH_2Cl_2$ (4x). The combined organic layers were dried over $Na_2SO_4$ and concentrated to provide (2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid (2.0 g, 99%). $^1H$-NMR: 400 MHz, ($CDCl_3$) $\delta$: (mixture of rotomers, major reported) 4.33 (t, 1H), 3.65 (m, 1H), 3.35 (m, 2H), 3.32 (s, 3H), 3.16 (t, 1H), 2.45 (m, 2H), 2.12 (m, 1H), 1.46 (s, 9H).

# Example AB-1



9-bromo-3-chloro-10,11-dihydro-5*H*-dibenzo[*c*,*g*]chromen-8(9*H*)-one

(2*S*,4*R*)-*tert*-butyl 2-(9-chloro-4,5-dihydro-5*H*-naphtho [*c*,*g*]chromeno[8,9-*d*]imidazol-2-yl)-4-(methoxymethyl) pyrrolidine-1-carboxylate

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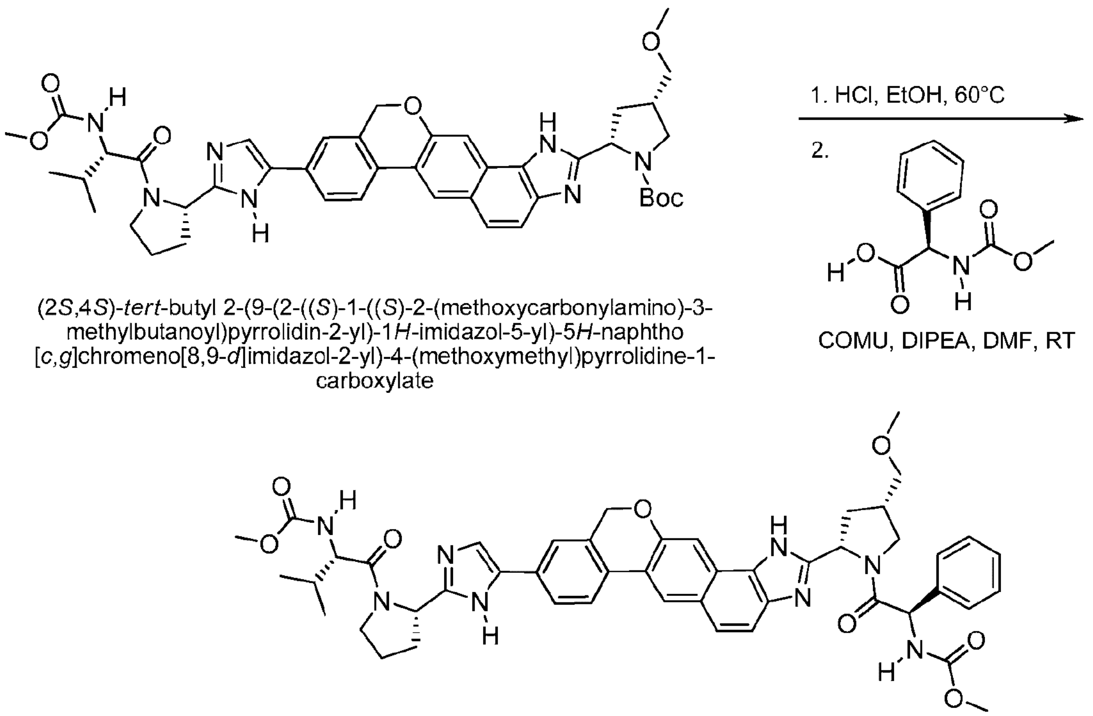
(2*S*,4*S*)-*tert*-butyl 2-(9-chloro-4,5-dihydro-5*H*-naphtho [*c*,*g*]chromeno[8,9-*d*]imidazol-2-yl)-4-(methoxymethyl) pyrrolidine-1-carboxylate

(2*S*,4*S*)-*tert*-butyl 2-(9-chloro-5*H*-naphtho[*c*,*g*]chromeno[8,9-*d*]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate

(2*S*,4*S*)-*tert*-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5*H*-naphtho [*c*,*g*]chromeno[8,9-*d*]imidazol-2-yl)pyrrolidine-1-carboxylate



(2*S*,4*S*)-*tert*-butyl 2-(9-(2-((*S*)-1-((*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)-5*H*-naphtho[*c*,*g*]chromeno[8,9-*d*]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate

methyl {2-[2-{9-[2-(1-{2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**(2S,4S)-tert-butyl-2-(9-chloro-4,5-dihydro-*5H*-naphtho[2,3-c]chromeno[8,9-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate**: To a solution of ((S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid (5.9 g, 23.1 mmol) and 9-bromo-3-chloro-10,11-dihydro-*5H*-naphtho[c,g]chromen-8(9H)-one (5.6 mg, 15.4 mmol) in acetonitrile (60 mL) was added diisopropylethylamine (5.35 mL, 30.8 mmol). The reaction was stirred at 50 °C for 18 hours and was then diluted with ethyl acetate. The organics were washed with water and brine, dried ($MgSO_4$) and concentrated. The resulting crude residue was purified by flash chromatography to yield (2S)-1-tert-butyl-2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-6H-naphtho[2,3-c]chromen-9-yl)-4(methoxymethyl) pyrrolidine-1,2-dicarboxylate (5.12 g, 61%). To a solution of (2S)-1-tert-butyl-2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-*6H*-naphtho[2,3-c]chromen-9-yl)-4(methoxymethyl)pyrrolidine-1,2-dicarboxylate (5.11 mg, 9.42 mmol) in a mixture of toluene (94 mL) and 2-methoxyethanol (0.1 mL) was added ammonium acetate (23.5 g, 304 mmol). The reaction mixture was heated to 110 °C for 18 hours, cooled to room temperature and diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield (2S,4R)-tert-butyl 2-(9-chloro-4,5-dihydro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (1.05g, 21%) and (2S,4S)-tert-butyl-2-(9-chloro-4,5-dihydro-6H-naphtho[2,3-c]chromeno[8,9-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (2.0 g, 41%). LCMS-ESI$^+$: calculated for $C_{29}H_{32}ClN_3O_{4\,2}$: 522.0; observed [M+1]$^+$: 522.2.

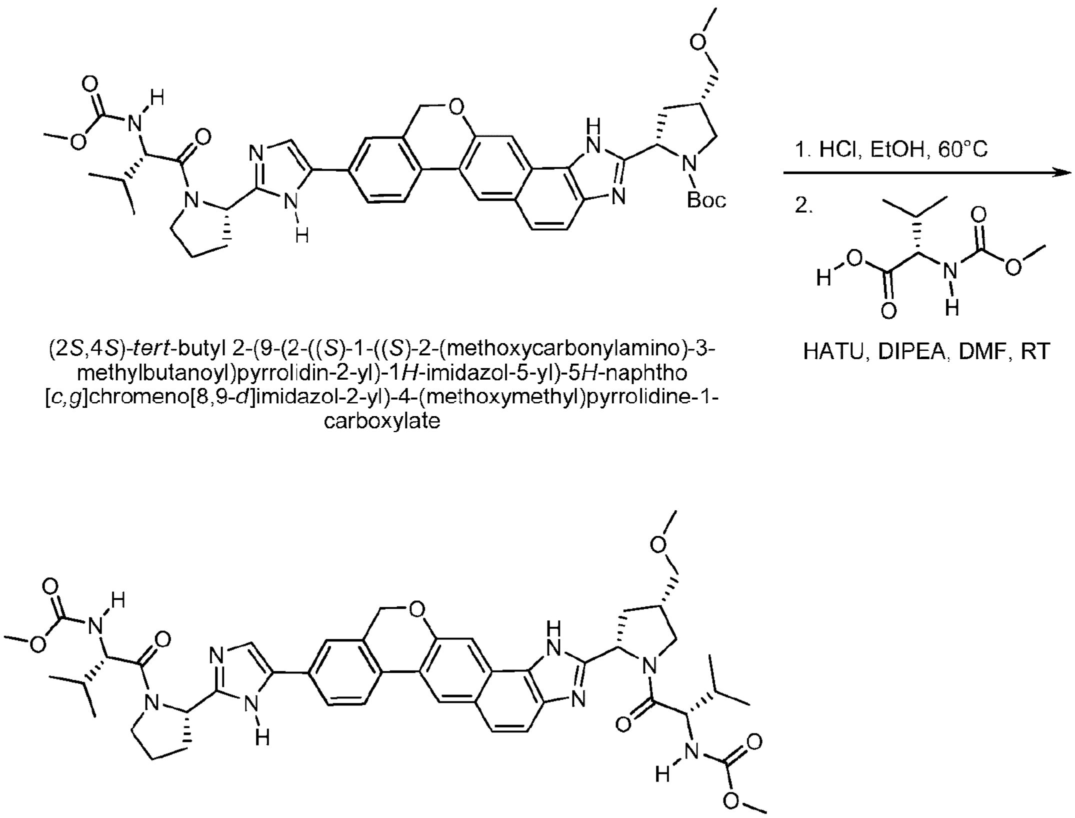
**(2S,4S)-tert-butyl-2-(9-chloro-*5H*-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate.** To a solution of (2S,4S)-tert-butyl-2-(9-chloro-4,5-dihydro-*5H*-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (1.99 g, 3.82 mmol) in dichloromethane (30 mL) was added manganese(IV) oxide (10 g, 115 mmol). The reaction mixture was stirred at room temperature for 18 hours, diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield(2S,4S)-tert-butyl-2-(9-chloro-6H-naphtho[2,3-c]chromeno[8,9-d]imidazol-2-yl)-4-methoxymethyl)pyrrolidine-1-carboxylate (1.05g, 21%) and (2S,4S)-tert-butyl-2-(9-chloro-4,5-dihydro-6H-naphtho[2,3-c]chromeno[8,9-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (1.64 g, 82%). LCMS-ESI$^+$: calculated for $C_{29}H_{30}ClN_3O_{42}$: 520.02; observed [M+1]$^+$: 520.97.

**(2S,4S)-tert-butyl-4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)pyrrolidine-1-carboxylate:** A degassed mixture of - (2S,4S)-tert-butyl-2-(9-chloro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-(methoxymethyl) pyrrolidine-1-carboxylate (649 mg1.25 mmol), bis(pinacolato)diboron (635 mg, 2.5 mmol), potassium acetate (368 mg, 3.7 mmol), tris(dibenzylideneacetone)palladium (46 mg, 0.05 mmol) and 2-dicyclohexylphosphino-2', 4', 6'-tri-i-propyl-1, 1'-biphenyl (60 mg, 0.12 mmol) in 1,4-dioxane (7 mL) was heated to 90 °C for 3 hours, cooled to room temperature and diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield (2S,4S)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)pyrrolidine-1-carboxylate (467 mg, 61%) LCMS-ESI$^+$: calculated for $C_{35}H_{42}BN_3O_6$: 611.54; observed [M+1]$^+$: 612.96.

**(2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4(methoxymethyl)pyrrolidine-1-carboxylate** To a solution of (2S,4S)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)pyrrolidine-1-carboxylate (467 mg, 0.76 mmol), methyl (S)-1-((S)-2-(5-bromo-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (342 mg, 0.92 mmol), tetrakis(triphenylphosphine) palladium(0) (44 mg, 0.04 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (56 mg, 0.07 mmol) in a mixture of 1,2-dimethoxyethane (11.0 mL) and dimethylformamide (1.9 mL) was added a solution of potassium carbonate (2M in water, 1.15 mL, 2.29 mmol). The resulting mixture was degassed and then heated to 85 °C under argon for 18 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield (2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g] chromeno [8,9-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (180 mg, 67%). LCMS-ESI$^+$: calculated for $C_{43}H_{51}N_7O_{73}$ 777.91; observed $[M+1]^+$: 778.84.

**methyl {2-[2-{9-[2-(1-{2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate**: A solution of (2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (196 mg, 0.25 mmol), ethanol (3 mL) and concentrated HCl (1 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and the crude material dissolved in DCM (6 mL). This solution was concentrated and to this material was added a solution of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (69 mg, 0.33 mmol) and COMU (124 mg, 029 mmol) in DMF (4 mL). To the resulting solution was added diisopropylethylamine (130 µL, 0.76 mmol). After stirring for 2 hours at room temperature, the reaction was diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 45% ACN/$H_2O$ + 0.1% TFA). The product fractions were lyophilized to give methyl {2-[2-{9-[2-(1-{2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (84 mg, 39%). LCMS-ESI$^+$: calculated for $C_{48}H_{52}N_8O_8$: 868.98; observed $[M+1]^+$: 870.11

## Example AC



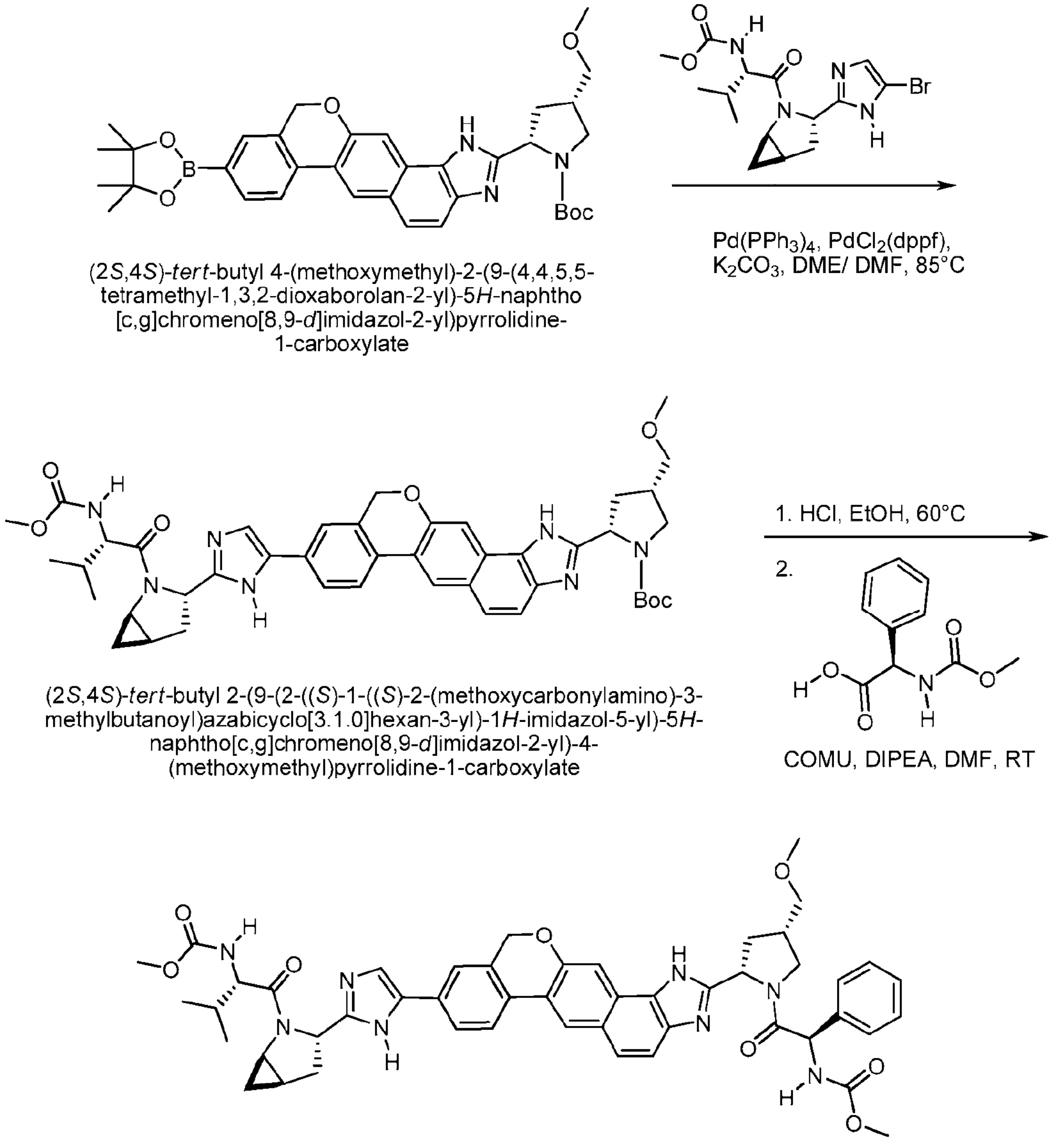
(2*S*,4*S*)-*tert*-butyl 2-(9-(2-((*S*)-1-((*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)-5*H*-naphtho[*c*,*g*]chromeno[8,9-*d*]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate

methyl {1-[2-{9-[2-(1-{2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**methyl {1-[2-{9-[2-(1-{2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate**: A solution of (2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (116 mg, 0.15 mmol), ethanol (5 mL) and concentrated HCl (1 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and the crude material dissolved in DCM (10 mL). This solution was concentrated and to this material was added a solution of 2-methoxycarbonylamino-3-methylbutyric acid (38 mg, 0.22 mmol) and HATU (79 mg, 0.21 mmol) in DMF (1.4 mL). To the resulting solution was added diisopropylethylamine (270 μL, 1.5 mmol). After stirring for 18 hours at room temperature, the reaction was diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$), concentrated and purified by preparative reverse phase

HPLC (Gemini, 15 to 45% ACN/$H_2O$ + 0.1% TFA). The product fractions were lyophilized to give methyl {1-[2-{9-[2-(1-{2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (58 mg, 13%). LCMS-ESI$^+$: calculated for $C_{45}H_{54}N_8O_8$: 834.96; observed [M+1]$^+$: 835.70.

## Example AD



(2*S*,4*S*)-*tert*-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5*H*-naphtho[c,g]chromeno[8,9-*d*]imidazol-2-yl)pyrrolidine-1-carboxylate

Pd($PPh_3$)$_4$, $PdCl_2$(dppf), $K_2CO_3$, DME/ DMF, 85°C

(2*S*,4*S*)-*tert*-butyl 2-(9-(2-((*S*)-1-((*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl)azabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazol-5-yl)-5*H*-naphtho[c,g]chromeno[8,9-*d*]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate

1. HCl, EtOH, 60°C

2.

COMU, DIPEA, DMF, RT

methyl {2-[2-{9-[2-(2-{2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

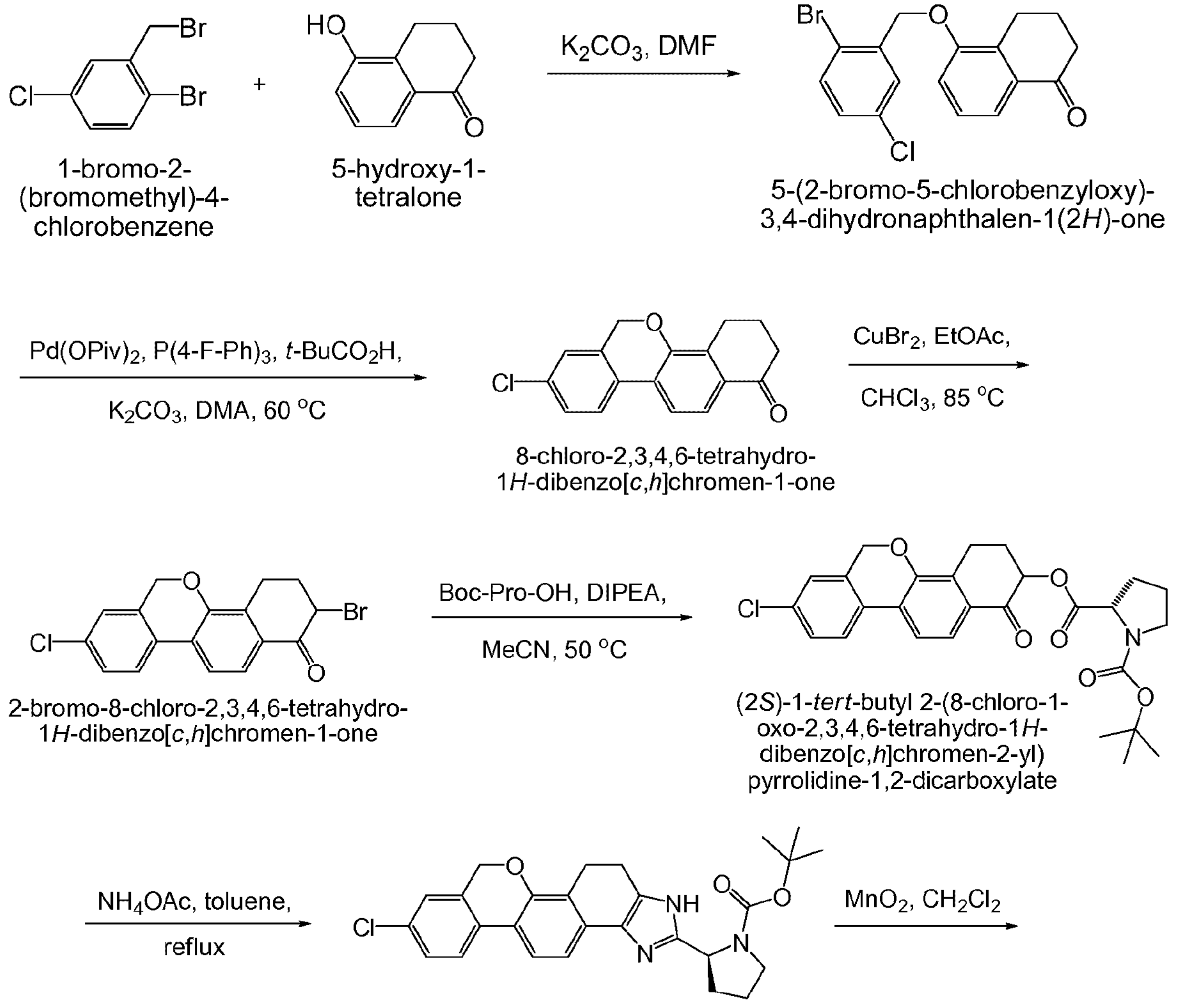
**(2S,4S)-tert-butyl-2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino) methylbutanoyl)azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)-5H-**

**naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate** To a solution of (2S,4S)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)pyrrolidine-1-carboxylate (557 mg, 0.91 mmol), methyl (S)-1-((1S,3S,5S)-3-(5-bromo-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate (350 mg, 0.91 mmol) tetrakis(triphenylphosphine) palladium(0) (53 mg, 0.04 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (67 mg, 0.07 mmol) in a mixture of 1,2-dimethoxyethane (11.0 mL) and dimethylformamide (1.9 mL) was added a solution of potassium carbonate (2M in water, 1.37 mL, 2.7 mmol). The resulting mixture was degassed and then heated to 85 °C under argon for 18 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield (2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (271 mg, 38%). LCMS-ESI$^+$: calculated for C44H51N7O7. 789.92; observed $[M+1]^+$: 790.76.

**methyl {2-[2-{9-[2-(2-{2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate:** A solution of (2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (196 mg, 0.25 mmol), ethanol (3 mL) and concentrated HCl (1 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and the crude material dissolved in DCM (6 mL). This solution was concentrated and to this material was added a solution of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (69 mg, 0.33 mmol) and COMU (124 mg, 029 mmol) in DMF (4 mL). To the resulting solution was added diisopropylethylamine (130 µL, 0.76 mmol). After stirring for 2 hours at room temperature, the reaction was diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 45% ACN/$H_2O$ + 0.1% TFA). The product fractions were lyophilized to give methyl {2-[2-{9-[2-(2-{2-[(methoxycarbonyl)amino]-3-

methylbutanoyl}-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (84 mg, 39%). LCMS-ESI$^+$: calculated for C49H52N8O8: 880.99; observed $[M+1]^+$: 882.09

## Example AE



1-bromo-2-(bromomethyl)-4-chlorobenzene

5-hydroxy-1-tetralone

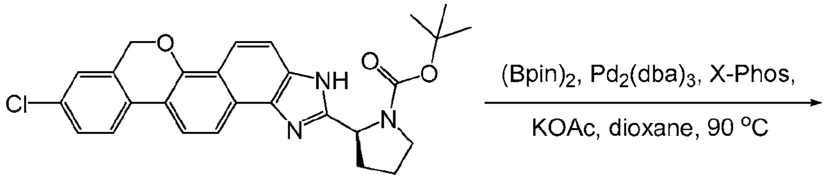
5-(2-bromo-5-chlorobenzyloxy)-3,4-dihydronaphthalen-1(2*H*)-one

8-chloro-2,3,4,6-tetrahydro-1*H*-dibenzo[*c*,*h*]chromen-1-one

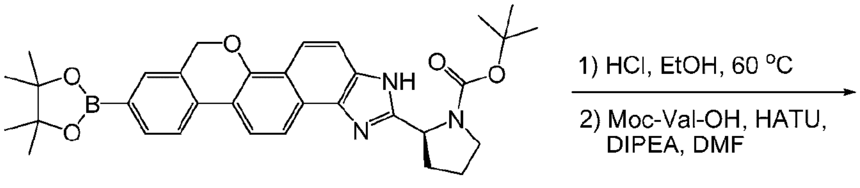
2-bromo-8-chloro-2,3,4,6-tetrahydro-1*H*-dibenzo[*c*,*h*]chromen-1-one

(2*S*)-1-*tert*-butyl 2-(8-chloro-1-oxo-2,3,4,6-tetrahydro-1*H*-dibenzo[*c*,*h*]chromen-2-yl) pyrrolidine-1,2-dicarboxylate

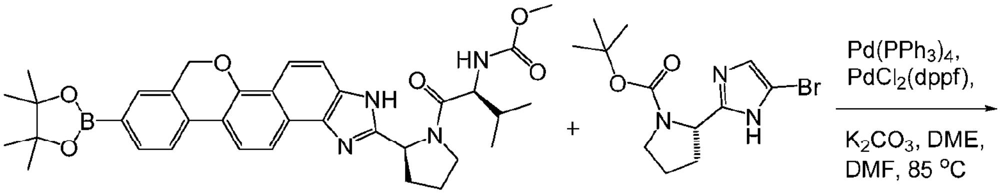
tert-butyl (2S)-2-(9-chloro-3,4,5,7-tetrahydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate



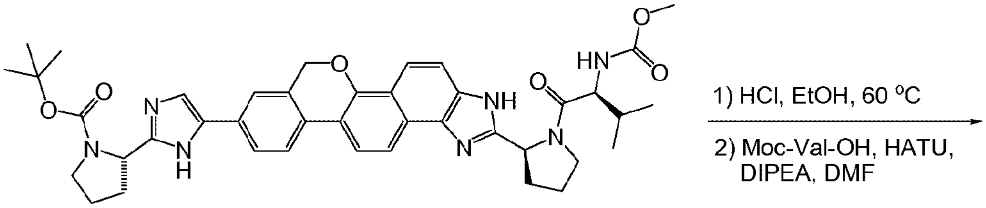
tert-butyl (2S)-2-(9-chloro-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate



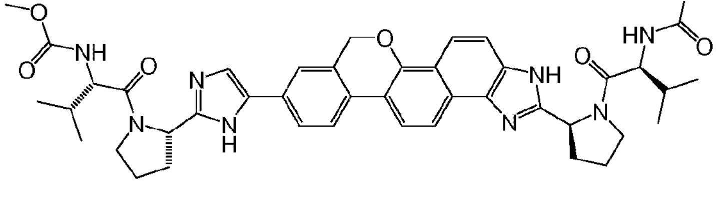
tert-butyl (2S)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate



methyl [(2S)-3-methyl-1-oxo-1-{(2S)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}butan-2-yl]carbamate



tert-butyl (2R)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate



methyl {(2S)-1-[(2R)-2-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**5-(2-bromo-5-chlorobenzyloxy)-3,4-dihydronaphthalen-1(2*H*)-one:** To a stirred solution of 5-hydroxy-1-tetralone (2.0 g, 12.3 mmol) and 1-bromo-2-(bromomethyl)-4-chlorobenzene (3.6 g, 12.7 mmol) in dimethylformamide (125 mL) was added potassium carbonate (3.5 g, 25.1 mmol). The reaction was stirred under argon for 1 hour then diluted with ethyl acetate (1 L). The organics were washed three times with water and once with brine. The organic layer was then dried with magnesium sulfate, filtered and concentrated. To the resulting oil was added methanol (100 mL) and the suspension was agitated for thirty minutes. 5-(2-bromo-5-chlorobenzyloxy)-3,4-dihydronaphthalen-1(*2H*)-one (4.25 g, 94% yield) was isolated by filtration.

**8-chloro-2,3,4,6-tetrahydro-*1H*-dibenzo[c,h]chromen-1-one:** To a flask containing palladium(II) pivalate (68 mg, 0.22 mmol), tri(4-fluorophenyl)phosphine (70 mg, 0.22 mmol), pivalic acid (135 mg, 1.3 mmol) and potassium carbonate (1.83 g, 13.1 mmol) was added a solution of 5-(2-bromo-5-chlorobenzyloxy)-3,4-dihydronaphthalen-1(2*H*)-one (1.61 g, 4.4 mmol) in dimethyacetamide (23 mL). The flask was evacuated and backfilled with argon 5 times and then stirred under argon at 60 °C for 24 hours. The reaction was poured directly onto a silica gel column and purified by flash column chromatography (hexanes/DCM) to yield 8-chloro-2,3,4,6-tetrahydro-*1H*-dibenzo[c,h]chromen-1-one (1.22 g, 97% yield) as an off-white solid.

**2-bromo-8-chloro-2,3,4,6-tetrahydro-*1H*-dibenzo[c,h]chromen-1-one:** To a mixture of 8-chloro-2,3,4,6-tetrahydro-*1H*-dibenzo[c,h]chromen-1-one (2.58 g, 9.1 mmol) in chloroform (9.1 mL) and ethyl acetate (9.1 mL) was added copper(II) bromide (4.65 g, 19.9 mmol). The reaction was heated to 80 °C for 5 hours and then cooled to room temperature. The mixture was diluted with dichloromethane and washed twice with a 5:1 solution of saturated aqueous ammonium chloride and aqueous ammonium hydroxide (~28%), and washed once with water. The organic layer was dried with magnesium sulfate, filtered and concentrated. The crude material was purified by flash column chromatography (hexanes/DCM) to yield 2-bromo-8-chloro-2,3,4,6-tetrahydro-*1H*-dibenzo[c,h]chromen-1-one (2.45 g, 75% yield).

**(2*S*)-1-*tert*-butyl 2-(8-chloro-1-oxo-2,3,4,6-tetrahydro-1*H*-dibenzo[c,h]chromen-2-yl) pyrrolidine-1,2-dicarboxylate**: To a solution of 2-bromo-8-chloro-2,3,4,6-tetrahydro-*1H*-dibenzo[c,h]chromen-1-one (1.05 g, 2.9 mmol) and Boc-Pro-OH (1.75 g, 8.1 mmol) in acetonitrile (9.0 mL) was added diisopropylethylamine (1.5 mL, 8.7 mmol). The solution was stirred under argon at 50 °C for two hours. Extra Boc-Pro-OH (620 mg, 2.9 mmol) and diisopropylethylamine (0.5 mL, 2.9 mmol) were added and the reaction was stirred at 50 °C for 16 hours. The reaction was cooled to room temperature and diluted with ethyl acetate. The organics were washed with water and brine, dried with magnesium sulfate and concentrated. The crude material was purified by flash column chromatography and the product (2*S*)-1-tert-butyl 2-(8-chloro-1-oxo-2,3,4,6-tetrahydro-*1H*-dibenzo[c,h]chromen-2-yl) pyrrolidine-1,2-dicarboxylate was isolated as a mixture of diastereomers (0.99 g, 69% yield).

**tert-butyl (2S)-2-(9-chloro-3,4,5,7-tetrahydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate**: To a solution of (2*S*)-1-tert-butyl 2-(8-chloro-1-oxo-2,3,4,6-tetrahydro-*1H*-dibenzo[c,h]chromen-2-yl) pyrrolidine-1,2-dicarboxylate (2.2 g, 4.4 mmol) in toluene (40 mL) was added ammonium acetate (7 g, 91 mmol). The reaction mixture was vigorously refluxed for 3 hours, then cooled to room temperature and diluted with ethyl acetate. The organics were washed with water and brine, dried with magnesium sulfate and concentrated. The crude material was purified by flash column chromatography to yield tert-butyl (2S)-2-(9-chloro-3,4,5,7-tetrahydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (1.13 g, 54% yield) as well as recovered (2*S*)-1-tert-butyl 2-(8-chloro-1-oxo-2,3,4,6-tetrahydro-*1H*-dibenzo[c,h]chromen-2-yl) pyrrolidine-1,2-dicarboxylate (0.8 g, 36%). ). LCMS-ESI$^+$: calculated for $C_{27}H_{28}N_3O_3$: 477.98; observed $[M+1]^+$: 478.54.

**tert-butyl (2S)-2-(9-chloro-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate**: To a solution of Intermediate tert-butyl (2S)-2-(9-chloro-3,4,5,7-tetrahydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (1.43 g, 3.0 mmol) in dichloromethane (30 mL) was added manganese(IV) oxide (15 g, 198 mmol). The mixture was stirred for four hours at room temperature then filtered through Celite. The $MnO_2$ was thoroughly rinsed with dichloromethane and the total filtrate was concentrated to yield tert-butyl (2S)-2-(9-chloro-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (1.37 g, 96% yield). This material was used without further purification.

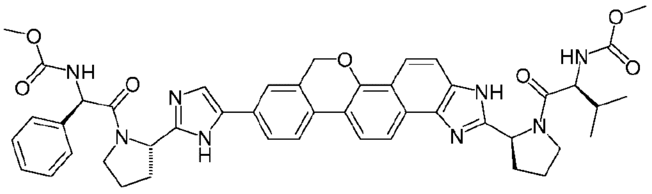
**tert-butyl (2S)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate**: To a solution of tert-butyl (2S)-2-(9-chloro-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (1.4 g, 2.9 mmol) in dioxane (20 mL) was added bis(pinacolato)diboron (1.5 g, 5.9 mmol), tris(dibenzylideneacetone)dipalladium(0) (110 mg, 0.12 mmol), X-Phos (145 mg, 0.30 mmol) and potassium acetate (870 mg, 8.9 mmol). The mixture was degassed with a stream of argon for ten minutes. The degassed reaction was heated under argon to 90 °C for 2.5 hours then cooled to room temperature and diluted with ethyl acetate. The organics were washed with water and brine, dried with magnesium sulfate and concentrated. The crude material was purified by flash column chromatography (DCM/EtOAc) to yield tert-butyl (2S)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate (1.5 g, 90% yield).

**methyl [(2S)-3-methyl-1-oxo-1-{(2S)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}butan-2-yl]carbamate**: A solution of tert-butyl (2S)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate (0.98 g, 1.7 mmol), concentrated HCl (2 mL) and ethanol (20 mL) was heated to 60 °C for 2 hours. The reaction was concentrated and redissolved in a minimal amount of methanol. An equal volume of dichloromethane was added and the solution was again concentrated. Dichloromethane was added to the resulting residue and concentrated off two more times. The resulting crude material was dissolved in dimethylformamide (17 mL). To this solution was added (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (455 mg, 2.6 mmol), HATU (955 mg, 2.5 mmol) and diisopropylethylamine (3 mL, 17 mmol). The reaction was stirred at room temperature for one hour then diluted with ethyl acetate. The organics were washed with water (x2) and brine, dried with magnesium sulfate and concentrated. The resulting residue was purified by flash column chromatography to yield Intermediate methyl [(2S)-3-methyl-1-oxo-1-{(2S)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}butan-2-yl]carbamate (780 mg, 72% yield over 2 steps).

**tert-butyl (2R)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate**: A mixture of Pentacyclic Intermediate methyl [(2S)-3-methyl-1-oxo-1-{(2S)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}butan-2-yl]carbamate (780 mg, 1.3 mmol), (*S*)-*tert*-butyl 2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (450 mg, 1.4 mmol), tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.03 mmol), $PdCl_2$(dppf) (60 mg, 0.08 mmol), 2M aqueous potassium carbonate (1.9 mL, 3.9 mmol), dimethoxyethane (10 mL) and dimethylformamide (2 mL) was degassed with argon for 15 minutes. The reaction was then heated to 85 °C for 3 hours. Upon completion, the reaction was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was washed with water and brine, dried ($MgSO_4$) and concentrated. The resulting crude material was purified by flash column chromatography (EtOAc/MeOH) to yield Intermediate tert-butyl (2R)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate (390 mg, 43% yield).

**methyl {(2S)-1-[(2R)-2-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate**: A mixture of Intermediate tert-butyl (2R)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate (390 mg, 0.53 mmol), concentrated HCl (2 mL) and ethanol (10 mL) was heated to 60 °C for 2 hours. The reaction was concentrated and redissolved in a minimal amount of methanol. An equal volumne of dichloromethane was added and the solution was again concentrated. Dichloromethane was added to the resulting residue and concentrated off two more times. One half of the crude material (~0.27 mmol) was dissolved in dimethylformamide (2.5 mL). To this solution was added (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (66 mg, 0.38 mmol), HATU (140 mg, 0.37 mmol) and diisopropylethylamine (0.48 mL, 2.7 mmol). The reaction was stirred at room temperature for 2 hours, and then diluted with acetonitrile (2 mL) and methanol (2 mL). To this solution was added ten drops of 5M aqueous NaOH solution and stirring was continued for 30 minutes. The reaction was diluted with ethyl acetate and the organic layer was washed with water and brine. The combined aqueous washings were extracted three times with ethyl acetate, and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude material was purified by reverse phase HPLC (Gemini, 15 to 45% ACN/$H_2O$ + 0.1% TFA) to yield methyl {(2S)-1-[(2R)-2-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (140 mg, 67% yield over 2 steps). LCMS-ESI$^+$: calculated for $C_{43}H_{50}N_8O_7$: 790.91; observed $[M+1]^+$: 791.71.

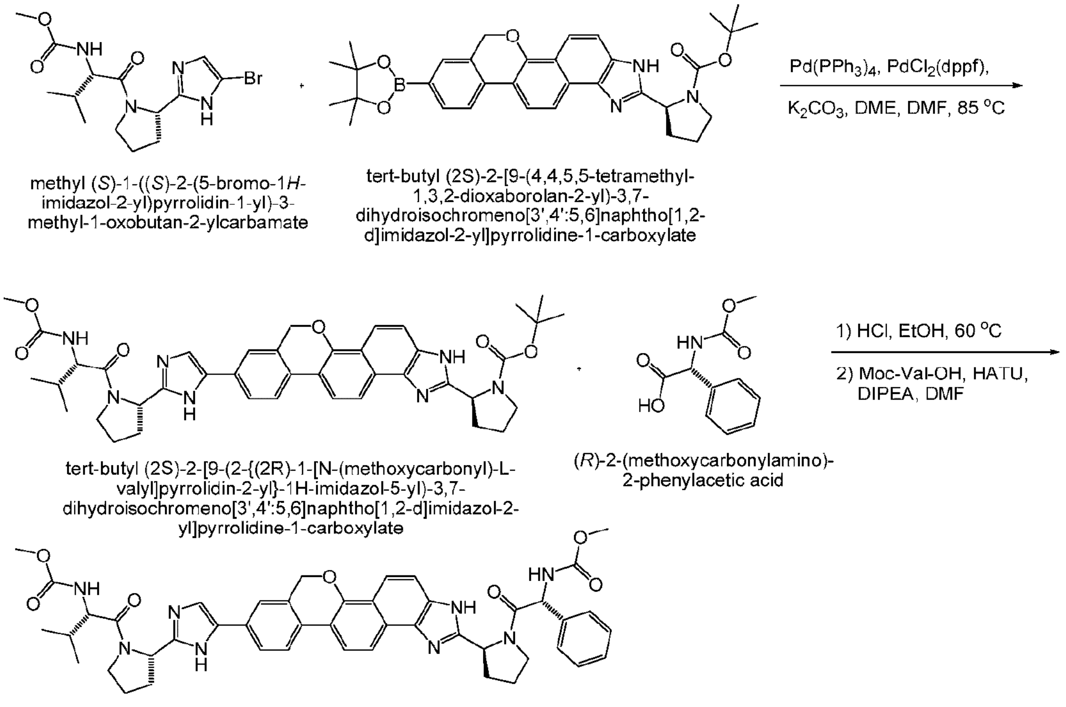
## Example AF



methyl {(1R)-2-[(2R)-2-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

This compound was made in an analogous manner to Example methyl {(2S)-1-[(2R)-2-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate, substituting (*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid for (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid and substituting COMU for HATU in the final amide coupling step. LCMS-ESI$^+$: calculated for $C_{46}H_{48}N_8O_7$: 824.92; observed $[M+1]^+$: 825.72.

## Example AG



methyl (*S*)-1-((*S*)-2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

tert-butyl (2S)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate

tert-butyl (2S)-2-[9-(2-{(2R)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate

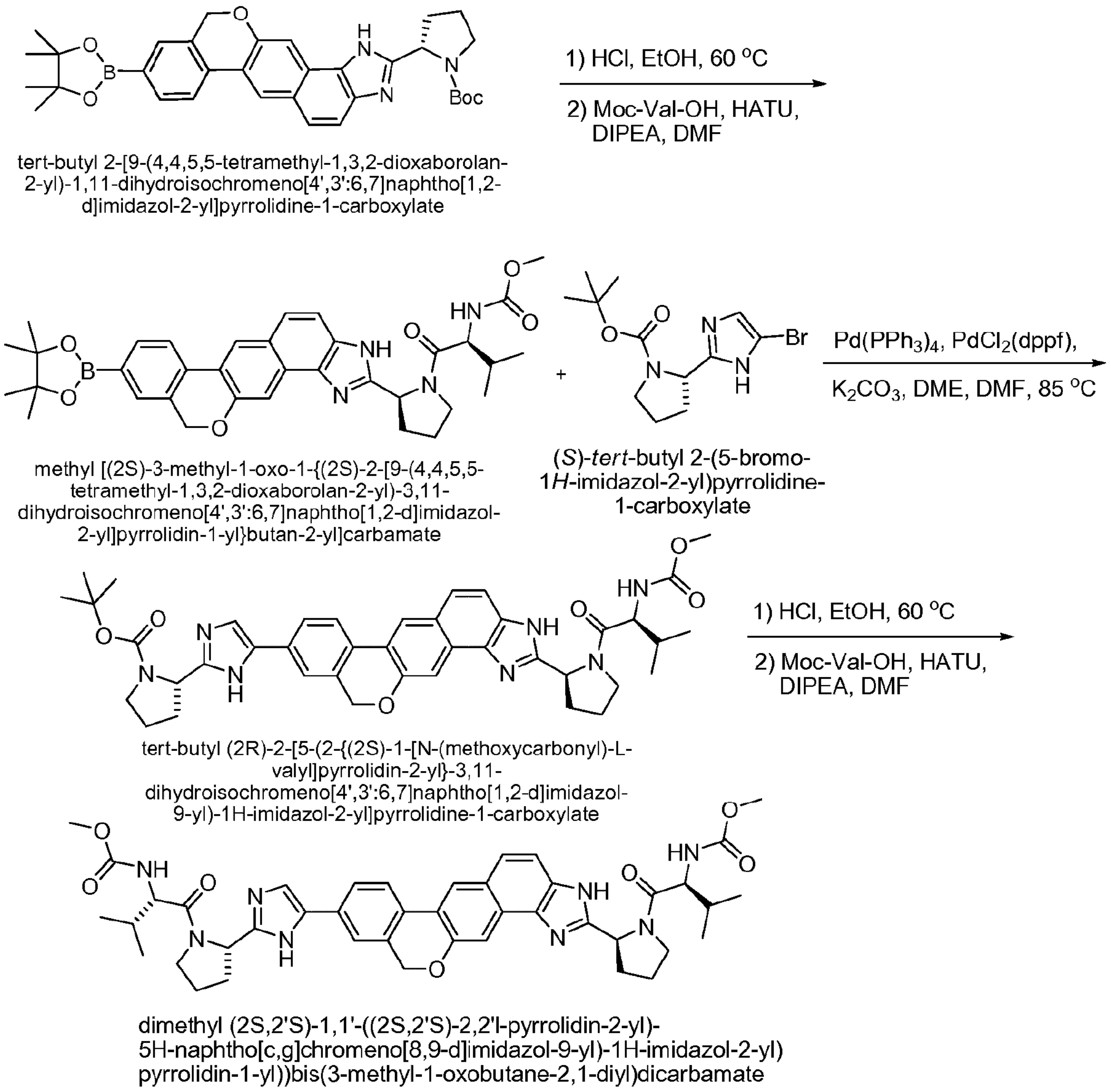
(*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid

methyl {(2S)-1-[(2R)-2-(5-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**tert-butyl (2S)-2-[9-(2-{(2R)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate:** A mixture of tert-butyl (2S)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate (450 mg, 0.79 mmol), methyl (*S*)-1-((*S*)-2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (325 mg, 0.87 mmol), tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.02 mmol), $PdCl_2$(dppf) (35 mg, 0.05 mmol), 2M aqueous potassium carbonate (1.2 mL, 2.4 mmol), dimethoxyethane (6.8 mL) and dimethylformamide (1.2 mL) was degassed with argon for 15 minutes. The reaction was then heated to 85 °C for 2.5 hours. Upon completion, the reaction was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was washed with water and brine, dried ($MgSO_4$) and concentrated. The resulting crude material was purified by flash column chromatography (EtOAc/MeOH) to yield tert-butyl (2S)-2-[9-(2-{(2R)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate (270 mg, 46% yield).

**methyl {(2S)-1-[(2R)-2-(5-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate**: A mixture of tert-butyl (2S)-2-[9-(2-{(2R)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate (270 mg, 0.37 mmol), concentrated HCl (1.5 mL) and ethanol (8 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and redissolved in a minimal amount of methanol. An equal volumne of dichloromethane was added and the solution was again concentrated. Dichloromethane was added to the resulting residue and concentrated off two more times. The crude material was dissolved in 5:1 dichloromethane/dimethylformamide (3.8 mL). To this solution was added (*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid (96 mg, 0.46 mmol), COMU (190 mg, 0.44 mmol) and diisopropylethylamine (0.20 mL, 1.1 mmol). The reaction was stirred at 0 °C for 30 minutes then warmed to room temperature. Upon completion, the reaction was diluted with acetonitrile (2 mL) and methanol (2 mL). To this solution was added ten drops of 5M aqueous NaOH solution and stirring was continued for 30 minutes. The reaction was diluted with ethyl acetate and the organic layer was washed with water and brine. The combined aqueous washings were extracted three times with ethyl acetate, and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude material was purified by reverse phase HPLC (Gemini, 15 to 45% ACN/$H_2O$ + 0.1% TFA) to yield methyl {(2S)-1-[(2R)-2-(5-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (155 mg, 51% yield over 2 steps). LCMS-ESI$^+$: calculated for $C_{46}H_{48}N_8O_7$: 824.92; observed $[M+1]^+$: 825.67.

## Example AH



tert-butyl 2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate

methyl [(2S)-3-methyl-1-oxo-1-{(2S)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}butan-2-yl]carbamate

(*S*)-*tert*-butyl 2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate

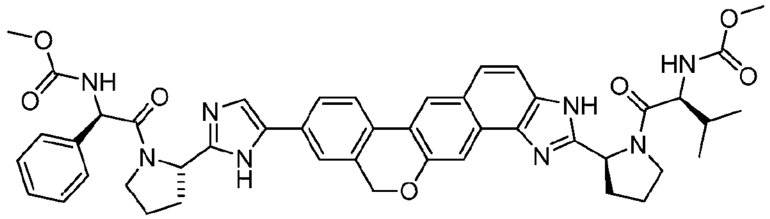
tert-butyl (2R)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'l-pyrrolidin-2-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-9-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

**dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'l-pyrrolidin-2-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-9-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl))bis(3-methyl-1-oxobutane-2,1-**

**diyl)dicarbamate:** This compound was made in an analogous manner to methyl {(2S)-1-[(2R)-2-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate, substituting 7-hydroxy-1-tetralone for 5-hydroxy-1-tetralone in the first step of the sequence. All reactions in the synthesis of Example AH gave similar product yields as in the synthesis of methyl {(2S)-1-[(2R)-2-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate. LCMS-ESI$^+$: calculated for $C_{43}H_{50}N_8O_7$: 790.91; observed $[M+1]^+$: 791.6.

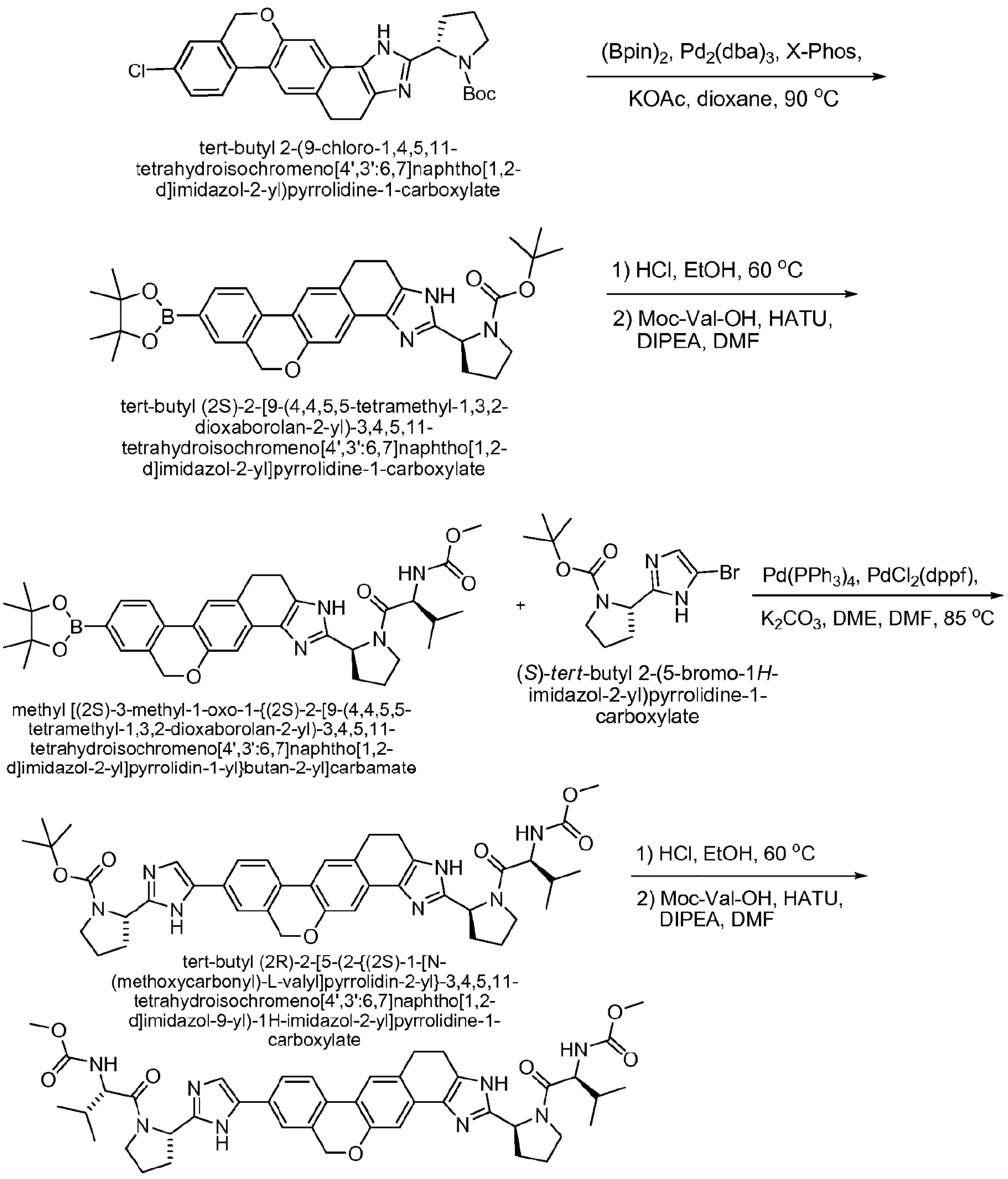
## Example AI



methyl [1-(2-{5-[2-(1-{[(methoxycarbonyl)amino]-3-methyl-1-oxobutan-2-yl}pyrrolidin-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl)-phenyl-1-oxoacet-2-yl]carbamate

**methyl [1-(2-{5-[2-(1-{[(methoxycarbonyl)amino]-3-methyl-1-oxobutan-2-yl}pyrrolidin-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl)-phenyl-1-oxoacet-2-yl]carbamate**: This compound was made in an analogous manner to dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'l-pyrrolidin-2-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-9-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate, substituting (*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid for (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid and substituting COMU for HATU in the final amide coupling step. LCMS-ESI$^+$: calculated for $C_{46}H_{48}N_8O_7$: 824.92; observed $[M+1]^+$: 825.67.

## Example AJ



tert-butyl 2-(9-chloro-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate

tert-butyl (2S)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate

methyl [(2S)-3-methyl-1-oxo-1-{(2S)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}butan-2-yl]carbamate

(*S*)-*tert*-butyl 2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate

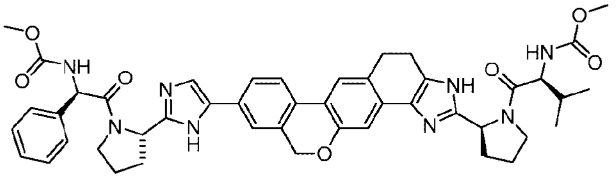
tert-butyl (2R)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-3,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'l-pyrrolidin-2-yl)-7H-dihydro-naphtho[c,g]chromeno[8,9-d]imidazol-9-yl)-1H-imidazol-2-yl) pyrrolidin-1-yl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

**dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'l-pyrrolidin-2-yl)-7H-dihydro-naphtho[c,g]chromeno[8,9-d]imidazol-9-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl))bis(3-**

**methyl-1-oxobutane-2,1-diyl)dicarbamate**: This compound was made in an analogous manner to dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'l-pyrrolidin-2-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-9-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate, omitting the $MnO_2$ oxidation of tert-butyl 2-(9-chloro-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate. LCMS-ESI$^+$: calculated for $C_{43}H_{52}N_8O_7$: 792.40; observed $[M+1]^+$: 793.69.

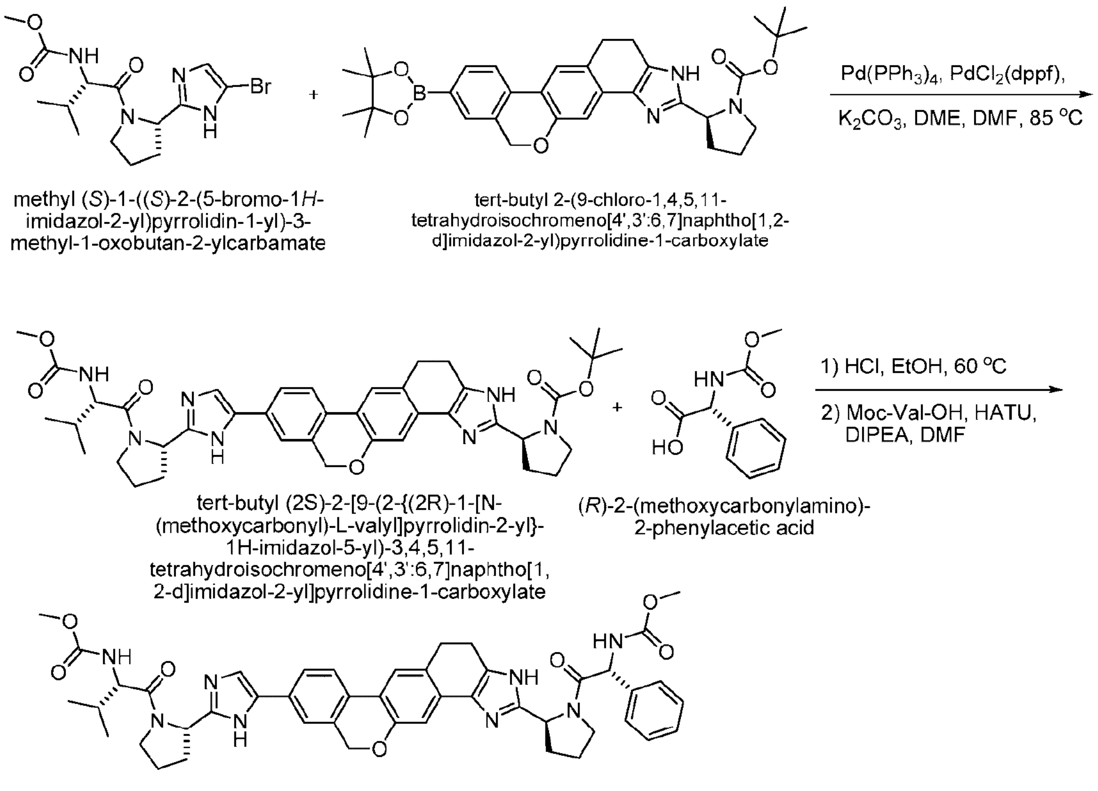
## Example AK



methyl [1-(2-{5-[2-(1-{[(methoxycarbonyl)amino]-3-methyl-1-oxobutan-2-yl}pyrrolidin-2-yl)-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl)-phenyl-1-oxoacet-2-yl]carbamate

**methyl [1-(2-{5-[2-(1-{[(methoxycarbonyl)amino]-3-methyl-1-oxobutan-2-yl}pyrrolidin-2-yl)-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl)-phenyl-1-oxoacet-2-yl]carbamate**: This compound was made in an analogous manner to dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'l-pyrrolidin-2-yl)-7H-dihydro-naphtho[c,g]chromeno[8,9-d]imidazol-9-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate, substituting (*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid for (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid and substituting COMU for HATU in the final amide coupling step. LCMS-ESI$^+$: calculated for $C_{46}H_{50}N_8O_7$: 826.94; observed $[M+1]^+$: 827.71.

## Example AL



methyl (*S*)-1-((*S*)-2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

tert-butyl 2-(9-chloro-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate

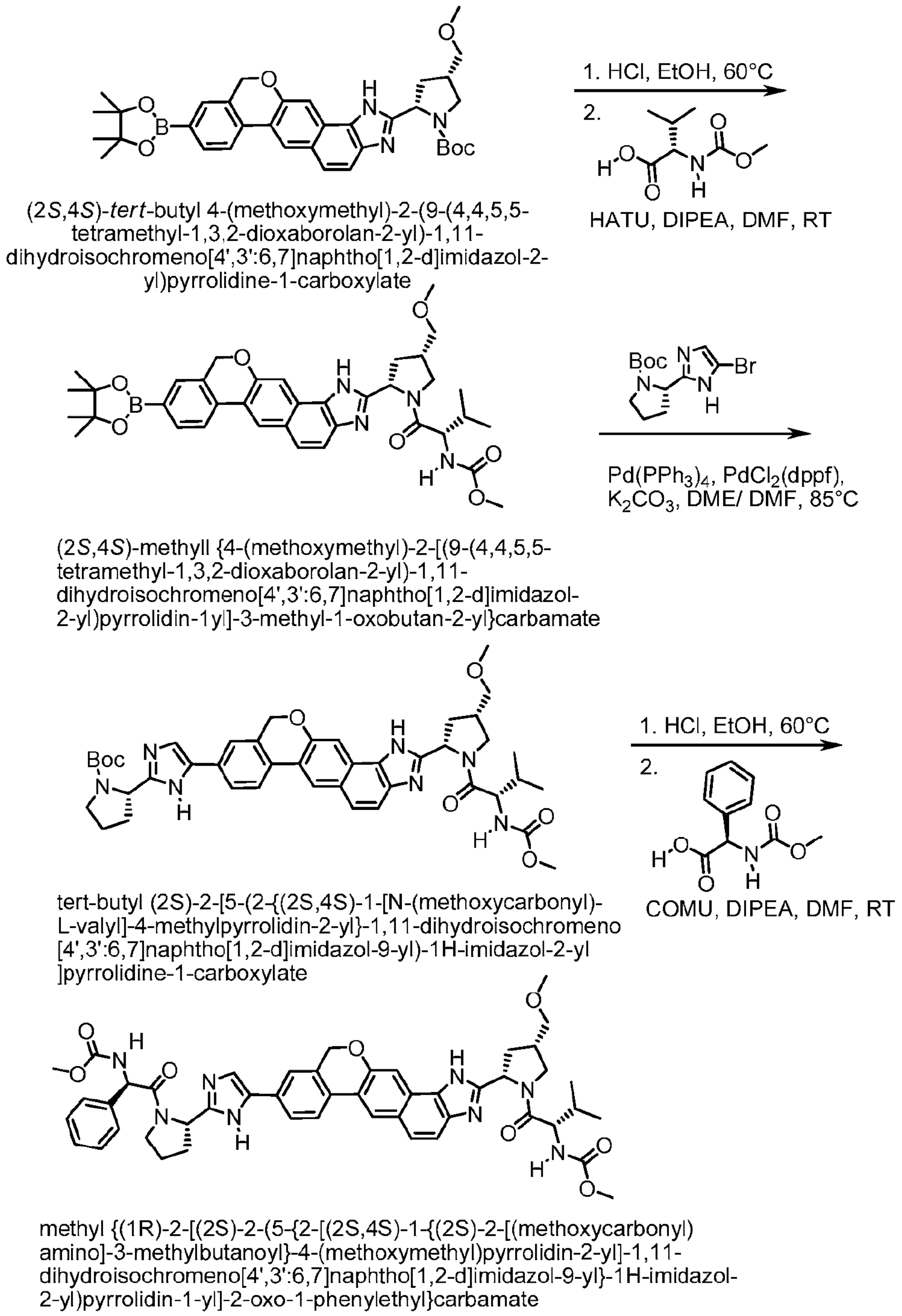
tert-butyl (2S)-2-[9-(2-{(2R)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-3,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate

(*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid

[1-(2-{5-[2-(1-{[(methoxycarbonyl)amino](phenyl)acetyl}pyrrolidin-2-yl)-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl]carbamic acid

**[1-(2-{5-[2-(1-{[(methoxycarbonyl)amino](phenyl)acetyl}pyrrolidin-2-yl)-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl]carbamic acid**: This compound was made in an analogous manner to methyl {(2S)-1-[(2R)-2-(5-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate, substituting tert-butyl (2S)-2-[9-(2-{(2R)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-3,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate for tert-butyl (2S)-2-[9-(2-{(2R)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-3,7-dihydroisochromeno[3',4':5,6]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate. LCMS-ESI$^+$: calculated for $C_{46}H_{50}N_8O_7$: 826.94; observed [M+1]$^+$: 827.64.

## Example AM



(2*S*,4*S*)-*tert*-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate

(2*S*,4*S*)-methyll {4-(methoxymethyl)-2-[(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1yl]-3-methyl-1-oxobutan-2-yl}carbamate

tert-butyl (2S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl ]pyrrolidine-1-carboxylate

methyl {(1R)-2-[(2S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**(2S,4S)-methyll {4-(methoxymethyl)-2-[(9-(4,4,5,5-tetramethyl-1,3,2-dioxa borolan-2-yl)- 1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl) pyrrolidin-1yl]-3-methyl-1-oxobutan-2-yl}carbamate:** A solution of (2S,4S)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)- 1,11-

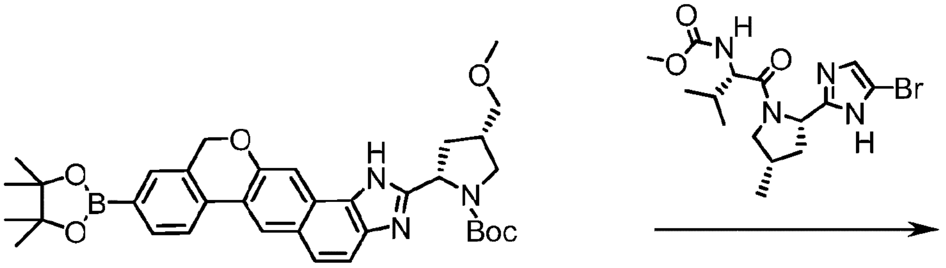
dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (424 mg, 0.69 mmol), ethanol (6 mL) and concentrated HCl (2 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and the crude material dissolved in DCM (10 mL). This solution was concentrated and to this material was added a solution of 2-methoxycarbonylamino-3-methylbutyric acid (152 mg, 0.86 mmol) and HATU (303 mg, 0.79 mmol) in DMF (6 mL). To the resulting solution was added diisopropylethylamine (360 μL, 2.08 mmol). After stirring for 2 hours at room temperature, the reaction was diluted with ethyl acetate, washed with 5% $NaHCO_3$ solution, water and brine, dried ($Na_2SO_4$), concentrated and dried under vacuum to give (2S,4S)-methyll {4-(methoxymethyl)-2-[(9-(4,4,5,5-tetramethyl-1,3,2-dioxaboro lan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate.

**tert-butyl(2S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrroli din-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate.** To a solution of (2S, 4S)-methyll{4-(methoxymethyl)-2-[(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroiso chromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1yl]-3-methyl-1-oxobutan-2-yl}carbamate (0.69 mmol), (S)-tert-butyl 2-(5-bromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (220 mg, 0.69 mmol), tetrakis(triphenylphosphine) palladium(0) (24 mg, 0.02 mmol) and dichloro[1,1'-bis(diphenylphosphino) ferrocene]palladium(II) (31 mg, 0.04 mmol) in a mixture of 1,2-dimethoxyethane (6.0 mL) and dimethylformamide (1.0 mL) was added a solution of potassium carbonate (2M in water, 1.04 mL, 2.0 mmol). The resulting mixture was degassed and then heated to 85 °C under argon for 18 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield (tert-butyl (2S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate (145 mg, 27%).

**methyl{(1R)-2-[(2S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroiso chromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate:** A solution of tert-butyl (2S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1,11-

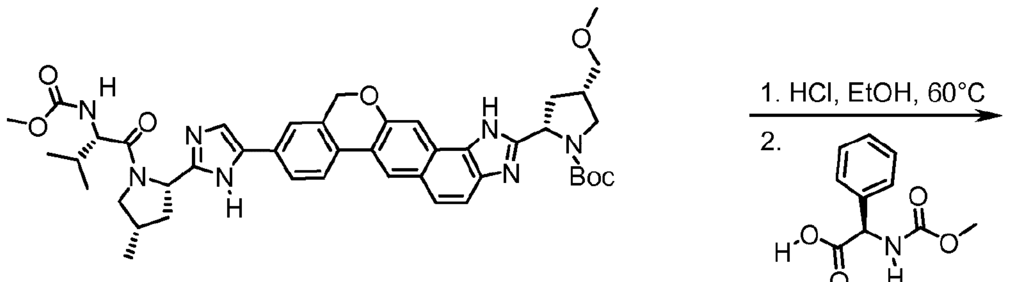
dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate (145 mg, 0.18 mmol), ethanol (3 mL) and concentrated HCl (1 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and the crude material dissolved in DCM (6 mL). This solution was concentrated and to this material was added a solution of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (51 mg, 0.24 mmol) and COMU (92 mg, 021 mmol) in DMF (3 mL). To the resulting solution was added diisopropylethylamine (100 μL, 0.56 mmol). After stirring for 2 hours at room temperature, the reaction was diluted with ethyl acetate, washed with water and brine, dried (Na$_2$SO$_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 43% ACN/H$_2$O + 0.1% TFA). The product fractions were lyophilized to give methyl {(1R)-2-[(2S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (68 mg, 39%). MS (ESI) *m/z* 870 [M + H]$^+$. 1H NMR (400 MHz, dmso) δ 8.71 (s, 1H), 8.22 (d, 1H, J = 8 Hz), 8.09 (m, 1H), 7.88 – 7.63 (m, 6H), 7.36 - 7.29 (m, 6H), 5.41 (d, 1H, *J* = 8.4 Hz), 5.30 – 5.24 (m, 2H), 5.14 – 5.10 (m, 1H), 4.13 - 3.09 (m, 15H), 2.47 - 1.80 (m, 8H), 0.80 (dd, 6H, *J* = 6.4 Hz, *J* = 23 Hz).

## Example AN

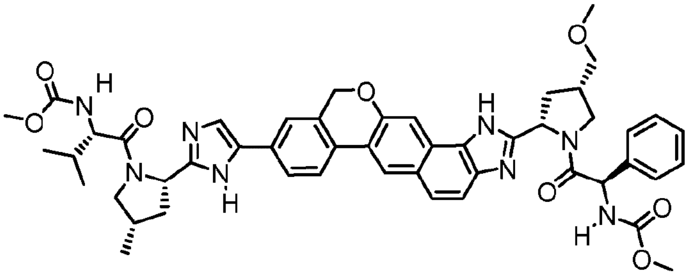


Pd(PPh$_3$)$_4$, PdCl$_2$(dppf), K$_2$CO$_3$, DME/ DMF, 85°C

(2*S*,4*S*)-*tert*-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate



tert-butyl (2S,4S)-2-[9-(2-{(2S4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate



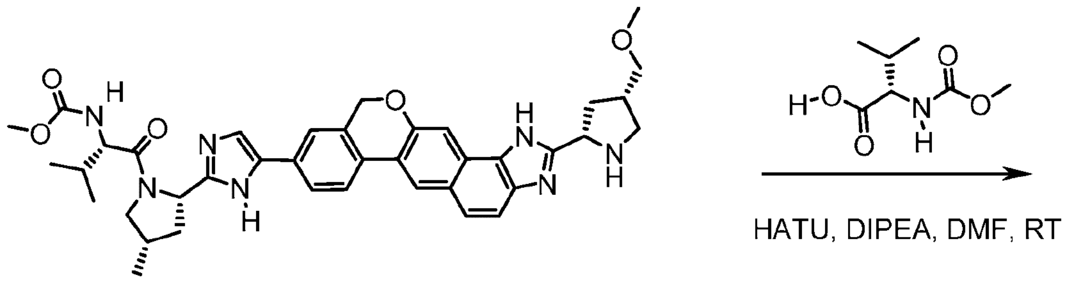
methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**tert-butyl(2S,4S)-2-[9-(2-{(2S4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methyl pyrrolidin-2-yl}-1H-imidazol-5-yl)-3,11-dihydroisochromeno[4',3':6,7]naphtho [1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate.** To a solution of (2S,4S)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7] naphtho [1,2-d]imidazol -2-yl)pyrrolidine-1-carboxylate (438 mg, 0.72 mmol), methyl (S)-1-((2S,4S)-2-(5-bromo-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (276 mg, 0.72 mmol), tetrakis(triphenylphosphine) palladium(0) (41 mg, 0.04 mmol) and dichloro[1,1'-bis(diphenylphosphino) ferrocene]palladium(II) (52 mg, 0.07 mmol) in a mixture of 1,2-dimethoxyethane (8.6 mL) and dimethylformamide (1.5 mL) was added a solution of potassium carbonate (2M in water, 1.07 mL, 2.15 mmol). The resulting mixture was degassed and then heated to 85 °C under argon for 18 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield tert-butyl (2S,4S)-2-[9-(2-{(2S4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-3,11-

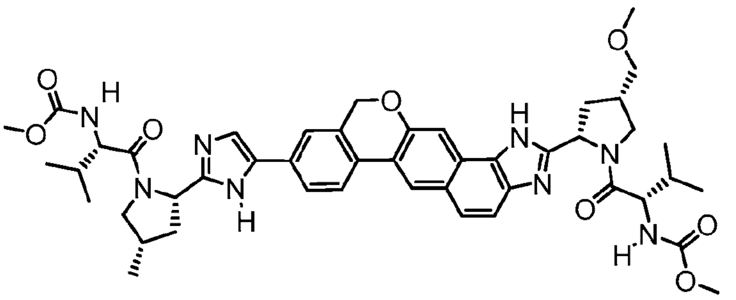
dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (182 mg, 32%).

**methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** A solution of tert-butyl (2S,4S)-2-[9-(2-{(2S4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxy methyl)pyrrolidine-1-carboxylate (182 mg, 0.18 mmol), ethanol (3 mL) and concentrated HCl (1 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and the crude material dissolved in DCM (6 mL). This solution was concentrated and to this material was added a solution of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (47 mg, 0.23 mmol) and COMU (85 mg, 0.2 mmol) in DMF (3 mL). To the resulting solution was added diisopropylethylamine (90 µL, 0.52 mmol). After stirring for 2 hours at room temperature, the reaction was diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 49% ACN/$H_2O$ + 0.1% TFA). The product fractions were lyophilized to give methyl{(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)ami no]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (32 mg, 39%). MS (ESI) *m/z* 884 $[M + H]^+$. $^1H$ NMR (400 MHz, dmso) δ 8.70 (s, 1H), 8.21 (d, 1H, *J* = 8 Hz), 8.08 (s, 1H), 7.90 – 7.64 (m, 6H), 7.34 – 7.31 (m, 3H), 7.64 (d, 1H, *J* = 8.4 Hz), 5.47 (d, 1H, *J* = 7.6 Hz), 5.28 – 5.25 (m, 3H), 5.05 – 5.01 (m, 1H), 4.19 – 4.04 (m, 3H), 3.67 – 3.15 (m, 15H), 2.51 -2.46 (m, 4H), 1.95 – 1.92 (m, 2H), 1.82 – 1.76 (m, 1H), 1.10 (d, 3H, *J* = 6 Hz), 0.75 (dd, 6H, *J* = 6.8 Hz, *J* = 14 Hz).

## Example AO



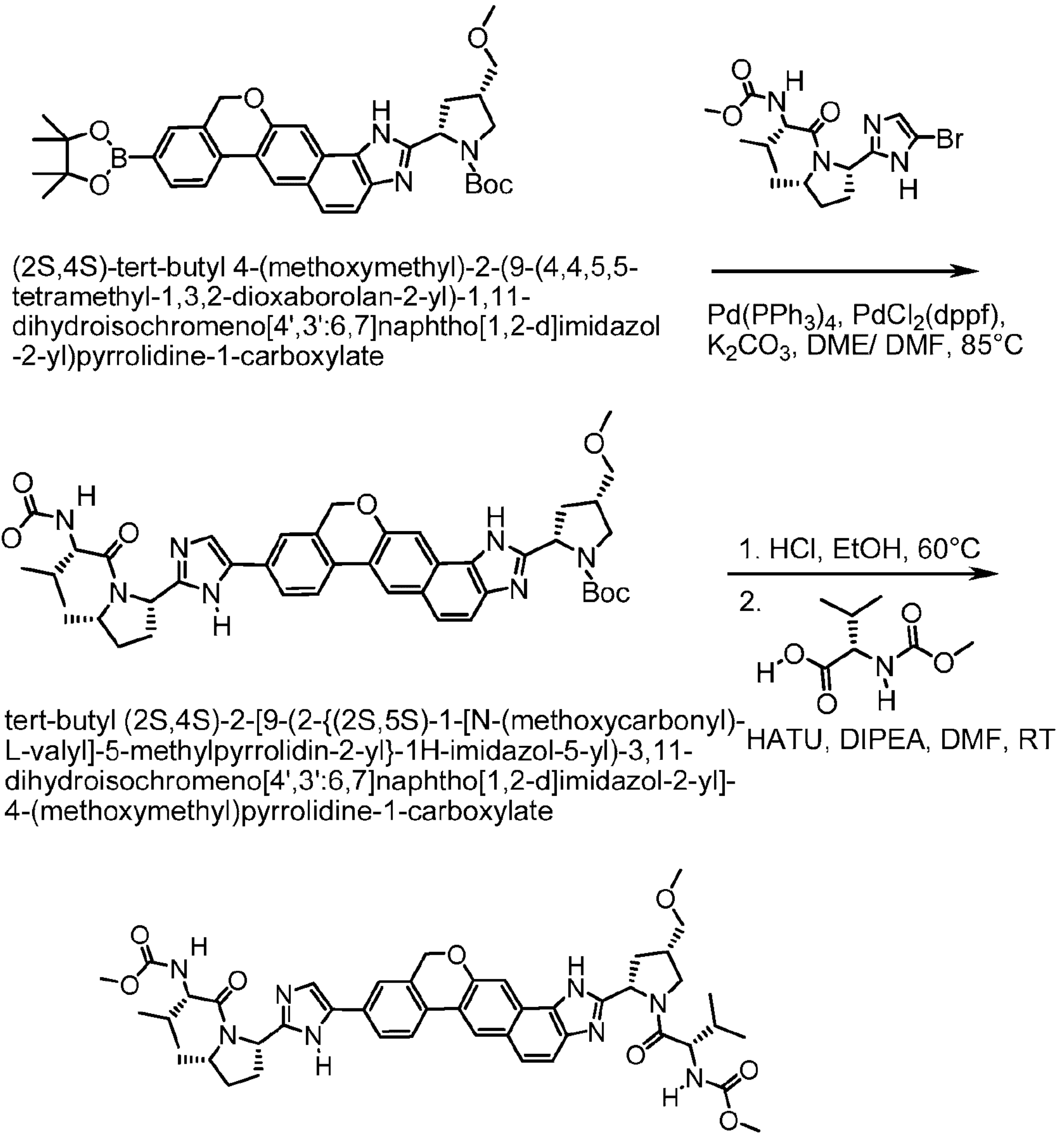
methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-4-(methoxy methyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl} carbamate



methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methoxy methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7] naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methoxymethylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** To a solution of methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7] naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (57 mg, 0.08 mmol), 2-methoxycarbonylamino-3-methylbutyric acid (19 mg, 0.1 mmol), HATU (303 mg, 0.79 mmol) in DMF (1 mL) was added diisopropylethylamine (43 μL, 0.24 mmol). After stirring for 2 hours at room temperature, the reaction was diluted with ethyl acetate, washed with 5% $NaHCO_3$ solution, water and brine, dried ($Na_2SO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 43% ACN/$H_2O$ + 0.1% TFA). The product fractions were lyophilized to give methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methyl butanoyl}-4-methoxymethylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazo--2-yl)-4-methylpyrrolidin-1-yl]-3-methyl- 1-oxobutan-2-yl}carbamate. (13 mg, 19%). MS (ESI) *m/z* 850 $[M + H]^+$. 1H NMR (400 MHz, dmso) δ 8.66 (s, 1H), 8.28 – 8.13 (m, 1H), 8.12 – 7.99 (m, 1H), 7.90 – 7.75 (m, 3H), 7.73 – 7.65 (m, 1H), 7.63 – 7.57 (m, 1H), 7.34 – 7.19 (m, 2H), 5.30 – 5.24 (m, 2H), 5.21 – 4.95 (m, 2H), 4.33 – 3.93 (m, 6H), 3.23 -3.58 (m, 12H), 2.76 – 2.59 (m, 2H), 2.02 – 1.73 (m, 6H), 1.12 – 1.07 (m, 3H), 0.86 – 0.68 (m, 12H).

## Example AP



(2S,4S)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate

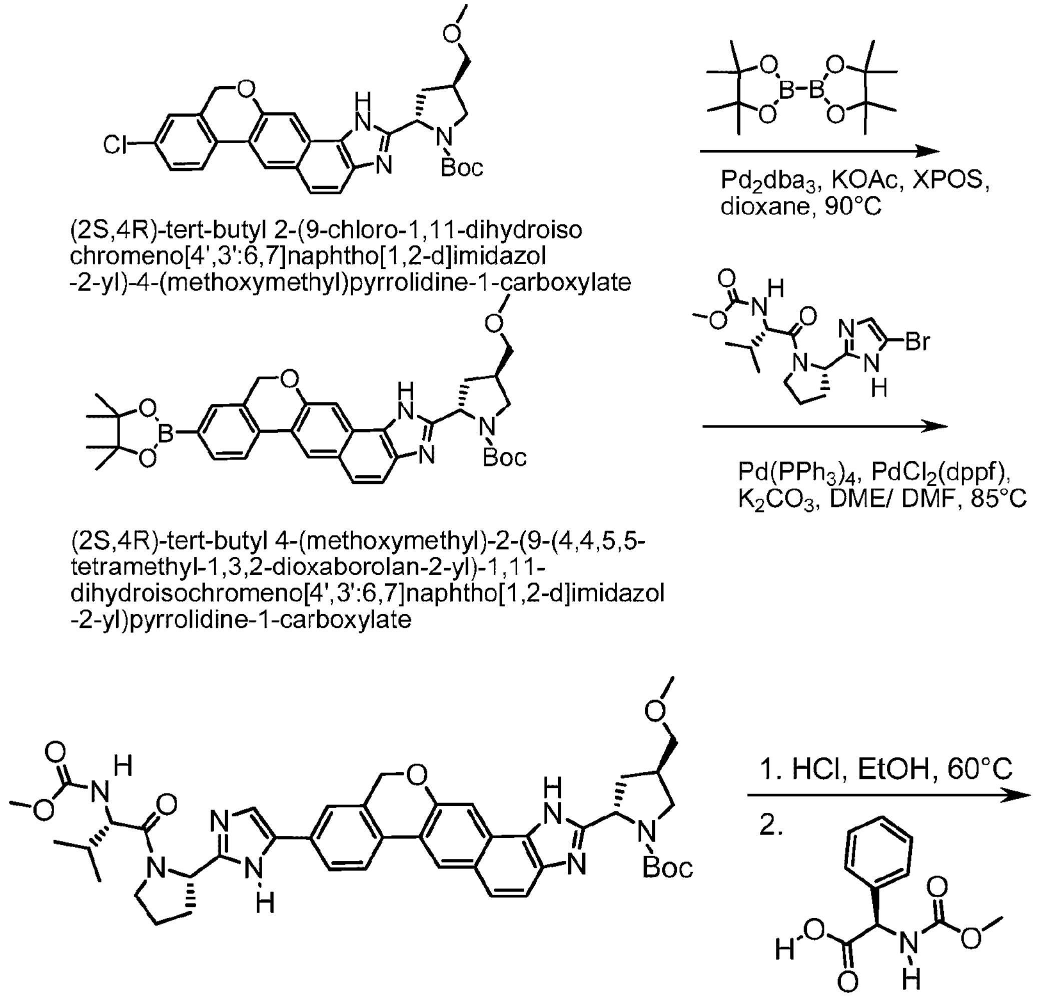
tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methoxymethylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**tert-butyl(2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methyl pyrrolidin-2-yl}-1H-imidazol-5-yl)-3,11-dihydroisochromeno[4',3':6,7]naphtho [1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate** To a solution of (2S,4S)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7] naphtho[1,2-d]imidazol -2-yl)pyrrolidine-1-carboxylate (217 mg, 0.35 mmol), methyl (S)-1-((2S,5S)-2-(5-bromo-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (170 mg, 0.39 mmol), tetrakis(triphenylphosphine) palladium(0) (21 mg, 0.02 mmol) and dichloro[1,1'-bis(diphenylphosphino) ferrocene]palladium(II) (26 mg, 0.04 mmol) in a mixture of 1,2-dimethoxyethane (4.3 mL) and dimethylformamide (0.75 mL) was added a solution of potassium carbonate (2M in water, 0.53 mL, 1.06 mmol). The resulting mixture was degassed and then heated to 85 °C under argon for 18 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxy methyl)pyrrolidine-1-carboxylate (110 mg, 39%).

**methyl{(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methoxymethylpyrrolidin-2-yl]-1,11-dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** A solution of tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxy methyl)pyrrolidine-1-carboxylate (108 mg, 0.14 mmol), ethanol (2 mL) and concentrated HCl (0.7 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and the crude material dissolved in DCM (10 mL). This solution was concentrated and to this material was added a solution of 2-methoxycarbonylamino-3-methylbutyric acid (31 mg, 0.18 mmol) and HATU (60 mg, 0.16 mmol) in DMF (2 mL). To the resulting solution was added diisopropylethylamine (70 μL, 0.41 mmol). After stirring for 2 hours at room temperature, the reaction was diluted with ethyl acetate, washed with 5% $NaHCO_3$ solution, water and brine, dried ($Na_2SO_4$), After stirring for 2 hours at room temperature, the reaction was diluted with ethyl acetate, washed with 5% $NaHCO_3$ solution, water and brine, dried ($Na_2SO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 43% ACN/$H_2O$ + 0.1% TFA). The product fractions were lyophilized to give methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methoxy methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (52 mg, 45%). MS (ESI) *m/z* 850 [M + H]$^+$. $^1$H NMR (400 MHz, dmso) δ 8.69 (s, 1H), 8.18 (d, 1H, *J* = 7.6 Hz), 7.99 – 7.86 (m, 4H), 7.72 (s, 1H), 7.64 (d, 1H, J = 8.8 Hz), 7.51 (d, 1H, *J* = 8 Hz), 7.23 (d, 1H, *J* = 8.4 Hz), 5.29 (s, 2H), 5.22 – 5.18 (m, 1H), 5.01 – 4.70 (m, 1H), 4.64 – 4.61 (m, 1H), 4.21-4.17 (m, 1H), 4.09-4.05 (m, 1H), 3.92 – 3.88 (m, 1H), 3.59 – 3.08 (m, 14H), 2.67 – 1.83 (m, 7H), 1.43 (d, 3H, *J* = 6.4 Hz), 0..91-0.71 (m, 12H).

## Example AQ



(2S,4R)-tert-butyl 2-(9-chloro-1,11-dihydroiso chromeno[4',3':6,7]naphtho[1,2-d]imidazol -2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate

$Pd_2dba_3$, KOAc, XPOS, dioxane, 90°C

(2S,4R)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol -2-yl)pyrrolidine-1-carboxylate

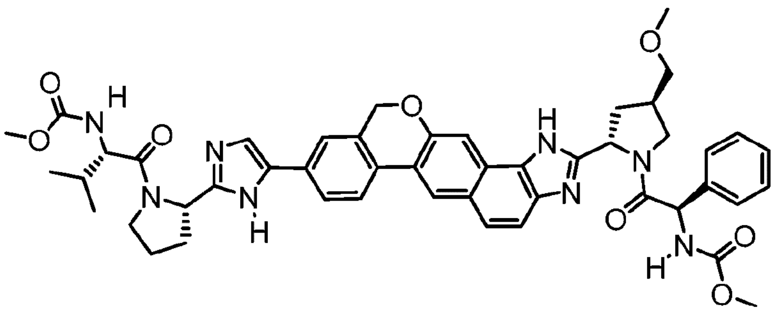
$Pd(PPh_3)_4$, $PdCl_2(dppf)$, $K_2CO_3$, DME/ DMF, 85°C

1. HCl, EtOH, 60°C

2.

COMU, DIPEA, DMF, RT

(2S,4R)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonyl amino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol -2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate



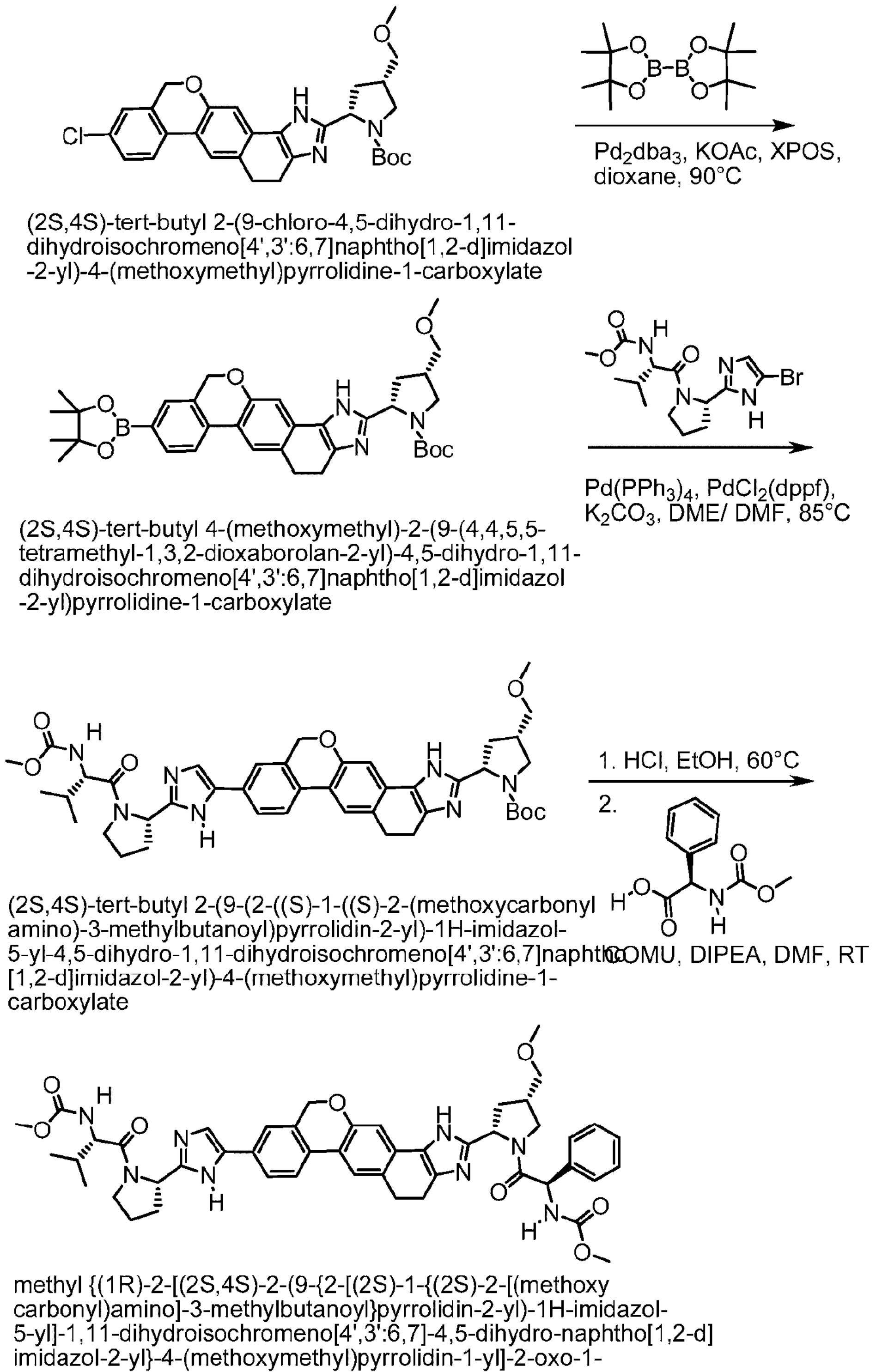
methyl {(1R)-2-[(2S,4R)-2-(9-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]-naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-phenylethyl}carbamate

**(2S,4R)-tert-butyl-4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxa borolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl) pyrrolidine-1-carboxylate:** A degassed mixture of - (2S,4R)-tert-butyl-2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl) pyrrolidine-1-carboxylate (335 mg, 0.64 mmol), bis(pinacolato)diboron (246 mg, 0.96 mmol), potassium acetate (190 mg, 1.9 mmol), tris(dibenzylideneacetone) palladium (24 mg, 0.02 mmol) and 2-dicyclohexylphosphino-2', 4', 6'-tri-i-propyl-1, 1'-biphenyl (31 mg, 0.06 mmol) in 1,4-dioxane (3.3 mL) was heated to 90 °C for 3 hours, cooled to room temperature and diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield (2S,4R)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol -2-yl)pyrrolidine-1-carboxylate (379 mg, 96%).

**(2S,4R)-tert-butyl2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methyl butanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7] naphtho[1,2-d]imidazol -2-yl)-4(methoxymethyl) pyrrolidine-1-carboxylate.** To a solution of (2S,4R)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)- 1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl) pyrrolidine-1-carboxylate (299 mg, 0.49 mmol), methyl (S)-1-((S)-2-(5-bromo-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (217 mg, 0.58 mmol), tetrakis(triphenylphosphine) palladium(0) (28 mg, 0.02 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (35 mg, 0.04 mmol) in a mixture of 1,2-dimethoxyethane (4.3 mL) and dimethylformamide (0.75 mL) was added a solution of potassium carbonate (2M in water, 0.73 mL, 1.46 mmol). The resulting mixture was degassed and then heated to 85 °C under argon for 18 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield (2S,4R)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (170 mg, 45%).

**methyl{(1R)-2-[(2S,4R)-2-(9-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-phenylethyl}carbamate:** A solution of (2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrroli dine-1-carboxy late (170 mg, 0.22 mmol), ethanol (3 mL) and concentrated HCl (1 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and the crude material dissolved in DCM (6 mL). This solution was concentrated and to this material was added a solution of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (59 mg, 0.28 mmol) and COMU (108 mg, 025 mmol) in DMF (3 mL). To the resulting solution was added diisopropylethylamine (110 µL, 0.66 mmol). After stirring for 2 hours at room temperature, the reaction was diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 44% ACN/$H_2O$ + 0.1% TFA). The product fractions were lyophilized to give methyl {(1R)-2-[(2S,4R)-2-(9-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]-naphtho[1,2-d]imidazol-2-yl}-(methoxymethyl) pyrrolidin-1-yl]-2-oxo-phenylethyl}carbamate (67 mg, 35%). MS (ESI) $m/z$ 870 $[M + H]^+$. 1H NMR (400 MHz, dmso) δ 8.71 (s, 1H), 8.20 (d, 1H, $J$ = 8.4 Hz), 8.01 (m, 1H), 7.91 – 7.64 (m, 6H), 7.38 - 7.28 (m, 6H), 6.85 (s, 1H), 5.51 (d, 1H, $J$ = 7.2 Hz), 5.39 – 5.29 (m, 3H), 5.13 – 5.09 (m, 1H), 4.11 -3.04 (m, 15H), 2.77 - 1.98 (m, 8H), 0.79 (dd, 6H, $J$ = 6.8 Hz, $J$ = 12.8 Hz).

## Example AR



(2S,4S)-tert-butyl 2-(9-chloro-4,5-dihydro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate

(2S,4S)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4,5-dihydro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate

(2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonyl amino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl-4,5-dihydro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate

methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S)-1-{(2S)-2-[(methoxy carbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]-4,5-dihydro-naphtho[1,2-d] imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**(2S,4S)-tert-butyl4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaboro lan-2-yl)-4,5-dihydro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol -2-**

**yl)pyrrolidine-1-carboxylate:** A degassed mixture of (2S,4S)-tert-butyl 2-(9-chloro-4,5-dihydro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol -2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (322 mg, 0.61 mmol), bis(pinacolato) diboron (235 mg, 0.92 mmol), potassium acetate (182 mg, 1.9 mmol), tris(dibenzylideneacetone)palladium (23 mg, 0.02 mmol) and 2-dicyclohexylphosphino-2', 4', 6'-tri-i-propyl-1, 1'-biphenyl (29 mg, 0.06 mmol) in 1,4-dioxane (3.3 mL) was heated to 90 °C for 3 hours, cooled to room temperature and diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield (2S,4S)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4,5-dihydro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (267 mg, 70%).

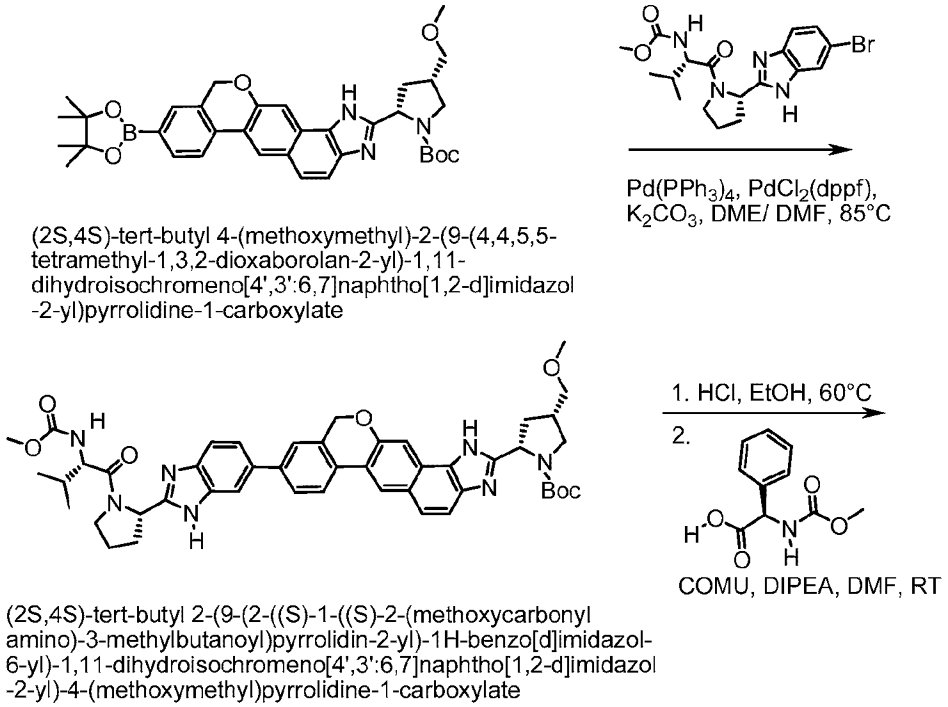
**(2S,4S)-tert-butyl2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl-4,5-dihydro-1,11-dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxy late.** To a solution of (2S,4S)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4,5-dihydro-1,11-dihydroisochrome no[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (267 mg, 0.52 mmol), methyl (S)-1-((S)-2-(5-bromo-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (195 mg, 0.52 mmol), tetrakis (triphenylphosphine) palladium(0) (25 mg, 0.02 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium(II) (32 mg, 0.04 mmol) in a mixture of 1,2-dimethoxyethane (4.3 mL) and dimethylformamide (0.75 mL) was added a solution of potassium carbonate (2M in water, 0.65 mL, 1.3 mmol). The resulting mixture was degassed and then heated to 85 °C under argon for 18 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to yield (2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl-4,5-dihydro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxy late (75 mg, 22%).

**methyl{(1R)-2-[(2S,4S)-2-(9-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno [4',3':6,7]-4,5-dihydro-naphtho[1,2-d]imidazol-2-yl}-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-**

**phenylethyl}carbamate:** A solution of (2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxy carbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl-4,5-dihydro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl) pyrrolidine-1-carboxylate (75 mg, 0.09 mmol), ethanol (2 mL) and concentrated HCl (0.6 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and the crude material dissolved in DCM (6 mL). This solution was concentrated and to this material was added a solution of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (26 mg, 0.13 mmol) and COMU (47 mg, 0.11 mmol) in DMF (2 mL). To the resulting solution was added diisopropylethylamine (50 µL, 0.29 mmol). After stirring for 2 hours at room temperature, the reaction was diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 44% ACN/$H_2O$ + 0.1% TFA). The product fractions were lyophilized to give methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]-4,5-dihydro-naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (15 mg, 18%).

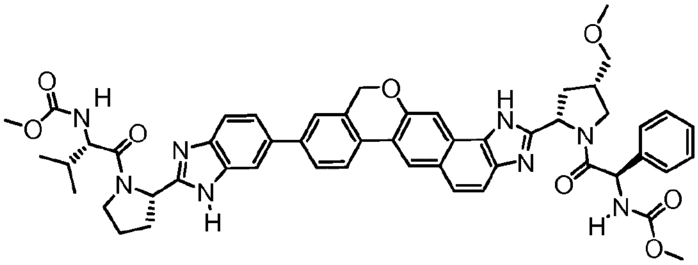
MS (ESI) *m/z* 872 $[M + H]^+$. $^1$H NMR (400 MHz, dmso) δ 7.95 – 7.63 (m, 6H), 7.35 - 7.25 (m, 7H), 6.97 (s, 1H), 5.42 (d, 1H, *J* = 6.8 Hz), 5.18 (s, 2H), 5.09 (s, 2H), 4.28 -2.63 (m, 19H), 2.47 - 1.80 (m, 8H), 0.77 (dd, 6H, *J* = 4.8 Hz, *J* = 12.4 Hz).

## Example AS



(2S,4S)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate

(2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonyl amino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate

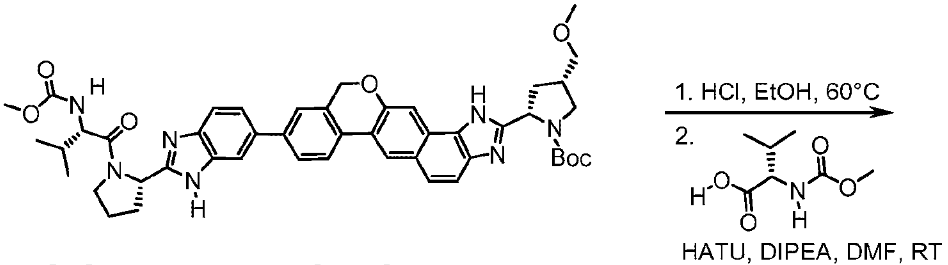


methyl {(2S)-2-[[(2S,4S)-2-{9-[2-((2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-y]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

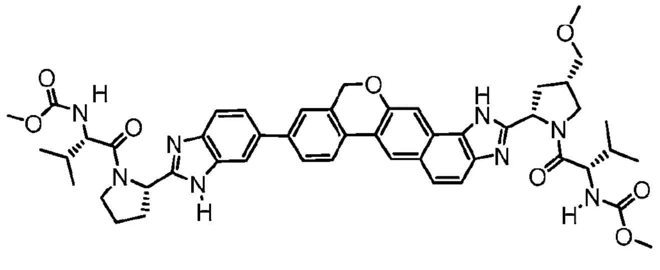
**(2S,4S)-tert-butyl2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)- 1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl) pyrrolidine-1-carboxylate.** To a solution of (2S,4S)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)- 1,11-dihydroisochromeno [4',3':6,7] naphtho[1,2-d]imidazol -2-yl)pyrrolidine-1-carboxylate (400 mg, 0.85 mmol), methyl (S)-1-((S)-2-(6-bromo-1H-benzo[d]imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (360 mg, 0.85 mmol), tetrakis(triphenylphosphine) palladium(0) (38 mg, 0.03 mmol) and dichloro[1,1'-bis(diphenylphosphino) ferrocene]palladium(II) (48 mg, 0.07 mmol) in a mixture of 1,2-dimethoxyethane (8.0 mL) and dimethylformamide (1.4 mL) was added a solution of potassium carbonate (2M in water, 0.98 mL, 1.96 mmol). The resulting mixture was degassed and then heated to 85 °C under argon for 18 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to (2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (156 mg, 29%).

**methyl{(2S)-2-[[(2S,4S)-2-{9-[2-((2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-y]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate:** A solution of (2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-benzo[d] imidazol-6-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-car boxylate (156 mg, 0.18 mmol), ethanol (3 mL) and concentrated HCl (1 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and the crude material dissolved in DCM (6 mL). This solution was concentrated and to (90 mg, 0.12 mmol) of this material was added a solution of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (34 mg, 0.16 mmol) and COMU (61 mg, 014 mmol) in DMF (2 mL). To the resulting solution was added diisopropylethylamine (60 µL, 0.37 mmol). After stirring for 2 hours at room temperature, the reaction was diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 49% ACN/$H_2O$ + 0.1% TFA). The product fractions were lyophilized to give methyl {(2S)-2-[[(2S,4S)-2-{9-[2-((2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-y]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (62 mg, 56%). MS (ESI) *m/z* 920 $[M + H]^+$. $^1H$ NMR (400 MHz, dmso) δ 8.73 (s, 1H), 8.17 (d, 2H, *J* = 8.4 Hz), 7.94 (d, 3H, *J* = 8.8 Hz), 7.84 – 7.67 (m, 6H), 7.37 - 7.29 (m, 6H), 5.48 (d, 1H, *J* = 7.6 Hz), 5.35 – 5.20 (m, 5H), 4.14 -3.12 (m, 15H), 2.52 - 1.92 (m, 8H), 0.80 (dd, 6H, *J* = 6.8 Hz, *J* = 6.4 Hz).

## Example AT



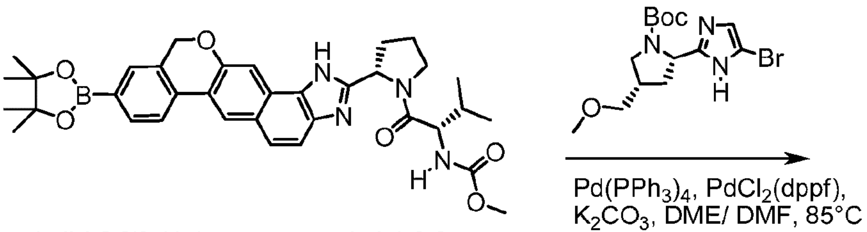
(2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonyl amino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-benzo[d] imidazol-6-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho [1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate



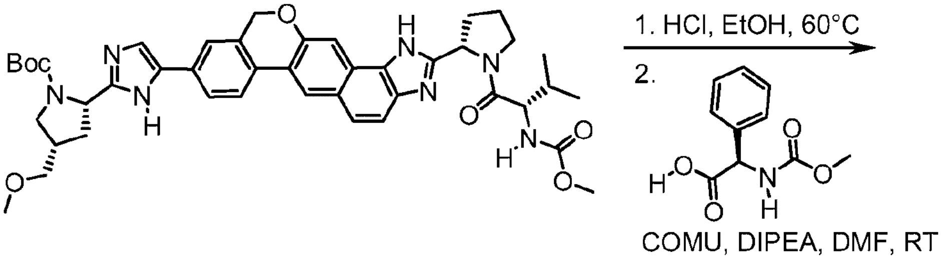
methyl {(2S)-2-[(2S,4S)-2-{9-[2-((2S)-1-{(2S)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-y]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxy methyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**methyl{(2S)-2-[(2S,4S)-2-{9-[2-((2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-y]-1,11-dihydroiso chromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** A solution of (2S,4S)-tert-butyl-2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-benzo [d]imidazol-6-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (156 mg, 0.18 mmol), ethanol (3 mL) and concentrated HCl (1 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and the crude material dissolved in DCM (6 mL). This solution was concentrated and to (68 mg, 0.09 mmol) of this material was added a solution of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (21 mg, 0.12 mmol) and COMU (41 mg, 01 mmol) in DMF (1 mL). To the resulting solution was added diisopropylethylamine (50 µL, 0.28 mmol). After stirring for 2 hours at room temperature, the reaction was diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 44% ACN/$H_2O$ + 0.1% TFA). The product fractions were lyophilized to give methyl {(2S)-2-[(2S,4S)-2-{9-[2-((2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-y]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (32 mg, 40%). MS (ESI) *m/z* 886 $[M + H]^+$. $^1H$ NMR (400 MHz, dmso) δ 8.71 (s, 1H), 8.15 (d, 1H, *J* = 8 Hz), 7.95 – 7.64 (m, 8H), 7.28 (dd, 2H, *J* = 8.8 Hz, *J* = 14.4 Hz), 5.31 (s, 2H), 5.23 – 5.19 (m, 2H), 4.09 – 3.85 (m, 5H), 3.58 -3.28 (m, 14H), 2.47 – 1.89 (m, 9H), 0.83 – 0.72 (m, 12H).

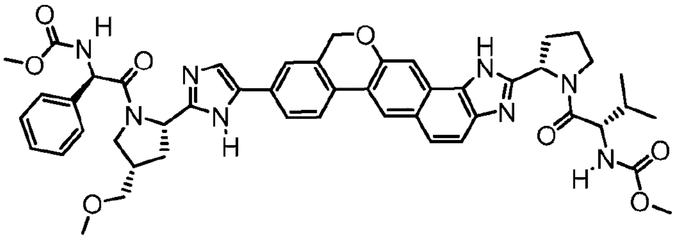
## Example AU



(2S)-methyll {-2-[(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7] naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1yl]-3-methyl-1-oxobutan-2-yl}carbamate



tert-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-pyrrolidin-2-yl}-1,11-dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate



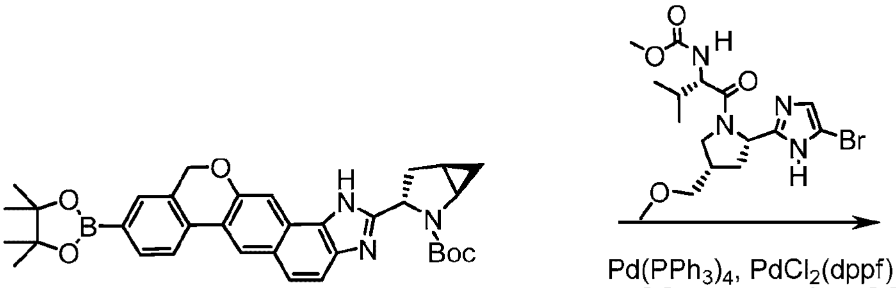
methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}-pyrrolidin-2-yl]-1,11-dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**tert-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate.** To a solution of (2S)-methyll {-2-[(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1yl]-3-methyl-1-oxobutan-2-yl} carbamate (460 mg, 0.74 mmol), (2S,4S)-tert-butyl 2-(5-bromo-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (250 mg, 0.61 mmol), tetrakis (triphenylphosphine) palladium(0) (35 mg, 0.03 mmol) and dichloro[1,1'-bis (diphenylphosphino) ferrocene]palladium(II) (45 mg, 0.06 mmol) in a mixture of 1,2-dimethoxyethane (9.0 mL) and dimethylformamide (1.5 mL) was added a solution of potassium carbonate (2M in water, 0.92 mL, 1.84 mmol). The resulting mixture was degassed and then heated to 85 °C under argon for 18 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to tert-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7] naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (123 mg, 26

**methyl{(1R)-2-[(2S,4S)-2-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]**

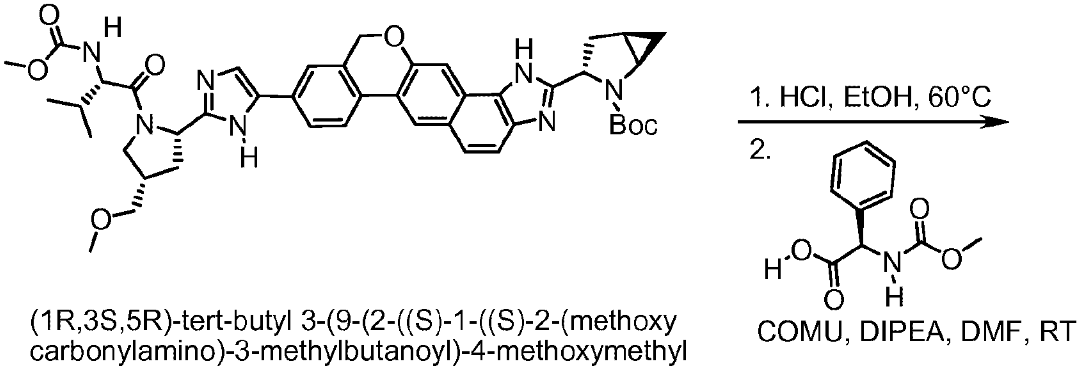
**imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate:** A solution tert-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxy carbonyl)-L-valyl]-pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d] imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-carboxylate (122 mg, 0.16 mmol), ethanol (3 mL) and concentrated HCl (1 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and the crude material dissolved in DCM (3 mL). This solution was concentrated and to this material was added a solution of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (43 mg, 0.2 mmol) and COMU (77 mg, 018 mmol) in DMF (3 mL). To the resulting solution was added diisopropylethylamine (80 μL, 0.37 mmol). After stirring for 2 hours at room temperature, the reaction was diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 44% ACN/$H_2O$ + 0.1% TFA). The product fractions were lyophilized to give methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (60 mg, 44%). MS (ESI) *m/z* 870 [M + H]$^+$. $^1$H NMR (400 MHz, dmso) δ 8.71 (s, 1H), 8.22 (d, 1H, *J* = 8 Hz), 8.09 (m, 1H), 7.88 – 7.63 (m, 6H), 7.36 - 7.29 (m, 6H), 5.41 (d, 1H, *J* = 8.4 Hz), 5.30 – 5.24 (m, 2H), 5.14 – 5.10 (m, 1H), 4.13 -3.09 (m, 15H), 2.47 - 1.80 (m, 8H), 0.80 (dd, 6H, *J* = 6.4 Hz, *J* = 23 Hz).

## Example AV

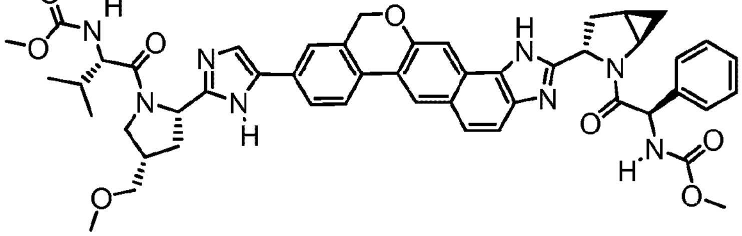


Pd(PPh$_3$)$_4$, PdCl$_2$(dppf), K$_2$CO$_3$, Dioxane/ DMSO, 95°C

(1R,3S,5R)-tert-butyl -3-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo [3.1.0]hexane-2-carboxylate



(1R,3S,5R)-tert-butyl 3-(9-(2-((S)-1-((S)-2-(methoxy carbonylamino)-3-methylbutanoyl)-4-methoxymethyl pyrrolidin-2-yl)-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

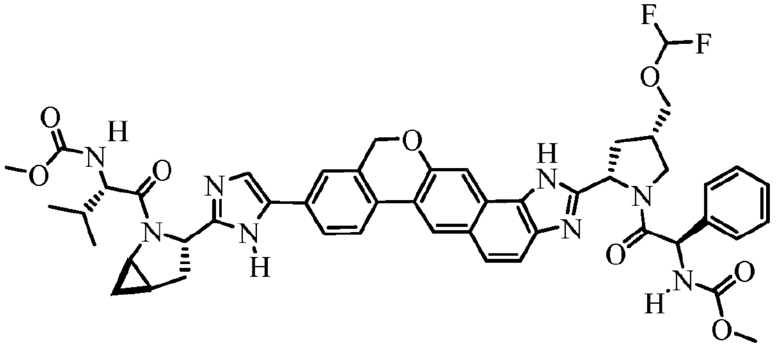


methyl {(1R)-2-[(1R,3S,5R)-2-(9-{2-[(2S,5S)-1-{(2S)-2-[(methoxy carbonyl)amino]-3-methylbutanoyl}-4-methoxymethylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d] imidazol-2-yl)-2-azabicyclo[3.1.0]hex-3-yl]-2-oxo-1-phenylethyl}carbamate

**(1R,3S,5R)-tert-butyl3-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-4-methoxymethylpyrrolidin-2-yl)-1H-imidazol-5-yl)- 1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0] hexane-2-carboxylate.** To a solution of (1R,3S,5R)-tert-butyl -3-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)- 1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo [3.1.0]hexane-2-carboxylate (213 mg, 0.37 mmol), methyl (S)-1-((2S,4S)-2-(5-bromo-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (142 mg, 0.31 mmol), tetrakis (triphenylphosphine) palladium(0) (35 mg, 0.03 mmol) and dichloro[1,1'-bis (diphenylphosphino) ferrocene]palladium(II) (22 mg, 0.03 mmol) in a mixture of 1,4-dioxane (3.0 mL) and dimethylsulfoxide (3.0 mL) was added a solution of potassium carbonate (2M in water, 0.46 mL, 0.9 mmol). The resulting mixture was degassed and then heated to 95 °C under argon for 7 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate. The organics were washed with water and brine, dried ($Na_2SO_4$), and concentrated. The crude residue was purified by flash chromatography to (1R,3S,5R)-tert-butyl 3-(9-(2-((S)-1-((S)-2-(methoxycarbonyl amino)-3-methylbutanoyl)-4-methoxymethylpyrrolidin-2-yl)-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0] hexane-2-carboxylate (101 mg, 42%).

**methyl{(1R)-2-[(1R,3S,5R)-2-(9-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methoxymethylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-azabicyclo[3.1.0]hex-3-yl]-2-oxo-1-phenylethyl}carbamate** A solution (1R,3S,5R)-tert-butyl 3-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-4-methoxymethylpyrrolidin-2-yl)-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (101 mg, 0.16 mmol), ethanol (3 mL) and concentrated HCl (1 mL) was heated to 60 °C for 1 hour. The reaction was concentrated and the crude material dissolved in DCM (3 mL). This solution was concentrated and to this material was added a solution of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (35 mg, 0.17 mmol) and COMU (63 mg, 015 mmol) in DMF (3 mL). To the resulting solution was added diisopropylethylamine (70 µL, 0.38 mmol). After stirring for 2 hours at room temperature, the reaction was diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$), concentrated and purified by preparative reverse phase HPLC (Gemini, 15 to 44% ACN/$H_2O$ + 0.1% TFA). The product fractions were lyophilized to give methyl methyl {(1R)-2-[(1R,3S,5R)-2-(9-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methoxymethylpyrrolidin-2-yl]-1H-imidazol-5 yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo [3.1.0]hex-3-yl]-2-oxo-1-phenylethyl}carbamate (71 mg, 63). MS (ESI) *m/z* 882 $[M + H]^+$. $^1H$ NMR (400 MHz, dmso) δ 8.66 (s, 1H), 8.17 (d, 1H, *J* = 8.8 Hz), 8.04 (s, 1H), 7.87 – 7.59 (m, 6H), 7.39 - 7.22 (m, 6H), 5.72 (d, 1H, *J* = 7.6 Hz), 5.68 (s, 1H), 5.25 (s, 1H), 5 .13 – 5.01 (m, 2H), 4.12 - 4.00 (m, 2H), 3.81 – 3.00 (m, 13H), 2.60 (m, 1H), 2.43 – 2.37 (m, 3H), 1.92-1.82 (m, 3H), 0.83 – 0.58 (m, 7H), 0.59 (s, 1H), 0.00 (s, 1H).

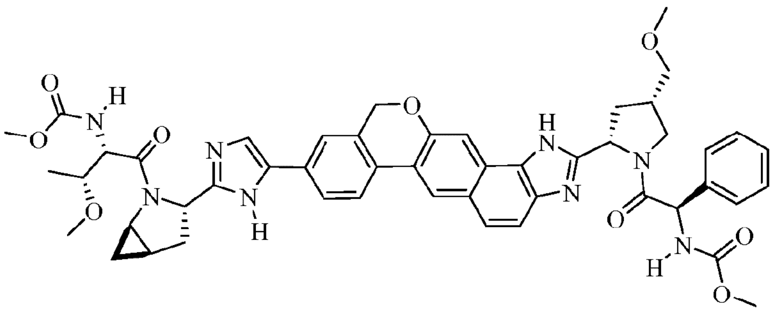
### Example AW



methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(1R,3S,5R)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-azabicyclo[3.1.0]hex-3-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(difluoromethoxy)methylpyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

This compound was synthesized using the same conditions as Example BX substituting with the respective (1R,3S,5R)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid and (2S,4S)-1-(tert-butoxycarbonyl)-4-((difluoromethoxy)methyl)pyrrolidine-2-carboxylic acid as appropriate. MS (ESI) *m/z* 918 $[M + H]^+$.

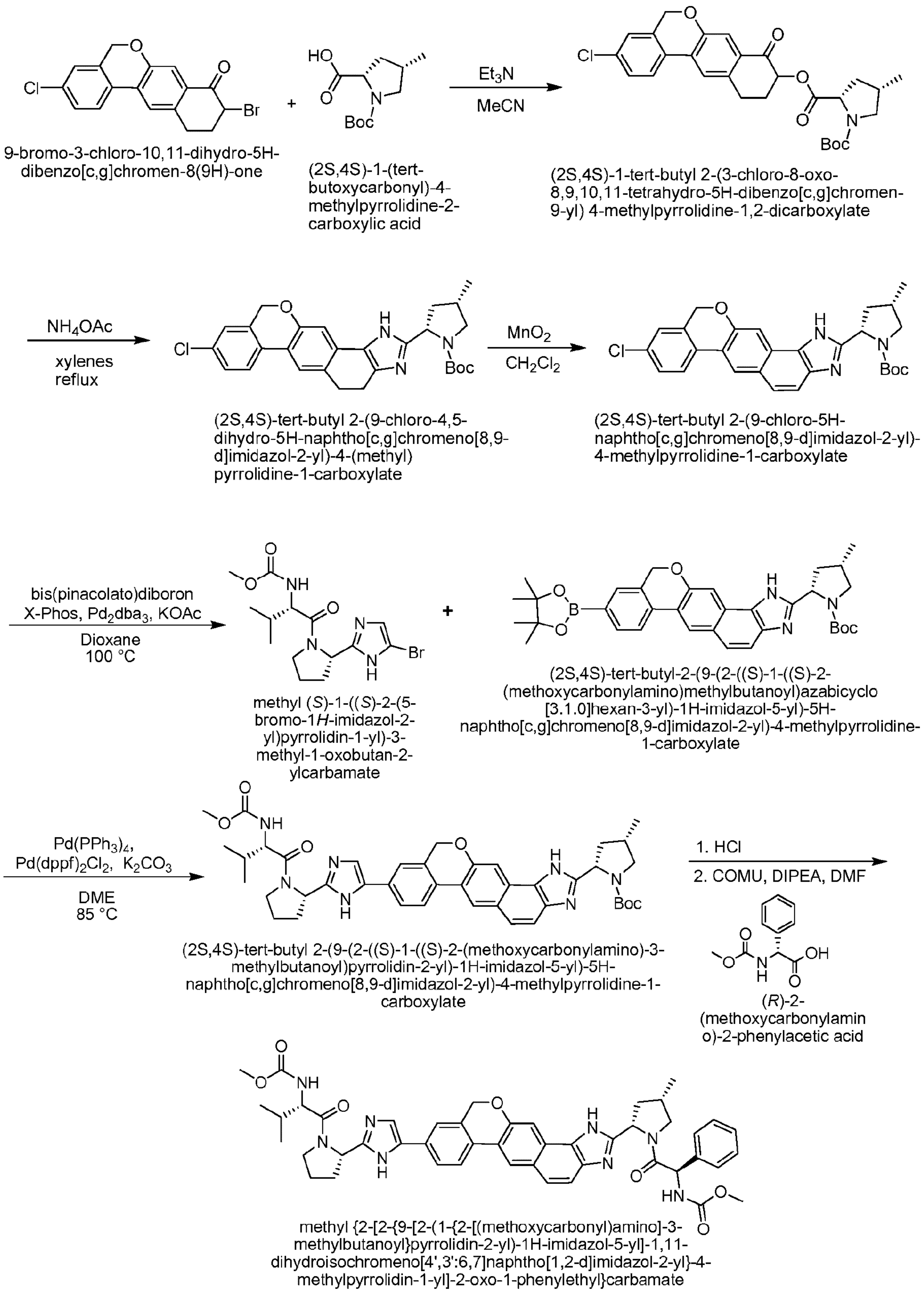
### Example AX



methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(1R,3S,5R)-1-{(2S,3S)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}-5-azabicyclo[3.1.0]hex-3-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(difluoromethoxy)methylpyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

This compound was synthesized using the same conditions as Example BX substituting with the respective (1R,3S,5R)-2-((2S,3S)-3-methoxy-2 (methoxycarbonylamino) butanoyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid and (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid as appropriate. MS (ESI) *m/z* 898 $[M + H]^+$.

## Example AY



9-bromo-3-chloro-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one

(2S,4S)-1-(tert-butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid

(2S,4S)-1-tert-butyl 2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-9-yl) 4-methylpyrrolidine-1,2-dicarboxylate

(2S,4S)-tert-butyl 2-(9-chloro-4,5-dihydro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-(methyl) pyrrolidine-1-carboxylate

(2S,4S)-tert-butyl 2-(9-chloro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate

methyl (*S*)-1-((*S*)-2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

(2S,4S)-tert-butyl-2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)methylbutanoyl)azabicyclo [3.1.0]hexan-3-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate

(2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate

(*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid

methyl {2-[2-{9-[2-(1-{2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-methylpyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**(2S,4S)-1-*tert*-butyl 2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-9-yl) 4-methylpyrrolidine-1,2-dicarboxylate:** To a solution of 9-bromo-3-chloro-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (1.32 g, 3.63 mmol) in MeCN (40 mL) was added (2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid (1.0 g, 4.36 mmol) and DIPEA (0.7 mL, 3.99 mmol). After stirring for 18 h, the solution was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (10% to 40% EtOAc/hexanes) to afford (2S,4S)-1-*tert*-butyl 2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-9-yl) 4-methylpyrrolidine-1,2-dicarboxylate (1.31 g, 70%).

**(2S,4S)-*tert*-butyl 2-(9-chloro-4,5-dihydro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate:** (2S,4S)-1-*tert*-butyl 2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-9-yl) 4-methylpyrrolidine-1,2-dicarboxylate (1.31 g, 2.56 mmol) was added xylenes (25 mL) and ammonium acetate (3.95 g, 51.2 mmol) and the solution was heated to 136 °C and stirred overnight. The following morning, the solution was cooled to rt and was diluted with EtOAc and washed successively with water, saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (60% to 100 % EtOAc/hexanes) to afford (2S,4S)-*tert*-butyl 2-(9-chloro-4,5-dihydro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (711 mg, 56%).

**(2S,4S)-*tert*-butyl 2-(9-chloro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate:** To a solution of (2S,4S)-*tert*-butyl 2-(9-chloro-4,5-dihydro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-(methyl)pyrrolidine-1-carboxylate (935 mg, 1.9 mmol) in $CH_2Cl_2$ (20 mL) was added $MnO_2$ (8.25 g, 95 mmol). The reaction mixture was stirred for 3 h, and then filtered over celite. The filter cake was washed with copious $CH_2Cl_2$ and MeOH, and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0% to 10 % MeOH/EtOAc) to afford (2S,4S)-*tert*-butyl 2-(9-chloro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (692 mg, 74%).

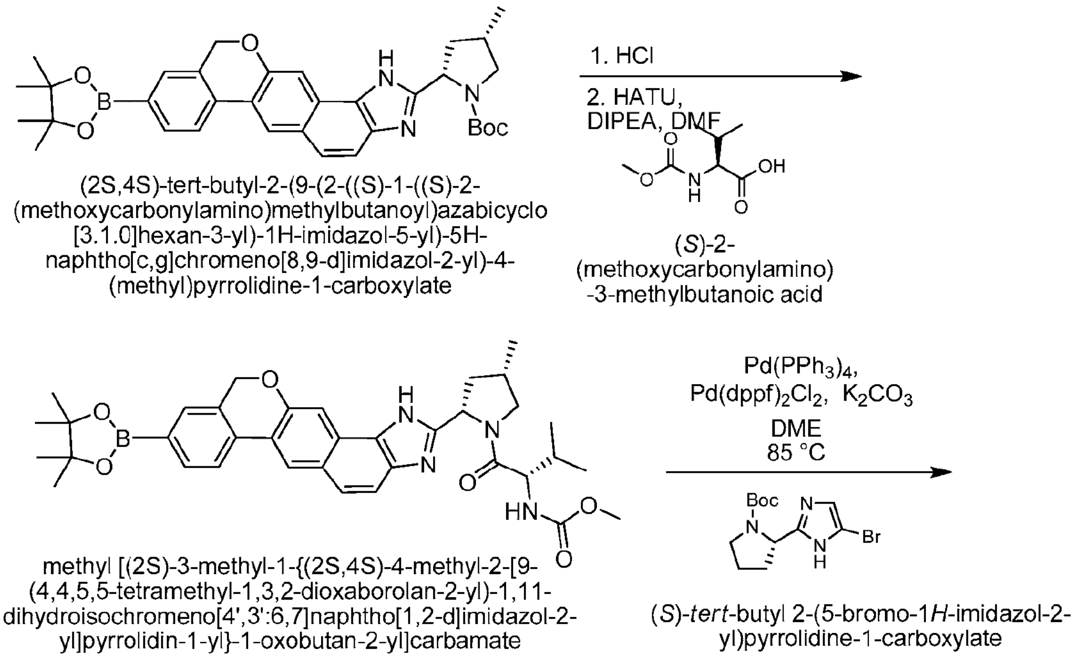
**(2S,4S)-*tert*-butyl-2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)methylbutanoyl)azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate:**

(2S,4S)-*tert*-butyl 2-(9-chloro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (692 mg, 1.41 mmol) in dioxane (15 mL) was added bis(pinacolato)diboron (1.07 g, 4.23 mmol), KOAc (415 mg, 4.23 mmol), X-Phos (52 mg, 0.11 mmol), and $Pd_2dba_3$ (26 mg, 0.03 mmol). The solution was degassed with $N_2$ for 10 min, then heated to 100 °C for 16 h. The solution was cooled to rt, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, brine, dried with $MgSO_4$, and concentrated. Purified by silica gel chromatography (0% to 30 % MeOH/EtOAc) to afford (2S,4S)-*tert*-butyl-2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)methylbutanoyl)azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (821 mg, quant).

**(2S,4S)-tert-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4(methyl)pyrrolidine-1-carboxylate:** To a solution of (2S,4S)-tert-butyl-2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)methylbutanoyl)azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (821 mg, 1.41 mmol), methyl (S)-1-((S)-2-(5-bromo-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (1.05 g, 2.82 mmol), tetrakis(triphenylphosphine) palladium(0) 162 mg, 0.14 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (102 mg, 0.14 mmol) in DME (15 mL) was added a solution of potassium carbonate (2M in water, 2.32 mL, 4.65 mmol). The resulting mixture was degassed and then heated to 85 °C for 18 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate. The organics were washed with saturated sodium bicarbonate and brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography to yield (2S,4S)-*tert*-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4methylpyrrolidine-1-carboxylate (386 mg, 37%).

**Methyl {2-[2-{9-[2-(1-{2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate:** A solution of (2S,4S)-*tert*-butyl 2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4methylpyrrolidine-1-carboxylate (386 mg, 0.52 mmol), $CH_2Cl_2$ (8 mL), MeOH (2 mL) and HCl (4M in Dioxane, 2 mL) and was stirred overnight. The reaction was concentrated and the crude material dissolved in DMF (8 mL). This solution was concentrated and to this material was added a solution of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (108 mg, 0.52 mmol) and COMU (248 mg, 0.52 mmol). To the resulting solution was added diisopropylethylamine (0.45 mL, 2.6 mmol). After stirring for 2 hours at room temperature, the reaction was diluted with 10% MeOH/EtOAc, washed with saturated $NaHCO_3$ water and brine, dried ($Na_2SO_4$), concentrated and purified by HPLC to give methyl {2-[2-{9-[2-(1-{2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-methylpyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (27 mg, 6%). LCMS-ESI$^+$: calculated for $C_{47}H_{50}N_8O_7$: 838.38; observed $[M+1]^+$: 840.12

## Example AZ

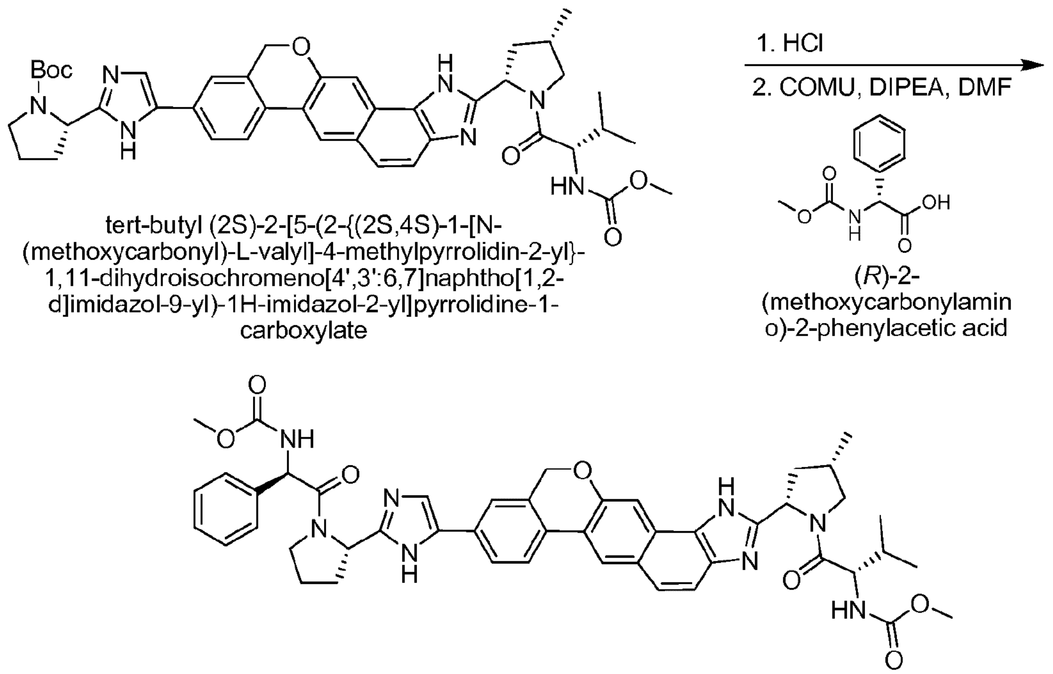


(2S,4S)-tert-butyl-2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)methylbutanoyl)azabicyclo [3.1.0]hexan-3-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-(methyl)pyrrolidine-1-carboxylate

(*S*)-2-(methoxycarbonylamino) -3-methylbutanoic acid

methyl [(2S)-3-methyl-1-{(2S,4S)-4-methyl-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate

(*S*)-*tert*-butyl 2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate



tert-butyl (2S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate

(*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid

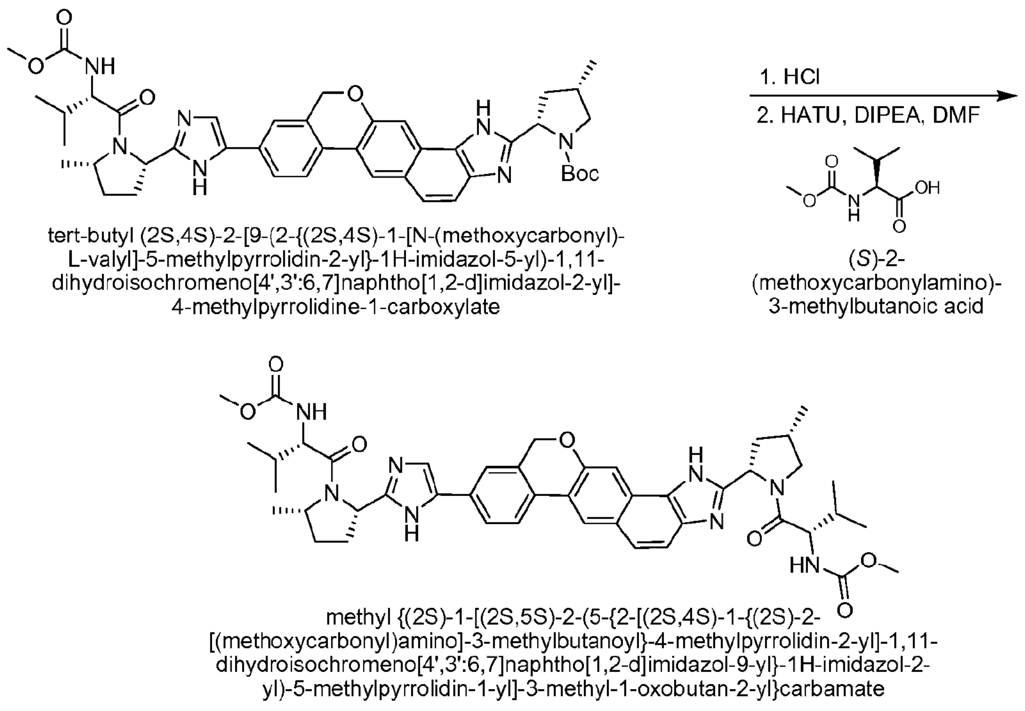
methyl {(1R)-2-[(2S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**Methyl [(2S)-3-methyl-1-{(2S,4S)-4-methyl-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate:** (2S,4S)-*tert*-butyl-2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)methylbutanoyl)azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-(methyl)pyrrolidine-1-carboxylate (950 mg, 1.63 mmol) was dissolved in DCM (12 mL), MeOH (3 mL) and HCl (4 M in dioxane, 3 mL) was added. The reaction mixture was stirred for 4 h and then concentrated under reduced pressure. The crude residue was treated with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (285 mg, 1.63 mmol), HATU (620 mg, 1.63 mmol) and DMF (15 mL), then DIPEA (1.42 mL, 8.15 mmol) was added dropwise. After 1 h, the mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0% to 30% MeOH/EtOAc) to afford methyl [(2S)-3-methyl-1-{(2S,4S)-4-methyl-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate (596 mg, 57%).

***Tert*-butyl (2S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate:** Methyl [(2S)-3-methyl-1-{(2S,4S)-4-methyl-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate (298 mg, 0.47 mmol), (S)-*tert*-butyl 2-(5-bromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (443 mg, 1.4 mmol), $Pd(PPh_3)_4$ (54 mg, 0.05 mmol), $PdCl_2(dppf)_2$ (36 mg, 0.05 mmol), and $K_2CO_3$ (2M in $H_2O$, 0.78 mL, 1.55 mmol) were combined in DME (5 mL). The mixture was degassed with bubbling $N_2$ for 10 min the heated to 85 °C for 16 h. After cooling, the reaction mixture was diluted with EtOAc, and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0% to 30% MeOH/EtOAc) to afford *tert*-butyl (2S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate (84 mg, 24%).

**Methyl {(1R)-2-[(2S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate:** *Tert*-butyl (2S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate (84 mg, 0.11 mmol) was dissolved in DCM (2.5 mL), MeOH (0.5 mL) and HCl (4 M in dioxane, 0.5 mL) was added. The reaction mixture was stirred for 18 h and then concentrated under reduced pressure. The crude residue was treated with (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (23 mg, 0.11 mmol), COMU (53 mg, 0.11 mmol) and DMF (3 mL), then DIPEA (0.10 mL, 0.56 mmol) was added dropwise. After 30 min, the mixture was diluted with 10% MeOH/EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by HPLC to afford methyl {(1R)-2-[(2S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (41 mg, 45%). LCMS-ESI$^+$: calculated for C47H50N8O7: 838.38; observed $[M+1]^+$: 839.39

## Example BA



tert-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate

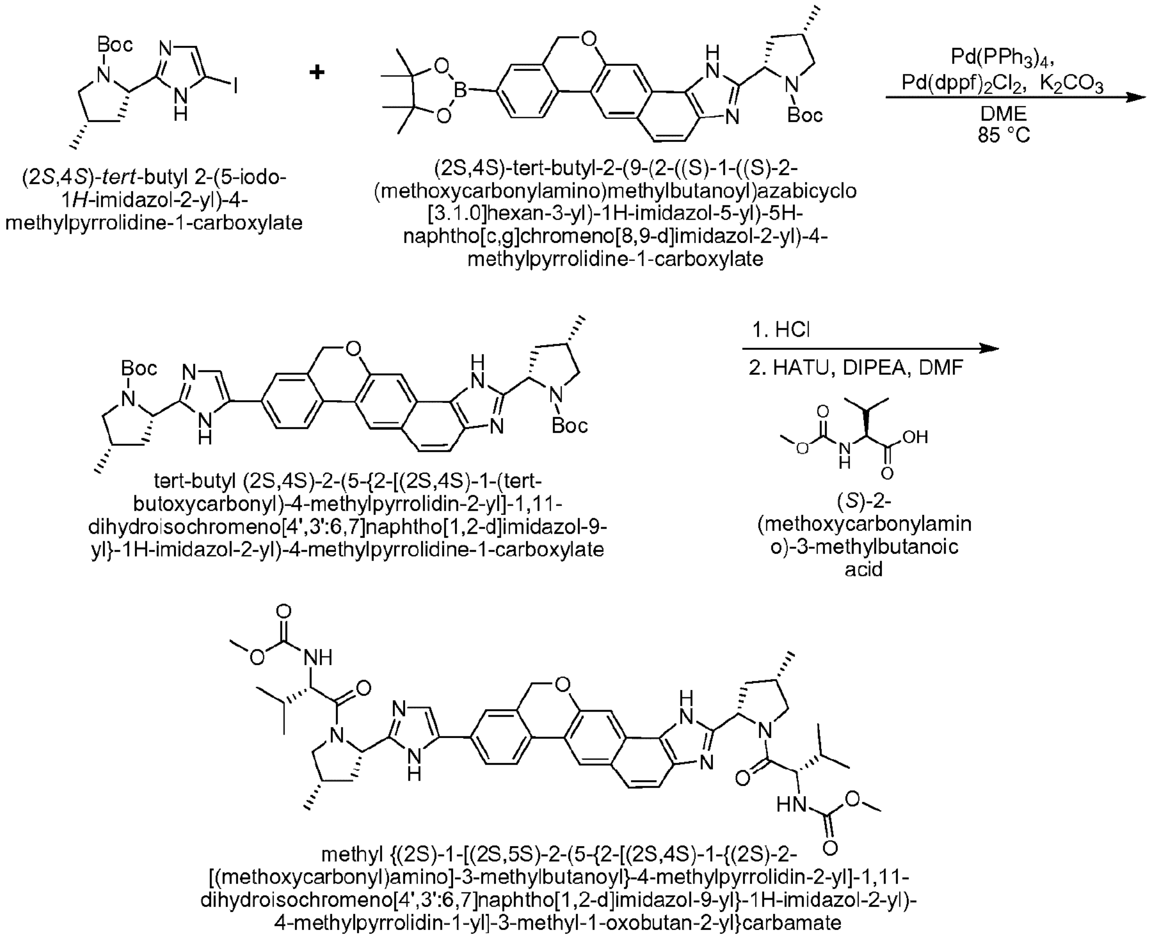
(*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid

methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**Methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** *Tert*-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (164 mg, 0.23 mmol) was dissolved in DCM (2.57 mL), MeOH (0.7 mL) and HCl (4 M in dioxane, 0.7 mL) was added. The reaction mixture was stirred for 16 h and then concentrated under reduced pressure. The crude residue was treated with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (30 mg, 0.17 mmol), HATU (65 mg, 0.17 mmol) and DMF (3 mL), then DIPEA (0.15 mL, 0.85 mmol) was added dropwise. After 45 min, the mixture was diluted with 10% MeOH/EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by HPLC to afford methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-

yl}carbamate (23 mg, 16%). LCMS-ESI$^+$: calculated for C45H54N8O7: 818.41; observed [M+1]$^+$: 820.70.

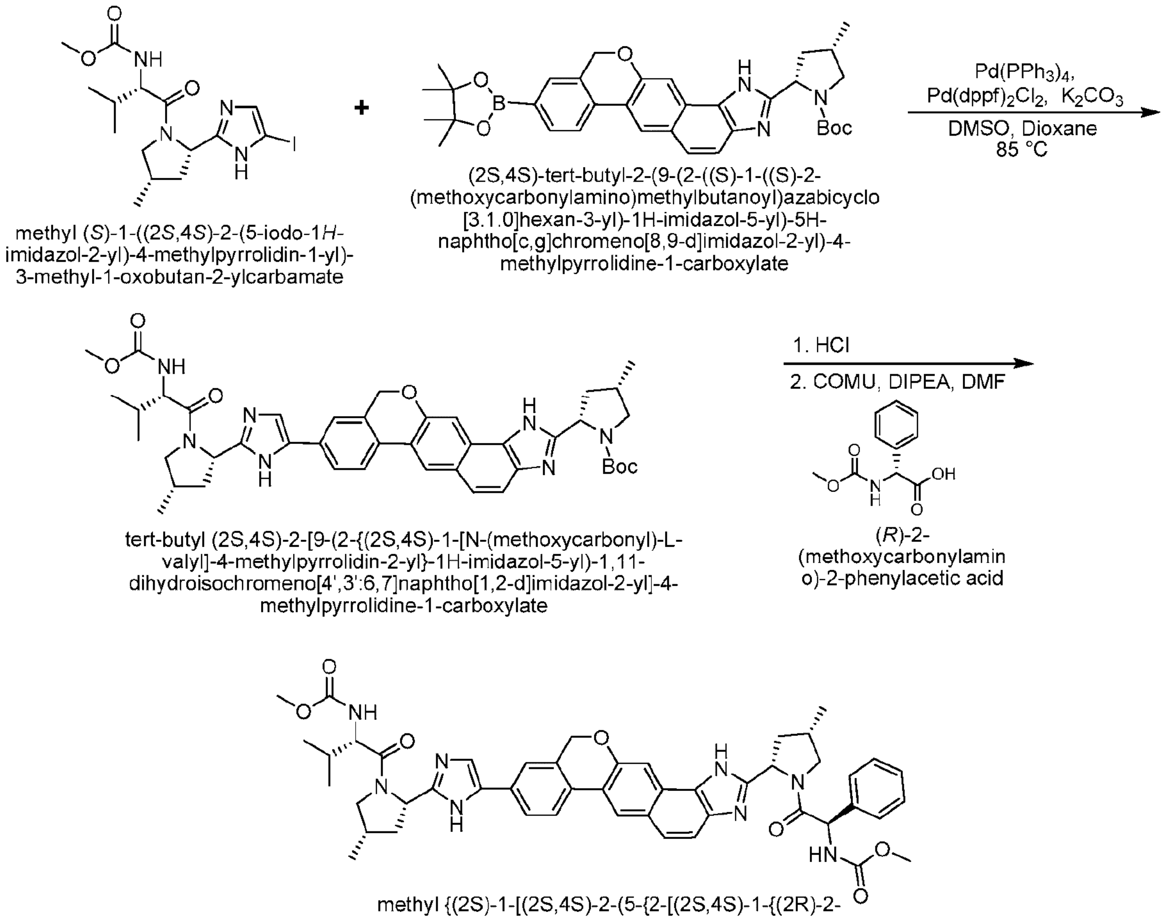
## Example BB



***Tert*-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate:** (2S,4S)-*tert*-butyl-2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)methylbutanoyl)azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (293 mg, 0.0.78 mmol), (2S,4S)-*tert*-butyl 2-(5-iodo-1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (300 mg, 0.52 mmol), Pd(PPh$_3$)$_4$ (60 mg, 0.052 mmol), PdCl$_2$(dppf)$_2$ (38 mg, 0.052 mmol), and K$_2$CO$_3$ (2M in H$_2$O, 0.86 mL, 1.72 mmoL) were combined in DME (6 mL). The mixture was degassed with bubbling N$_2$ for 10 min the heated to 85 °C for 16 h. After cooling, the reaction mixture was diluted with EtOAc, and washed successively with saturated aqueous NaHCO$_3$ and brine. The organics were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (100% EtOAc) to afford *tert*-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(tert-butoxycarbonyl)-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (183 mg, 50%).

**Methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** *Tert*-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (183 mg, 0.26 mmol) was dissolved in DCM (4 mL), MeOH (1 mL) and HCl (4 M in dioxane, 1 mL) was added. The reaction mixture was stirred for 2 h and then concentrated under reduced pressure. The crude residue was treated with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (91 mg, 0.52 mmol), HATU (198 mg, 0.52 mmol) and DMF (5 mL), then DIPEA (0.45 mL, 2.6 mmol) was added dropwise. After 1 h, the mixture was diluted with 10% MeOH/EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by HPLC to afford methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (6 mg, 3%). LCMS-ESI$^+$: calculated for C45H54N8O7: 818.41; observed [M+1]$^+$: 819.41.

## Example BC



methyl (*S*)-1-((2*S*,4*S*)-2-(5-iodo-1*H*-imidazol-2-yl)-4-methylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

(2S,4S)-tert-butyl-2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)methylbutanoyl)azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate

tert-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate

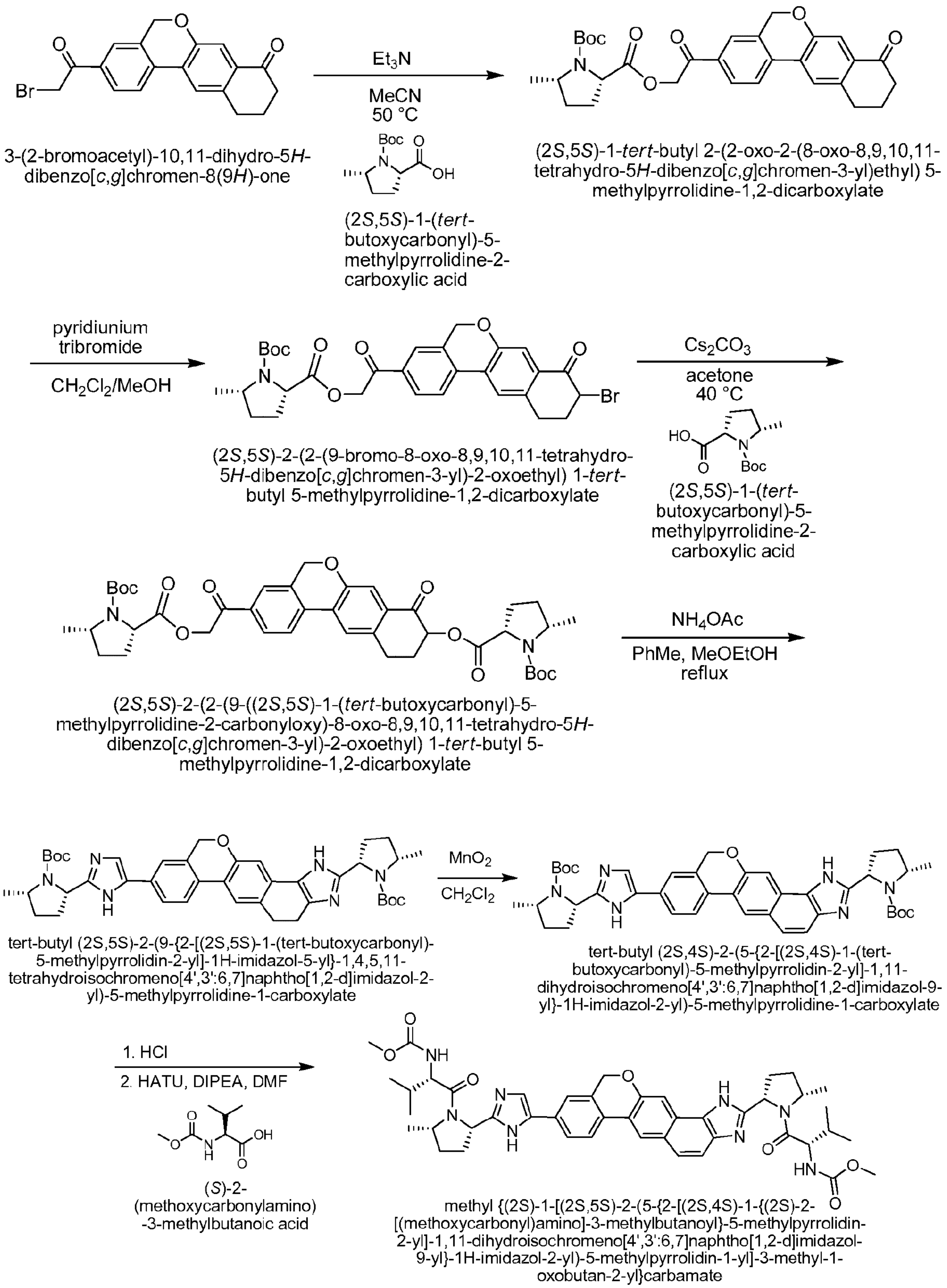
(*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid

methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

***Tert*-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate:** (2S,4S)-tert-butyl-2-(9-(2-((S)-1-((S)-2-(methoxycarbonylamino)methylbutanoyl)azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-5-yl)-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (558 mg, 0.96 mmol), methyl (S)-1-((2S,4S)-2-(5-iodo-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (501 mg, 1.15 mmol), Pd(PPh$_3$)$_4$ (111 mg, 0.096 mmol), PdCl$_2$(dppf)$_2$ (70 mg, 0.096 mmol), and K$_2$CO$_3$ (2M in H$_2$O, 1.6 mL, 3.17 mmoL) were combined in DMSO (6 mL) and dioxane (6 mL). The mixture was degassed with bubbling N$_2$ for 10 min the heated to 95 °C for 14 h. After cooling, the reaction mixture was diluted with EtOAc, and washed successively with saturated aqueous NaHCO$_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0 %- 30% MeOH/EtOAc) to afford *tert*-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (257 mg, 35%).

**Methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** *Tert*-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (257 mg, 0.34 mmol) was dissolved in DCM (4 mL), MeOH (1 mL) and HCl (4 M in dioxane, 1 mL) was added. The reaction mixture was stirred for 3 h and then concentrated under reduced pressure. The crude residue was treated with (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (71 mg, 0.34 mmol), COMU (161 mg, 0.34 mmol) and DMF (6 mL), then DIPEA (0.3 mL, 1.67 mmol) was added dropwise. After 15 h, the mixture was diluted with 10% MeOH/EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by HPLC to afford methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (152 mg, 53%). LCMS-ESI$^+$: calculated for C48H52N8O7: 852.40; observed $[M+1]^+$: 854.26. $^1$H NMR ($CD_3OD$): 8.677 (s, 1H), 8.232-7.837 (m, 5H), 7.695-7.673 (m, 2H), 7.496-7.426 (m, 5H), 5.499 (s, 1H), 5.445-5.401 (m, 1H), 5.337 (s, 1H), 5.253-5.208 (q, 1H, *J*= 7.2 Hz), 4.870 (m, 1H), 4.230 (d, 1H, *J*= 7.2 Hz), 3.781 (m, 1H), 3.671 (s, 3H), 3.607 (s, 3H), 3.425 (m, 3H), 2.750-2.689 (m, 2H), 2.683 (m, 2H), 2.384 (m, 1H), 1.894 (quint, 2H, *J*=12 Hz), 1.249-1.151 (m, 6H), 0.974-0.890 (m, 6H).

# Example BD


Et3N
MeCN
50 °C
3-(2-bromoacetyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one
(2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid
(2S,5S)-1-tert-butyl 2-(2-oxo-2-(8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)ethyl) 5-methylpyrrolidine-1,2-dicarboxylate
pyridiunium tribromide
CH2Cl2/MeOH
(2S,5S)-2-(2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-tert-butyl 5-methylpyrrolidine-1,2-dicarboxylate
Cs2CO3
acetone
40 °C
(2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid
(2S,5S)-2-(2-(9-((2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-tert-butyl 5-methylpyrrolidine-1,2-dicarboxylate
NH4OAc
PhMe, MeOEtOH
reflux
tert-butyl (2S,5S)-2-(9-{2-[(2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate
MnO2
CH2Cl2
tert-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate
1. HCl
2. HATU, DIPEA, DMF
(S)-2-(methoxycarbonylamino)-3-methylbutanoic acid
methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate
Boc
O
OH
Br
N
H
NH
HN

**(2S,5S)-1-*tert*-butyl 2-(2-oxo-2-(8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)ethyl) 5-methylpyrrolidine-1,2-dicarboxylate:** To a solution of 3-(2-bromoacetyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one in MeCN (30 mL) was added (2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid (1.2 g, 3.23 mmol) and triethyl amine (0.48 mL, 3.55 mmol) and the solution was heated to 50 °C. After stirring for 15 h, the solution was cooled to rt, and diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (20% to 50% EtOAc/hexanes) to afford (2S,5S)-1-*tert*-butyl 2-(2-oxo-2-(8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)ethyl) 5-methylpyrrolidine-1,2-dicarboxylate (1.09 g, 65%).

**(2S,5S)-2-(2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate:** (2S,5S)-1-*tert*-butyl 2-(2-oxo-2-(8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)ethyl) 5-methylpyrrolidine-1,2-dicarboxylate (1.29 g, 2.48 mmol) was dissolved in a solution of DCM (17.5 mL) and MeOH (7 mL), then treated with pyridinium tribromide (873 mg, 2.73 mmol). After stirring at RT for 1 h, the reaction mixture was diluted with DCM and 10% HCl, and extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure and the crude material was carried on without further purification.

**(2S,5S)-2-(2-(9-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-tert-butyl 5-methylpyrrolidine-1,2-dicarboxylate:** (2S,5S)-2-(2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate (700 mg, 1.17 mmol) was treated with a solution of (2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid (375 mg, 1.64 mmol) in acetone (6 mL) and $Cs_2CO_3$ (267 mg, 0.82 mmol). The stirred reaction mixture was heated to 40 °C for 16 h, then cooled to RT and diluted with $CH_2Cl_2$ and extracted 3X. The organic phase was washed with brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (40% to 100% EtOAc/hexanes) to afford (2S,5S)-2-(2-(9-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-tert-butyl 5-methylpyrrolidine-1,2-dicarboxylate (464 mg, 53%).

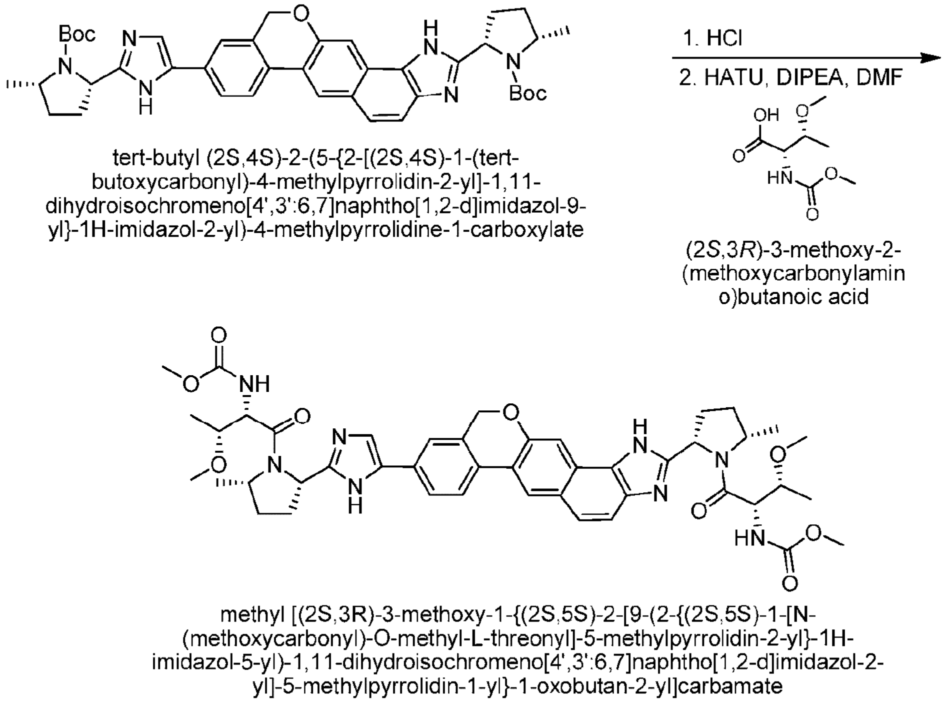
***Tert*-butyl (2S,5S)-2-(9-{2-[(2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate:** (2S,5S)-2-(2-(9-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate (464 mg, 0.62 mmol) and $NH_4OAc$ (8.48 g, 110.0 mmol) were suspended in a solution of 10:1 PhMe/2-methoxyethanol (22 mL). The stirred reaction mixture was heated to 110 °C for 20 h, then cooled to RT and diluted with EtOAc. The organic phase was washed with water, saturated aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0% to 30% MeOH/EtOAc) to afford *tert*-butyl (2S,5S)-2-(9-{2-[(2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (393 mg, 90%).

***Tert*-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate:** *Tert*-butyl (2S,5S)-2-(9-{2-[(2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (393 mg, 0.55 mmol) was suspended in DCM (7 mL) and activated $MnO_2$ (1.45 g, 16.7 mmol) was added in a single portion. The reaction mixture was heated to 40 °C. After stirring for 2.5 h, the mixture was cooled to rt and the slurry was filtered over celite. The filter cake was washed with copious $CH_2Cl_2$ and MeOH and the filtrate was concentrated under reduced pressure. The crude material was taken on to the next step without further purification to afford *tert*-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (328 g, 85%).

**Methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** *Tert*-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (164 mg, 0.23 mmol) was dissolved in DCM (7 mL), MeOH

(1.5 mL) and HCl (4 M in dioxane, 1.5 mL) was added. The reaction mixture was stirred for 16 h and then concentrated under reduced pressure. The crude residue was treated with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (81 mg, 0.46 mmol), HATU (175 mg, 0.46 mmol) and DMF (5 mL), then DIPEA (0.4 mL, 2.34 mmol) was added dropwise. After 35 min, the mixture was diluted with 10% MeOH/EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by HPLC to afford methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (132 mg, 69%). LCMS-ESI$^+$: calculated for C45H54N8O7: 818.41; observed $[M+1]^+$: 820.19. $^1H$ NMR ($CD_3OD$): 8.492 (m, 1H), 8.179-7.538 (m, 7H), 5.267-5.201 (m, 3H), 5.125-5.082 (m, 1H), 4.070 (m, 1H), 3.383-3.592 (m, 4 H), 3.225 (s, 3H), 2.466-2.249 (m, 5H), 1.992-1.892 (m, 3H), 1.568 (d, 3H, $J$=6.4 Hz), 1.490 (d, 3H, $J$=6.8 Hz), 1.266 (m, 2H), 1.020-0.806 (m, 14H).

## Example BE



tert-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(tert-butoxycarbonyl)-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate

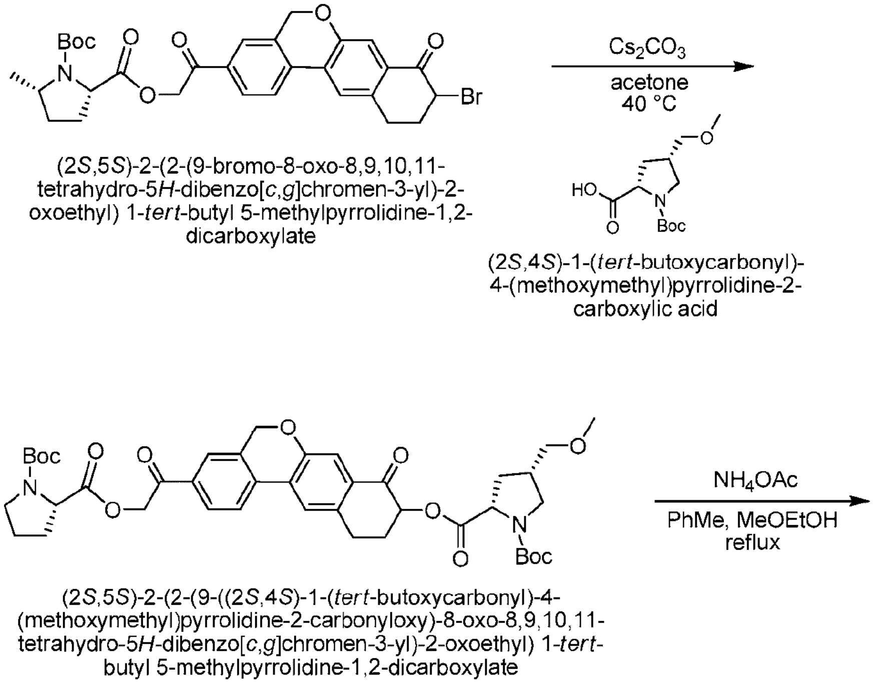
(2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid

methyl [(2S,3R)-3-methoxy-1-{(2S,5S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-5-methylpyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate

**Methyl [(2S,3R)-3-methoxy-1-{(2S,5S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-5-methylpyrrolidin-1-yl}-1-**

**oxobutan-2-yl]carbamate:** *Tert*-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (164 mg, 0.23 mmol) was dissolved in DCM (7 mL), MeOH (1.5 mL) and HCl (4 M in dioxane, 1.5 mL) was added. The reaction mixture was stirred for 16 h and then concentrated under reduced pressure. The crude residue was treated with (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (90 mg, 0.46 mmol), HATU (175 mg, 0.46 mmol) and DMF (6 mL), then DIPEA (0.4 mL, 2.34 mmol) was added dropwise. After 30 min, the mixture was diluted with 10% MeOH/EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by HPLC to afford methyl [(2S,3R)-3-methoxy-1-{(2S,5S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-5-methylpyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate (97 mg, 50%). LCMS-ESI$^+$: calculated for C45H54N8O9: 850.40; observed $[M+1]^+$: 851.58. $^1$H NMR ($CD_3OD$): 8.631 (s, 1H), 8.191-7.938 (m, 7 H), 6.100 (m, 1 H), 5.925 (m, 1H), 5.303 (m, 3H), 5.179 (t, 1H, *J*=6.8 Hz), 4.406-4.358 (m, 2H), 3.754-3.598 (m, 8H), 3.376 (s, 3H), 3.263 (s, 3H), 2.625-2.256 (m, 6H), 2.038-1.955 (m, 2H), 1.598 (d, 3H, *J*=6.4 Hz), 1.530 (d, 3H, *J*=6.8 Hz), 1.302-1.099 (m, 6H).

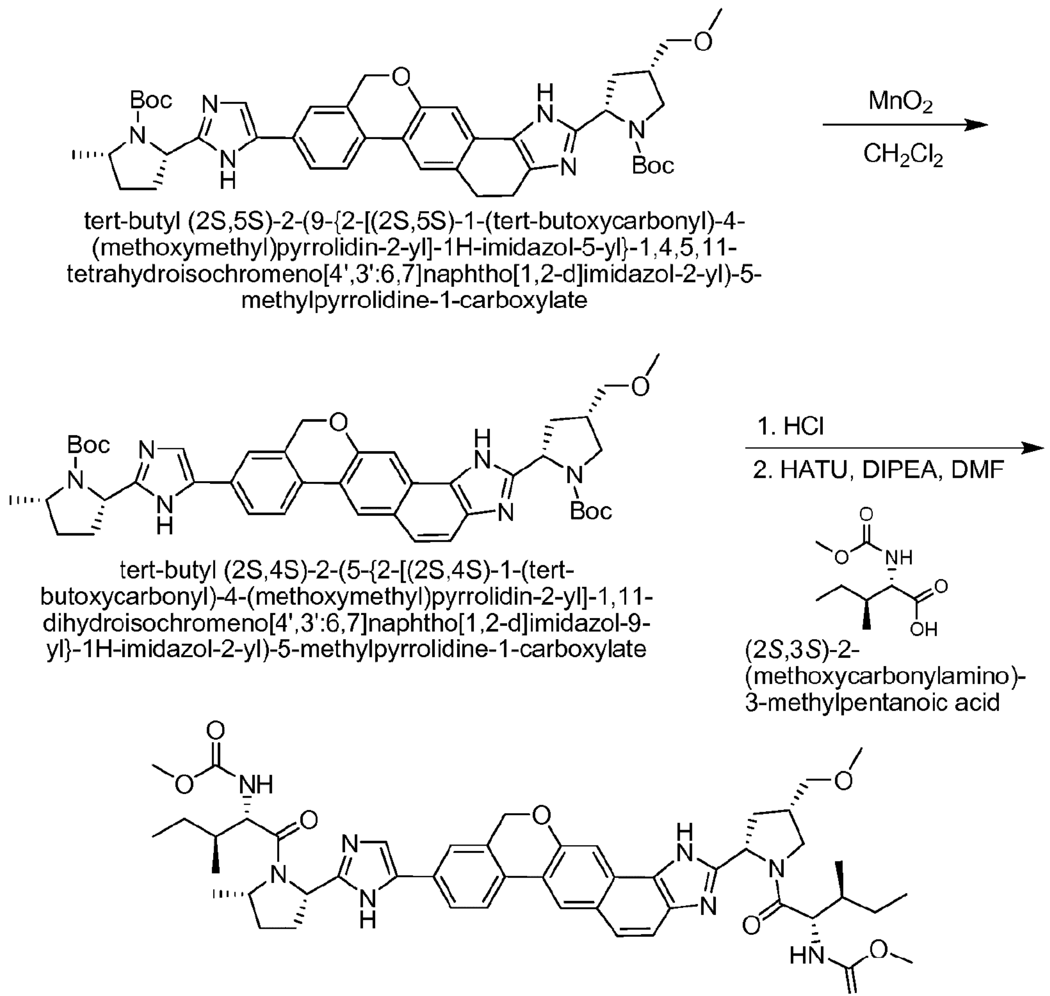
## Example BF



(2*S*,5*S*)-2-(2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5*H*-dibenzo[*c*,*g*]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate

(2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid

(2*S*,5*S*)-2-(2-(9-((2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5*H*-dibenzo[*c*,*g*]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate



tert-butyl (2S,5S)-2-(9-{2-[(2S,5S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate

tert-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate

(2*S*,3*S*)-2-(methoxycarbonylamino)-3-methylpentanoic acid

methyl {(2S,3S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S,3S)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate

**(2S,5S)-2-(2-(9-((2S,4S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate:** (2S,5S)-2-(2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate (800 mg, 1.34 mmol) was treated with a solution of (2S,4S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid (485 mg, 1.87 mmol) in acetone (6 mL) and $Cs_2CO_3$ (306 mg, 0.94 mmol). The stirred reaction mixture was heated to 40 °C for 16 h, then cooled to RT and diluted with $CH_2Cl_2$ and extracted 3X. The organic phase was washed with brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (40% to 100% EtOAc/hexanes) to afford (2S,5S)-2-(2-(9-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-

methylpyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate (680 mg, 65%).

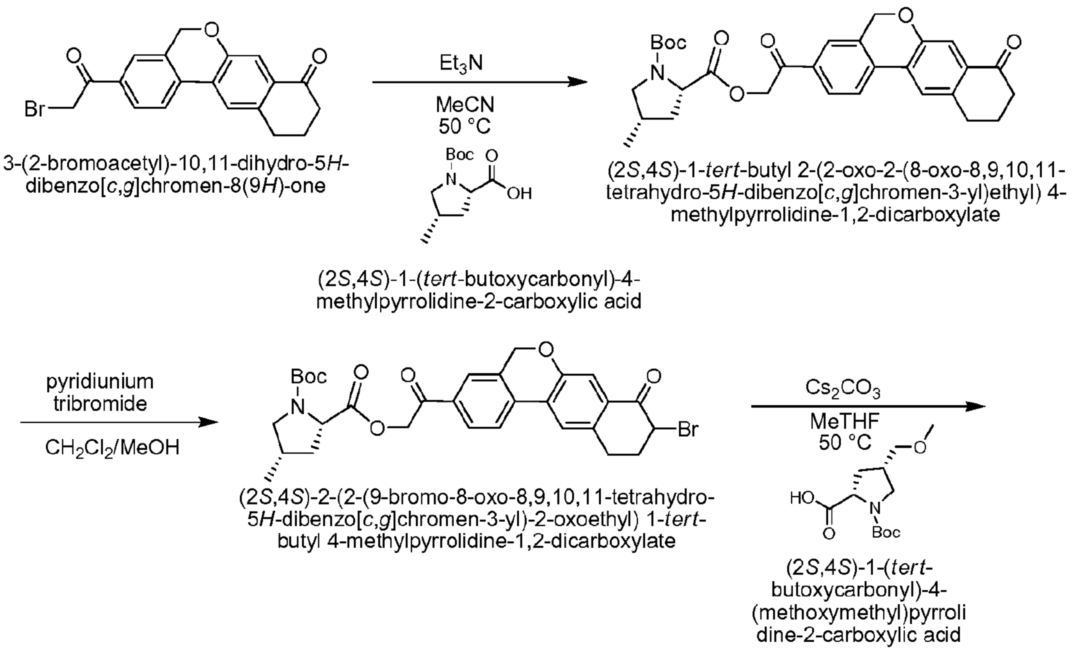
***Tert*-butyl (2S,5S)-2-(9-{2-[(2S,5S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate:** (2S,5S)-2-(2-(9-((2S,5S)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 5-methylpyrrolidine-1,2-dicarboxylate (680 mg, 0.87 mmol) and $NH_4OAc$ (10.0 g, 130.0 mmol) were suspended in a solution of 10:1 PhMe/2-methoxyethanol (22 mL). The stirred reaction mixture was heated to 110 °C for 24 h, then cooled to RT and diluted with EtOAc. The organic phase was washed with water, saturated aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0% to 30% MeOH/EtOAc) to afford *tert*-butyl (2S,5S)-2-(9-{2-[(2S,5S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (461 mg, 72%).

***Tert*-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate:** *Tert*-butyl (2S,5S)-2-(9-{2-[(2S,5S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (461 mg, 0.62 mmol) was suspended in DCM (7 mL) and activated $MnO_2$ (1.6 g, 18.8 mmol) was added in a single portion. The reaction mixture was heated to 40 °C. After stirring for 5.5 h, the mixture was cooled to rt and the slurry was filtered over celite. The filter cake was washed with copious $CH_2Cl_2$ and MeOH and the filtrate was concentrated under reduced pressure. The crude material was taken on to the next step without further purification to afford *tert*-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (414 g, 90%).

**Methyl {(2S,3S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S,3S)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-**

**methylpyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate:** *Tert*-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (207 mg, 0.28 mmol) was dissolved in DCM (4 mL), MeOH (1 mL) and HCl (4 M in dioxane, 1 mL) was added. The reaction mixture was stirred for 1.5 h and then concentrated under reduced pressure. The crude residue was treated with (2S,3S)-2-(methoxycarbonylamino)-3-methylpentanoic acid (106 mg, 0.56 mmol), HATU (214 mg, 0.56 mmol) and DMF (5 mL), then DIPEA (0.49 mL, 2.8 mmol) was added dropwise. After 30 min, the mixture was diluted with 10% MeOH/EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by HPLC to afford methyl {(2S,3S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S,3S)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate (132 mg, 69%). LCMS-ESI$^+$: calculated for C45H54N8O7: 876.45; observed [M+1]$^+$: 879.02

## Example BG



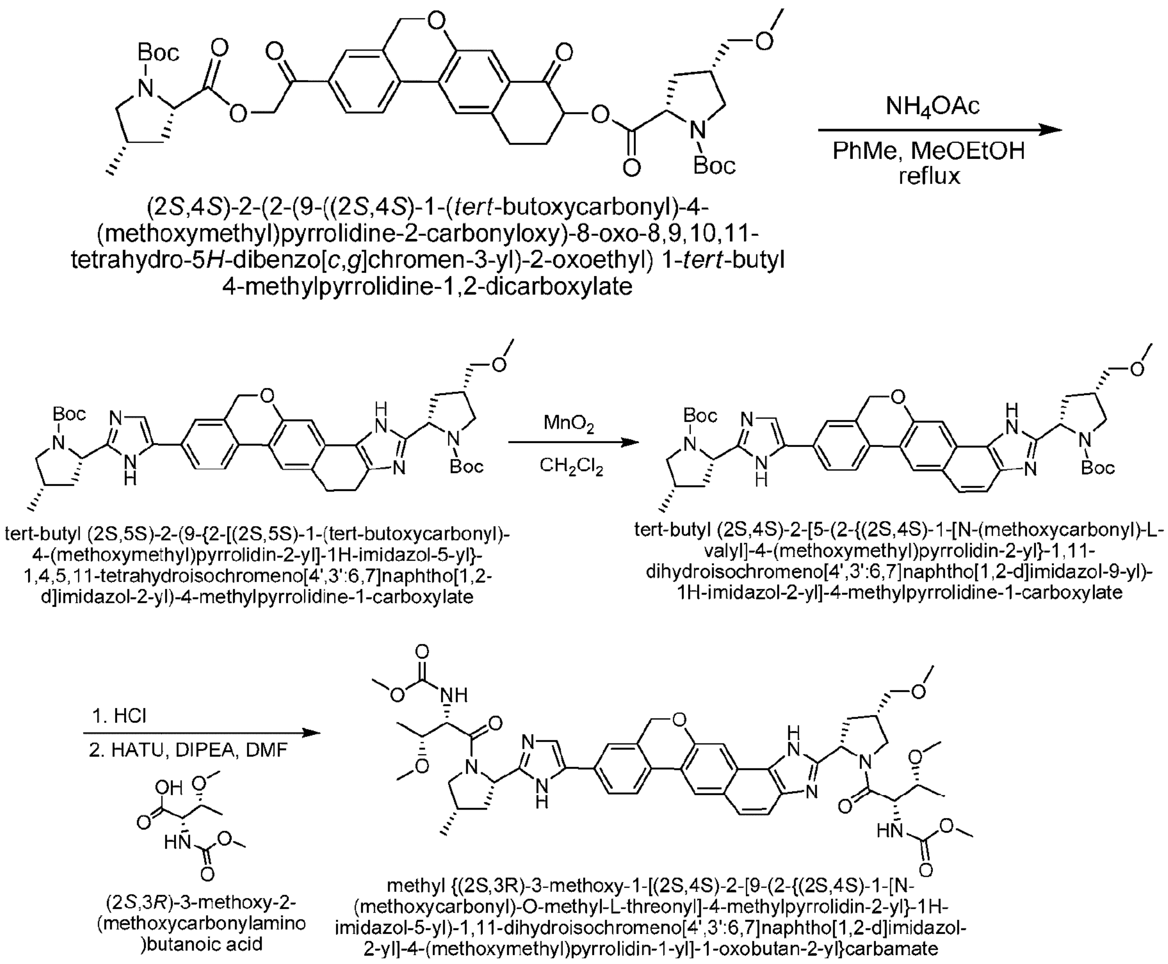
3-(2-bromoacetyl)-10,11-dihydro-5*H*-dibenzo[*c*,*g*]chromen-8(9*H*)-one

(2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid

(2*S*,4*S*)-1-*tert*-butyl 2-(2-oxo-2-(8-oxo-8,9,10,11-tetrahydro-5*H*-dibenzo[*c*,*g*]chromen-3-yl)ethyl) 4-methylpyrrolidine-1,2-dicarboxylate

(2*S*,4*S*)-2-(2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5*H*-dibenzo[*c*,*g*]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 4-methylpyrrolidine-1,2-dicarboxylate

(2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid



(2*S*,4*S*)-2-(2-(9-((2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5*H*-dibenzo[*c*,*g*]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 4-methylpyrrolidine-1,2-dicarboxylate

tert-butyl (2S,5S)-2-(9-{2-[(2S,5S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate

tert-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-(methoxymethyl)pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate

(2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid

methyl {(2S,3R)-3-methoxy-1-[(2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidin-1-yl]-1-oxobutan-2-yl}carbamate

**(2S,4S)-1-*tert*-butyl 2-(2-oxo-2-(8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)ethyl) 4-methylpyrrolidine-1,2-dicarboxylate:** To a solution of 3-(2-bromoacetyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (647 mg, 1.74 mmol) in MeCN (20 mL) was added ((2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid (559 mg, 2.44 mmol) and DIPEA (0.36 mL, 2.09 mmol) and the solution was heated to 60 °C. After stirring for 3 h, the solution was cooled to rt, and diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (20% to 50% EtOAc/hexanes) to afford (2S,4S)-1-*tert*-butyl 2-(2-oxo-2-(8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)ethyl) 4-methylpyrrolidine-1,2-dicarboxylate (621 mg, 69%).

**(2S,4S)-2-(2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 4-methylpyrrolidine-1,2-dicarboxylate:** (2S,4S)-1-*tert*-butyl 2-(2-

oxo-2-(8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)ethyl) 4-methylpyrrolidine-1,2-dicarboxylate (621 mg, 1.19 mmol) was dissolved in a solution of DCM (10 mL) and MeOH (4 mL), then treated with pyridinium tribromide (421 mg, 1.3 mmol). After stirring at RT for 1.5 h, the reaction mixture was diluted with DCM and 10% HCl, and extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure and the crude material was carried on without further purification.

**(2S,4S)-2-(2-(9-((2S,4S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 4-methylpyrrolidine-1,2-dicarboxylate:** (2S,4S)-2-(2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 4-methylpyrrolidine-1,2-dicarboxylate (709 mg, 1.18 mmol) was treated with a solution of (2S,4S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid (614 mg, 2.36 mmol) in Me-THF (12 mL) and $Cs_2CO_3$ (384 mg, 1.18 mmol). The stirred reaction mixture was heated to 50 °C for 16 h, then cooled to RT and diluted with $CH_2Cl_2$ and extracted 3X. The organic phase was washed with brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (40% to 100% EtOAc/hexanes) to afford (2S,4S)-2-(2-(9-((2S,4S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 4-methylpyrrolidine-1,2-dicarboxylate (651 mg, 71%).

***Tert*-butyl (2S,5S)-2-(9-{2-[(2S,5S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate:** (2S,4S)-2-(2-(9-((2S,4S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 4-methylpyrrolidine-1,2-dicarboxylate (651 mg, 0.84 mmol) and $NH_4OAc$ (10.0 g, 129.7 mmol) were suspended in a solution of 10:1 PhMe/2-methoxyethanol (22 mL). The stirred reaction mixture was heated to 110 °C for 20 h, then cooled to RT and diluted with EtOAc. The organic phase was washed with water, saturated aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0% to 30% MeOH/EtOAc) to afford *tert*-butyl (2S,5S)-2-(9-{2-[(2S,5S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,4,5,11-

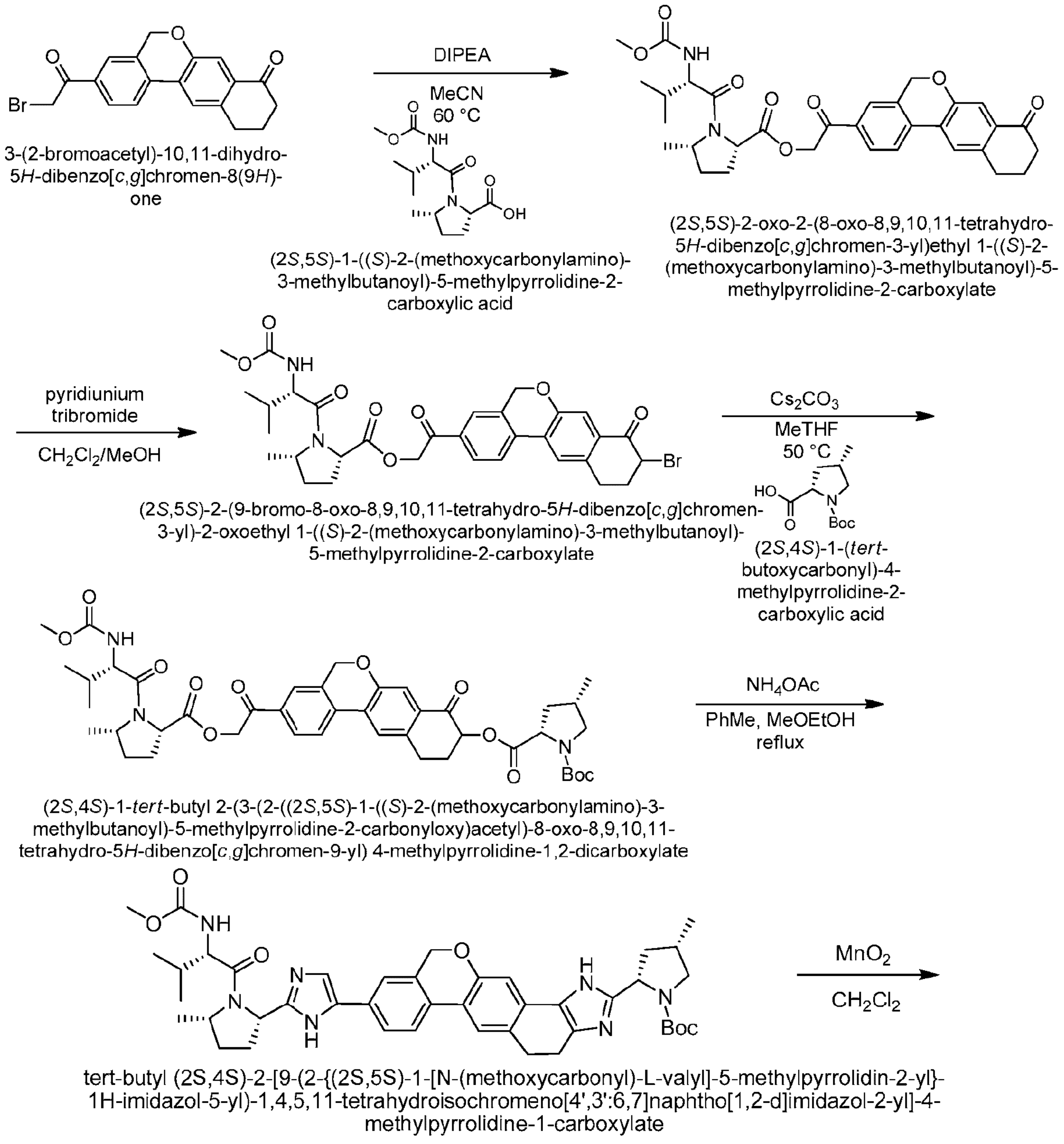
tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (382 mg, 62%).

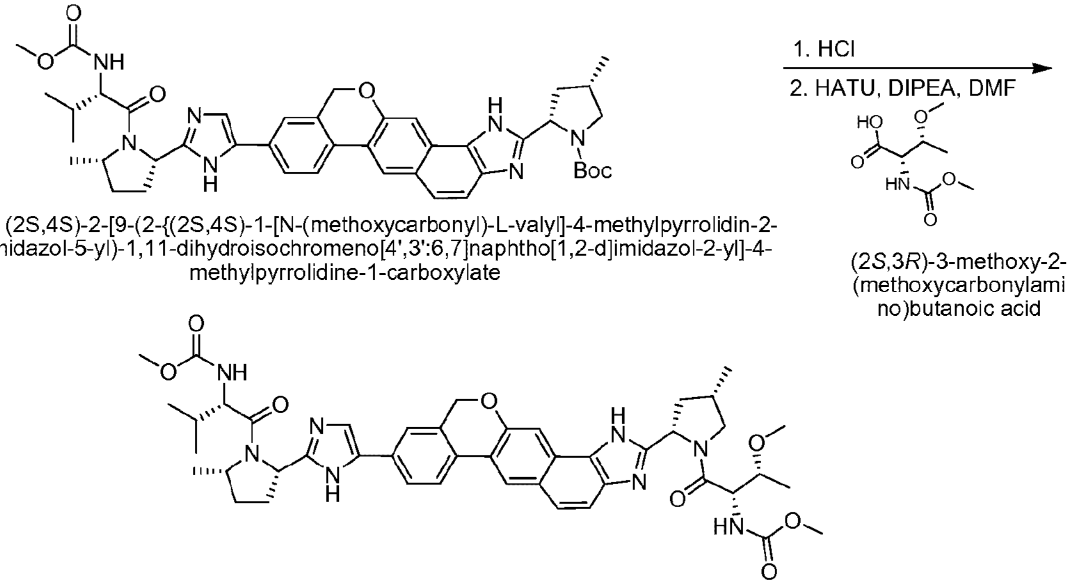
***Tert*-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-(methoxymethyl)pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate:** *Tert*-butyl (2S,5S)-2-(9-{2-[(2S,5S)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (382 mg, 0.52 mmol) was suspended in DCM (8 mL) and activated $MnO_2$ (1.35 g, 15.5 mmol) was added in a single portion. The reaction mixture was heated to 35 °C. After stirring for 15 h, the mixture was cooled to rt and the slurry was filtered over celite. The filter cake was washed with copious $CH_2Cl_2$ and MeOH and the filtrate was concentrated under reduced pressure. The crude material was taken on to the next step without further purification to afford *tert*-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-(methoxymethyl)pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (347 g, 91%).

**Methyl {(2S,3R)-3-methoxy-1-[(2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidin-1-yl]-1-oxobutan-2-yl}carbamate:** *Tert*-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-(methoxymethyl)pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (174 mg, 0.24 mmol) was dissolved in DCM (4 mL), MeOH (1 mL) and HCl (4 M in dioxane, 1 mL) was added. The reaction mixture was stirred for 5 h and then concentrated under reduced pressure. The crude residue was treated with ((2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (92 mg, 0.48 mmol), HATU (182 mg, 0.48 mmol) and DMF (5 mL), then DIPEA (0.31 mL, 2.4 mmol) was added dropwise. After 35 min, the mixture was diluted with 10% MeOH/EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by HPLC to afford methyl {(2S,3R)-3-methoxy-1-[(2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidin-1-

yl]-1-oxobutan-2-yl}carbamate (72 mg, 34%). LCMS-ESI$^+$: calculated for C46H56N8O10: 880.41; observed $[M+1]^+$: 882.39. $^1$H NMR ($CD_3OD$): 8.558 (s, 1H), 8.123-7.572 (m, 7H), 5.436-5.391 (dd, 1H, *J*=7.2, 3.6 Hz), 5.252 (s, 2H), 5.220 (m, 1H), 4.493-4.444 (m, 2H), 4.287-4.206 (m, 2H), 3.756-3.256 (m, 21H), 2.834 (m, 1H), 2.717-2.621 (m, 2H), 2.500 (m, 1H), 2.150 (m, 1H), 1.882 (m, 1H), 1.208 (d, 3H, *J*=6.4 Hz), 1.159-1.099 (m, 6H).

## Example BH





tert-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate

(2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid

methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S,3R)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**(2S,5S)-2-oxo-2-(8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)ethyl 1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylate:** To a solution of 3-(2-bromoacetyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (750 mg, 2.02 mmol) in MeCN (20 mL) was added (2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylic acid (600 mg, 2.09 mmol) and DIPEA (0.35 mL, 2.02 mmol) and the solution was heated to 60 °C. After stirring for 4 h, the solution was cooled to rt, and diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (40% to 80% EtOAc/hexanes) to afford (2S,5S)-2-oxo-2-(8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)ethyl 1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylate (1.16 g, quant.).

**(2S,5S)-2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl 1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylate:** (2S,5S)-2-oxo-2-(8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)ethyl 1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylate (400 mg, 0.61 mmol) was dissolved in a solution of DCM (15 mL) and MeOH (6 mL), then treated with pyridinium tribromide (409 mg, 1.28 mmol). At 2 h, an additional portion of pyridinium tribromide (40 mg) was added. After stirring at RT for another 20 min, the reaction mixture was diluted with DCM and 10% HCl, and extracted with DCM. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure and the crude material was carried on without further purification.

**(2S,4S)-1-*tert*-butyl 2-(3-(2-((2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carbonyloxy)acetyl)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-9-yl) 4-methylpyrrolidine-1,2-dicarboxylate:** (2S,5S)-2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl 1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylate ) was treated with a solution of (2S,4S)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid (280 mg, 1.22 mmol) in Me-THF (6 mL) and $Cs_2CO_3$ (199 mg, 0.61 mmol). The stirred reaction mixture was heated to 50 °C for 2.5 h, then cooled to RT and diluted with $CH_2Cl_2$ and extracted 3X. The organic phase was washed with brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (50% to 100% EtOAc/hexanes) to afford (2S,4S)-1-*tert*-butyl 2-(3-(2-((2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carbonyloxy)acetyl)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-9-yl) 4-methylpyrrolidine-1,2-dicarboxylate (441 mg, 90%).

***Tert*-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate:** (2S,4S)-1-*tert*-butyl 2-(3-(2-((2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carbonyloxy)acetyl)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-9-yl) 4-methylpyrrolidine-1,2-dicarboxylate (441 mg, 0.55 mmol) and $NH_4OAc$ (5 g, 65.0 mmol) were suspended in a solution of 10:1 PhMe/2-methoxyethanol (11 mL). The stirred reaction mixture was heated to 110 °C for 7 h, then cooled to RT and diluted with EtOAc. The organic phase was washed with water, saturated aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0% to 30% MeOH/EtOAc) to afford *tert*-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (266 mg, 63%).

***Tert*-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-**

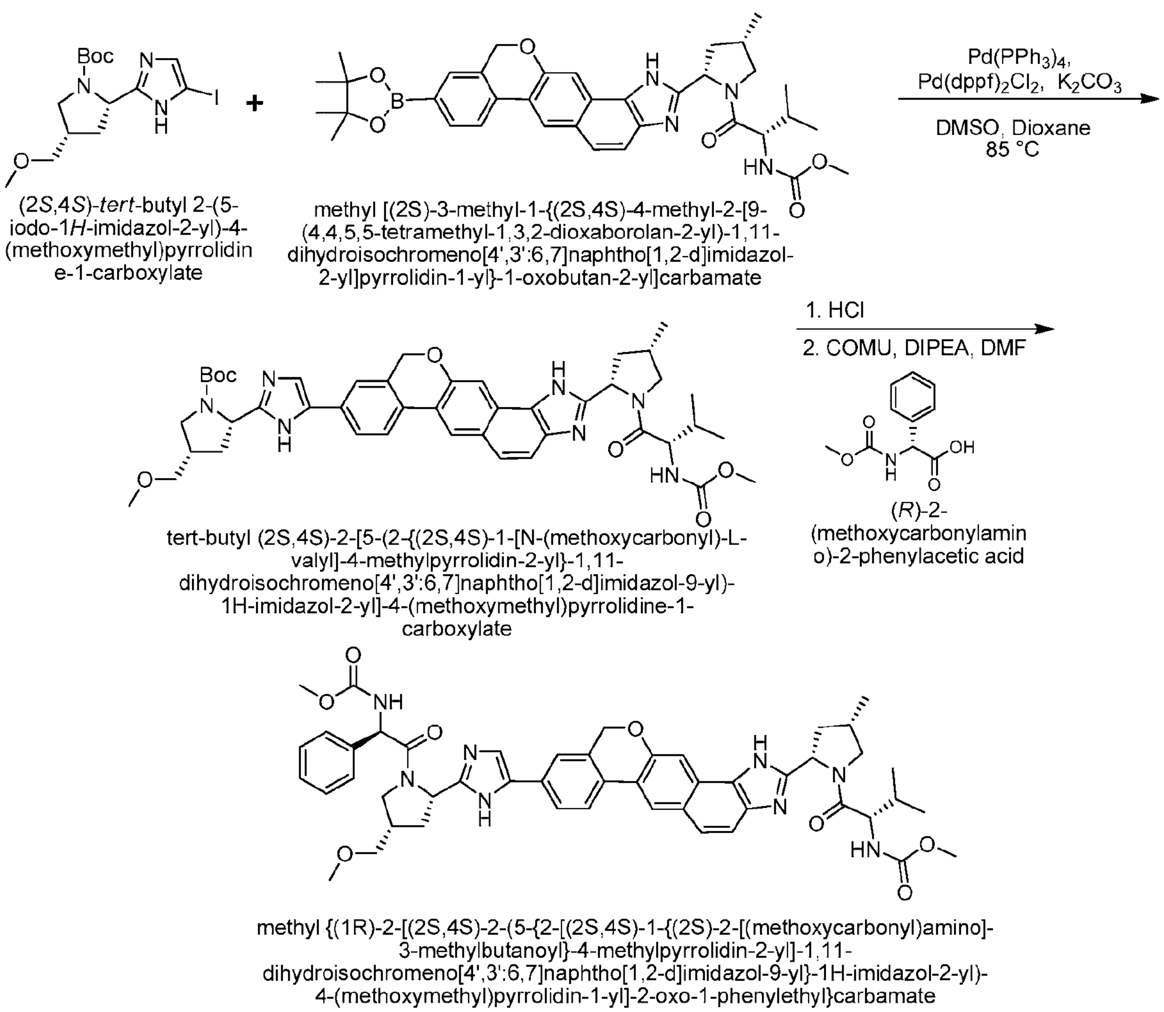
**dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate:** *Tert*-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,4,5,11 tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (266 mg, 0.35 mmol) was suspended in DCM (7 mL) and activated $MnO_2$ (908 mg, 10.45 mmol) was added in a single portion. The reaction mixture was stirred overnight. After stirring for 15 h, additional activated $MnO_2$ (500 mg, 5.75 mmol) was added in a single portion.

After stirring 2 h at 35 °C, the mixture was cooled to rt and the slurry was filtered over celite. The filter cake was washed with copious $CH_2Cl_2$ and MeOH and the filtrate was concentrated under reduced pressure. The crude material was taken on to the next step without further purification to afford *tert*-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (266 mg, quant).

**Methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S,3R)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** *Tert*-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (266 mg, 0.23 mmol) was dissolved in DCM (4 mL), MeOH (1mL) and HCl (4 M in dioxane, 1 mL) was added. The reaction mixture was stirred for 1.5 h and then concentrated under reduced pressure. The crude residue was treated with (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (44 mg, 0.23 mmol), HATU (87 mg, 0.23 mmol) and DMF (5 mL), then DIPEA (0.3 mL, 1.75 mmol) was added dropwise. After 30 min, the mixture was diluted with 10% MeOH/EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by HPLC to afford methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (59 mg, 31%). LCMS-ESI$^+$: calculated for C45H54N8O8: 834.41; observed $[M+1]^+$: 836.89. $^1$H NMR ($CD_3OD$): 8.186 (s, 1H), 7.800-7.291 (m, 7H), 5.258-5.213 (dd, 1H, *J*=7.2, 3.6 Hz), 5.027-

4.918 (m, 4H), 4.620 (t, 1H, *J*=6.8 Hz), 4.246 (m, 1H), 4.116 (m, 1H), 3.972 (d, 1H, *J*=8.8 Hz), 3.701-3.675 (m, 1H), 3.503 (s, 3H), 3.479 (s, 3H), 3.177 (s, 3H), 2.554-2.191 (m, 3H), 1.906-1.821 (m, 6H), 1.392 (d, 2H, *J*=6.4 Hz), 1.113-0.728 (m, 12H).

## Example BI



(2*S*,4*S*)-*tert*-butyl 2-(5-iodo-1*H*-imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate

methyl [(2S)-3-methyl-1-{(2S,4S)-4-methyl-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate

tert-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

(*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid

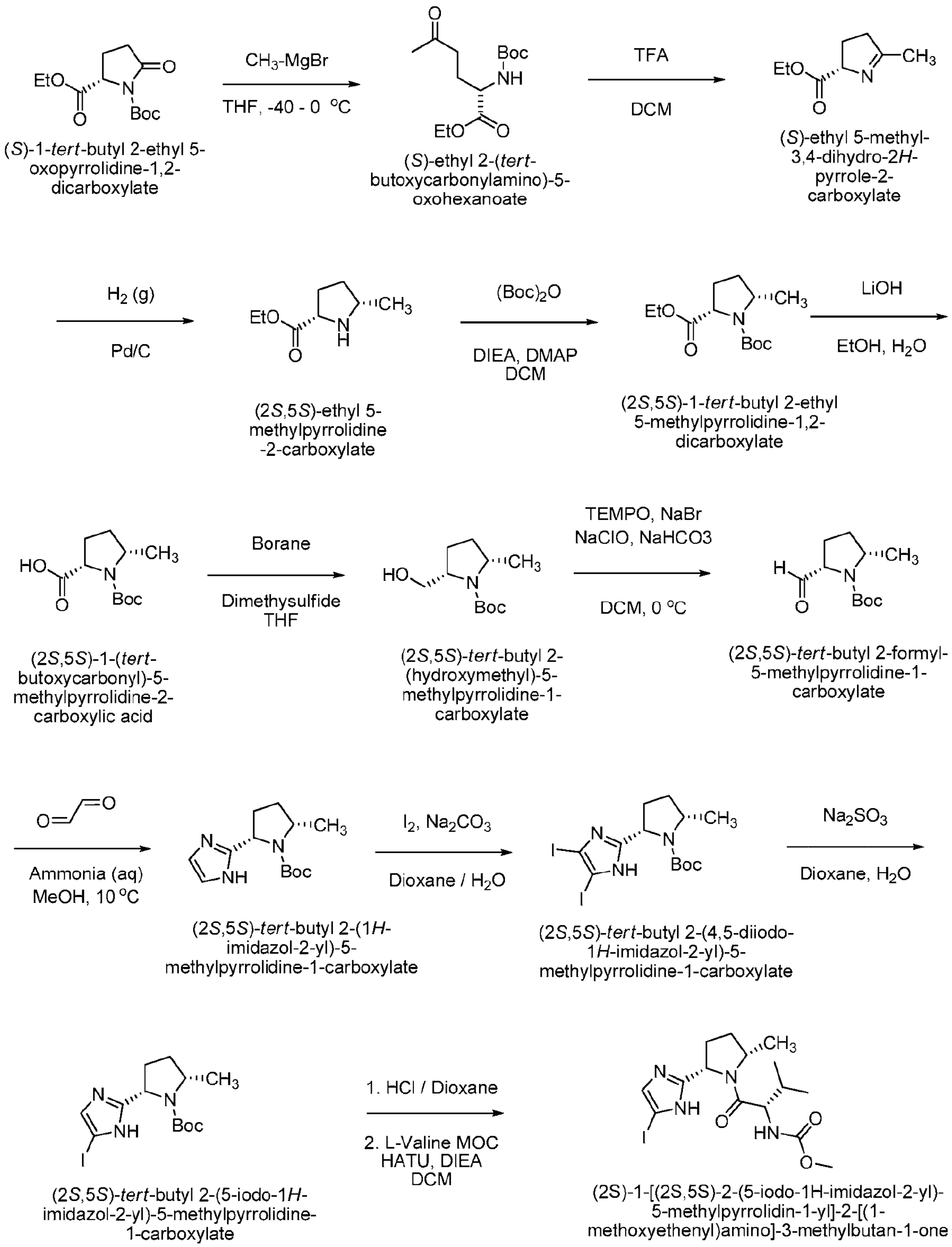
methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

***Tert*-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate:** Methyl [(2S)-3-methyl-1-{(2S,4S)-4-methyl-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate (312 mg, 0.49 mmol), methyl (S)-1-((2S,4S)-2-(5-iodo-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (219 mg, 0.54 mmol), Pd($PPh_3$)$_4$ (58 mg, 0.05 mmol), $PdCl_2(dppf)_2$ (36 mg, 0.05 mmol), and $K_2CO_3$ (2M in $H_2O$, 0.8 mL, 1.6

mmoL) were combined in DMSO (5 mL) and dioxane (5 mL). The mixture was degassed with bubbling $N_2$ for 10 min the heated to 95 °C for 5 h. After cooling, the reaction mixture was diluted with EtOAc, and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0 %- 30% MeOH/EtOAc) to afford *tert*-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (166 mg, 43%).

**Methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate:** *Tert*-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (166 mg, 0.21 mmol) was dissolved in DCM (4 mL), MeOH (1 mL) and HCl (4 M in dioxane, 1 mL) was added. The reaction mixture was stirred for 2 h and then concentrated under reduced pressure. The crude residue was treated with (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (44 mg, 0.21 mmol), COMU (100 mg, 0.21 mmol) and DMF (5 mL), then DIPEA (0.18 mL, 1.05 mmol) was added dropwise. After 1 h, the mixture was diluted with 10% MeOH/EtOAc and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by HPLC to afford methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (71 mg, 38%). LCMS-ESI$^+$: calculated for C49H54N8O8: 882.41; observed $[M+1]^+$: 884.34. $^1$H NMR ($CD_3OD$): 8.462 (s, 1H), 8.029-7.471 (m, 7H), 7.394-7.343 (m, 5H), 5.410 (d, 2H, *J*=6.8 Hz), 5.300 (m, 1H), 5.233 (m, 2H), 4.341 (m, 1H), 4.236 (d, 1H, *J*=7.2 Hz), 3.603 (s, 3H), 3.551 (s, 3H), 3.522-3.241 (m, 8H), 2.650 (m, 1H), 2.550 (m, 2H), 1.977-1.926 (m, 4H), 1.221 (d, 3H, J=3.2 Hz), 0.897-0.779 (dd, 6H, *J*=19.2, 6.8 Hz).

## Example BJ



**(S)-ethyl 2-(tert-butoxycarbonylamino)-5-oxohexanoate.** A solution of ethyl *N*-Boc (S)-pyroglutamate (20.0 g, 77.7 mmol) was in anhydrous THF (150 mL) in a two neck round bottom under argon was cooled to -40 °C. Methyl-magnesium bromide solution (3.0 M in Ether, 28.5 mL, 85.5 mmol) was added to the reaction mixture dropwise over 30 minutes. The reaction was stirred for 4 hrs at -40 °C then for 1 hr at 0 °C. The reaction was partitioned between ethyl acetate and saturated ammonium chloride solution and acidified with 1 N HCl. The aqueous layer was extracted two more times with ethylacetate. The organic layers were combined and dried with sodium sulfate. The crude material was purified by column chromatography (20% - 40% EtOAc/hexanes) to yield (S)-ethyl 2-(tert-butoxycarbonylamino)-5-oxohexanoate as a viscous oil and was used directly in the following step.

**(S)-ethyl 5-methyl-3,4-dihydro-2H-pyrrole-2-carboxylate**. (S)-ethyl 2-(tert-butoxycarbonylamino)-5-oxohexanoate in a 1 L flask was treated with a trifluoro acetic acid / dichloromethane solution (1:1 mixture, 100 mL). Effervescence was observed and the mixture was allowed to stir for 4 hours at room temperature. After which time the volatiles were removed *in vacuo* to yield (S)-ethyl 5-methyl-3,4-dihydro-2H-pyrrole-2-carboxylate as an oil, and used directly in the following step.

**(2S,5S)-ethyl 5-methylpyrrolidine-2-carboxylate**. The crude imine **3** in a 1L flask was dissolved with ethanol (400 mL) was evacuated and charged with argon three times (3x). Palladium on carbon (apprx. 750 mg, 10% w/w, dry) was added and the reaction was evacuated of gas and charged with hydrogen gas (3x). The reaction was allowed to stir under atmospheric hydrogen for 16 hours. The mixture was filtered through a plug of celite and the filtrate was concentrated *in vacuo*. Diethyl ether was added to the oil and a precipitate formed. The mixture was filtered to yield (2S,5S)-ethyl 5-methylpyrrolidine-2-carboxylate, as a white solid (10.6 g, 67.4 mmol, 86.7% over three steps). $^1$H NMR (400 MHz, cdcl$_3$) δ 4.48 (dd, 1H), 4.27 (q, 2H), 3.92 – 3.80 (m, 1H), 2.52 – 2.36 (m, 1H), 2.32 – 2.13 (m, 2H), 1.75 – 1.60 (m, 1H), 1.51 (d, 3H), 1.30 (t, 3H).

**(2S,5S)-1-tert-butyl 2-ethyl 5-methylpyrrolidine-1,2-dicarboxylate**. To a solution of (2S,5S)-ethyl 5-methylpyrrolidine-2-carboxylate (7.0 g, 44.5 mmol) in dichloromethane (250 mL), ditertbutylanhydride (10.7 g, 49.0 mmol), diisopropylethylamine (17.1 mL, 98.0 mmol) dropwise over 10 minutes, and dimethyl amino pyridine (0.27 g, 2.23 mmol) were added successively. Effervescence was observed and the mixture was allowed to stir for 16 hours at room temperature. The reaction was washed with HCl (250 mL, of 1N). The organic layer was then dried with sodium sulfate. The crude material was purified by column chromatography (5% - 25% EtOAc/hexanes) to yield (2S,5S)-1-tert-butyl 2-ethyl 5-

methylpyrrolidine-1,2-dicarboxylate as an oil (6.46 g, 25.1 mmol, 56%). LCMS-ESI$^+$: calc'd for $C_{13}H_{23}NO_4$: 257.16 (M$^+$); Found: 258.70 (M+H$^+$).

**(2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid**. To a solution of (2S,5S)-1-tert-butyl 2-ethyl 5-methylpyrrolidine-1,2-dicarboxylate (6.46 g, 25.1 mmol) in ethanol (20 mL) was added lithium hydroxide mono hydrate (2.11 g, 50.2 mmol) and deionized water (12mL). The mixture was allowed to stir for 16 hours then partitioned between ethylacetate and a 1:1 mixture of saturated brine and 1N HCl. The aqueous layer was extracted an additional time with ethyl acetate. The organic layers were combined, dried with sodium sulfate and the solvent was removed *in vacuo* to yield (2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid as a white solid (quant.) and was used directly in the following step.

**(2S,5S)-tert-butyl 2-(hydroxymethyl)-5-methylpyrrolidine-1-carboxylate.** To a solution of (2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid (5.91 g, 25.8 mmol) in tetrahydrofuran at 0 °C, was added borane in dimethylsulfide (1.0 M, 3.4 mL, 34 mmol) dropwise. The reaction was stirred for 4 hours at 0 °C then 18 hours at room temperature. The mixture was then cooled to 0 °C and methanol (70 mL) was added dropwise. The reaction was warmed to room temperature and the solvents were removed in vacuo. The residue was taken up in dichloromethane (200 mL) and extracted with saturated sodium bicarbonate. The organic layer was dried with sodium sulfate and the solvent was removed *in vacuo* to yield (2S,5S)-tert-butyl 2-(hydroxymethyl)-5-methylpyrrolidine-1-carboxylate as a clear oil (5.15 g, 23.9 mmol, 93%) and was used directly in the following step.

**(2S,5S)-tert-butyl 2-formyl-5-methylpyrrolidine-1-carboxylate.** To a solution of (2S,5S)-tert-butyl 2-(hydroxymethyl)-5-methylpyrrolidine-1-carboxylate (5.15 g, 23.9 mmol) in dichloromethane, was added TEMPO (0.075 g, 0.48 mmol), sodium bromide (0.246 g, 2.39 mmol) and sodium bicarbonate (0.442 g, 5.26 mmol). Sodium hypochlorite (2.67 g, 35.9 mmol) of a 6% solution was added and the biphasic mixture was vigorously stirred for 2 hours at room temperature. The reaction mixture was extracted two times with dichloromethane (2x100mL). The organic layers were combined and washed with saturated sodium thiosulfate solution, dried with sodium sulfate and the solvent was removed in vacuo to yield (2S,5S)-tert-butyl 2-formyl-5-methylpyrrolidine-1-carboxylate (3.9 g, 18.29 mmol, 77%) as a slight colored oil and was used directly in the following step.

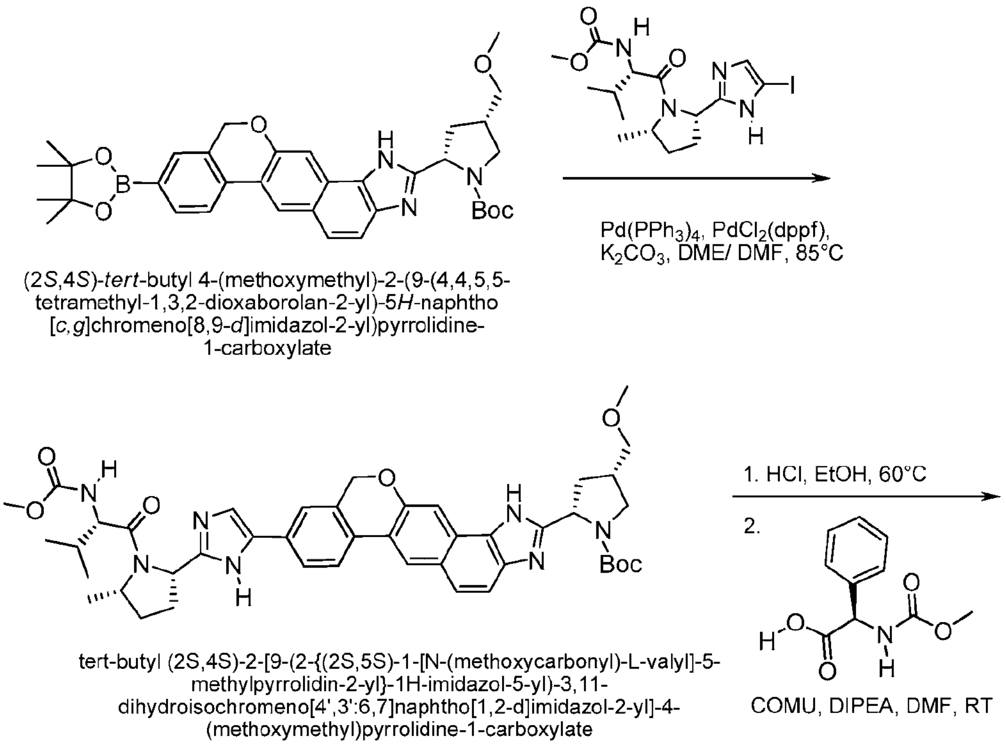
**(2S,5S)-tert-butyl 2-(1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate.** To a solution of (2S,5S)-tert-butyl 2-formyl-5-methylpyrrolidine-1-carboxylate (3.9g, 18.30 mmol) in MeOH (15 mL) and ammonium hydroxide (15 mL, 99.9%), glyoxal (11.7 mL, 40% w/v in water, 102.40 mmol) was added dropwise. The biphasic mixture turned orange and turbid. The reaction was stirred vigorously overnight at room temperature. The solvent was removed *in vacuo*. The crude mixture was redissolved in ethyl acetate and washed with water. The aqueous layer was washed an additional time with ethyl acetate. The organic layers were combined and washed with brine, dried with sodium sulfate and the solvent was removed *in vacuo*. The crude material was purified by column chromatography 85% to 100% ethyl acetate in hexanes to yield (2S,5S)-tert-butyl 2-(1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate as an off white solid (3.47 g, 13.8 mmol, 75%). LCMS-ESI$^+$: calc'd for $C_{13}H_{21}N_3O_2$: 251.16 (M$^+$); Found: 252.20 (M+H$^+$).

**(2S,5S)-tert-butyl 2-(4,5-diiodo-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate.** A 500 ml round bottom flask was charged with (2S,5S)-tert-butyl 2-(1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (3.47 g, 13.8 mmol), iodine (7.7 g, 30.4 mmol) and sodium carbonate (4.54 g, 42.8 mmol). Dioxane (70 mL) and water (45 mL) was added to mixture and the reaction was stirred vigorously overnight in the dark. The reaction was then partitioned between ethyl acetate and a 10% aqueous solution of sodium thiosulfate and extracted. The aqueous layer was extracted an additional time with ethyl acetate. The organic layers were combined, dried with sodium sulfate and the solvent was removed *in vacuo*. The crude material was filtered through a plug of silica with 25% ethyl acetate in hexanes to yield (2S,5S)-tert-butyl 2-(4,5-diiodo-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate as a white solid (4.28 g, 8.50 mmol, 62%). LCMS-ESI$^+$: calc'd for $C_{13}H_{19}I_2N_3O_2$: 502.96 (M$^+$); Found: 503.94 (M+H$^+$).

**(2S,5S)-tert-butyl 2-(5-iodo-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate.** To a solution of (2S,5S)-tert-butyl 2-(4,5-diiodo-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (4.28 g, 8.50 mmol) in ethanol (75 mL) and water (75 mL), sodium thiosulfate (10.72 g, 85.1 mmol) was added and the reaction mixture was stirred vigorously for 1 hour at 100 °C, 16 hours at 90 °C, and 5 hours at 100 °C. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was washed additionally with ethyl acetate and the organic layers were combined. The organic layer was dried with sodium sulfate, concentrated and the crude material was purified by column chromatography to yield (2S,5S)-tert-butyl 2-(5-iodo-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate as a white solid (2.34 g, 6.20 mmol, 73%). $^1$H NMR (400 MHz, cdcl$_3$) δ 7.04 (s, 1H), 4.89 (dd, 1H), 3.92 (m, 1H), 2.91 (s, 1H), 2.18 – 2.06 (m, 2H), 1.78 (m, 1H), 1.52 (m, 1H), 1.48 (s, 9H), 1.13 (d, 3H).

**(2S)-1-[(2S,5S)-2-(5-iodo-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-2-[(1-methoxyethenyl)amino]-3-methylbutan-1-one.** A round bottom flask was charged with (2S,5S)-tert-butyl 2-(5-iodo-1H-imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (1.5 g, 3.98 mmol) and treated with an excess of hydrochloric acid (100 mL of 4.0M in dioxane). The mixture was stirred vigorously for 3 hours in which time a precipitate formed and the solvent was removed *in vacuo*. To a mixture of the crude intermediate, (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.836 g, 4.77 mmol), HATU (1.81 g, 4.77 mmol) in dichloromethane (25 mL), diisopropylethylamine (3.46 mL, 19.9 mmol) was then added dropwise and was stirred over night under nitrogen. The reaction mixture was partitioned ethyl acetate and saturated sodium bicarbonate. The organic layer was dried with sodium sulfate, the solvent removed in vacuo. The crude product was purified by column chromatography to yield (2S)-1-[(2S,5S)-2-(5-iodo-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-2-[(1-methoxyethenyl)amino]-3-methylbutan-1-one as a white solid (1.63 g, 3.75 mmol, 94%). LCMS-ESI$^+$: calc'd for $C_{15}H_{23}IN_4O_3$: 434.08 (M$^+$); Found: 435.51 (M+H$^+$).

## Example BK



(2*S*,4*S*)-*tert*-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5*H*-naphtho[*c*,*g*]chromeno[8,9-*d*]imidazol-2-yl)pyrrolidine-1-carboxylate

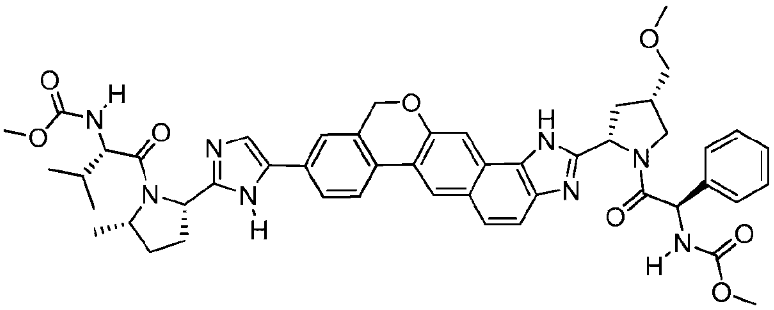
Pd(PPh$_3$)$_4$, PdCl$_2$(dppf), K$_2$CO$_3$, DME/ DMF, 85°C

tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

1. HCl, EtOH, 60°C

2.

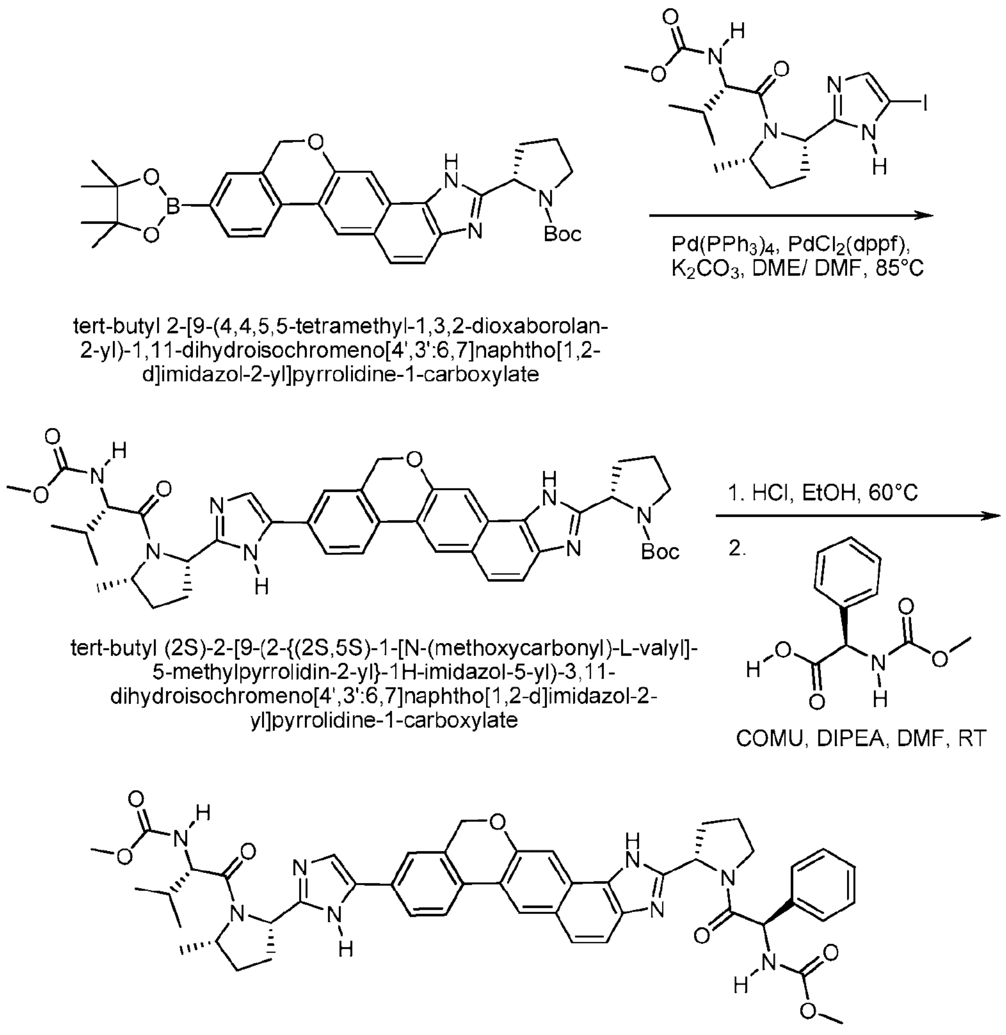
COMU, DIPEA, DMF, RT



Methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11 dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**Methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11 dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate.** The synthesis of this compound was prepared according to the procedure of Example AB-**1** with the following modification. During the suzuki coupling, (2S)-1-[(2S,5S)-2-(5-iodo-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-2-[(1-methoxyethenyl)amino]-3-methylbutan-1-one was used in lieu of (2S)-1-[(2S)-2-(5-bromo-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-[(1-methoxyethenyl)amino]-3-methylbutan-1-one. The crude material was purified by preparative HPLC to provide methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl) pyrrolidin-2-yl]-1,11 dihydroisochromeno [4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate as a white solid (17 mg, 0.019 mmol, 17%). $^1$H NMR (400 MHz, cd$_3$od) δ 8.63 (s, 1H), 8.19 (d, 1H), 8.04 (m, 1H), 7.87 (m, 2H), 7.66 (m, 2H), 7.52 – 7.39 (m, 6H), 5.50 (m, 2H), 5.32 (s, 2H), 5.16 (m, 1H), 4.12 (m, 1H), 3.80 (m, 4H), 3.66 (s, 6H), 3.43 (m, 4H), 3.23 (s, 3H), 2.72-1.99 (m, 9H), 1.56 (d, 3H), 1.29 (m, 1H), 0.99 (d, 3H), 0.88 (d, 3H).

## Example BL



tert-butyl 2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate

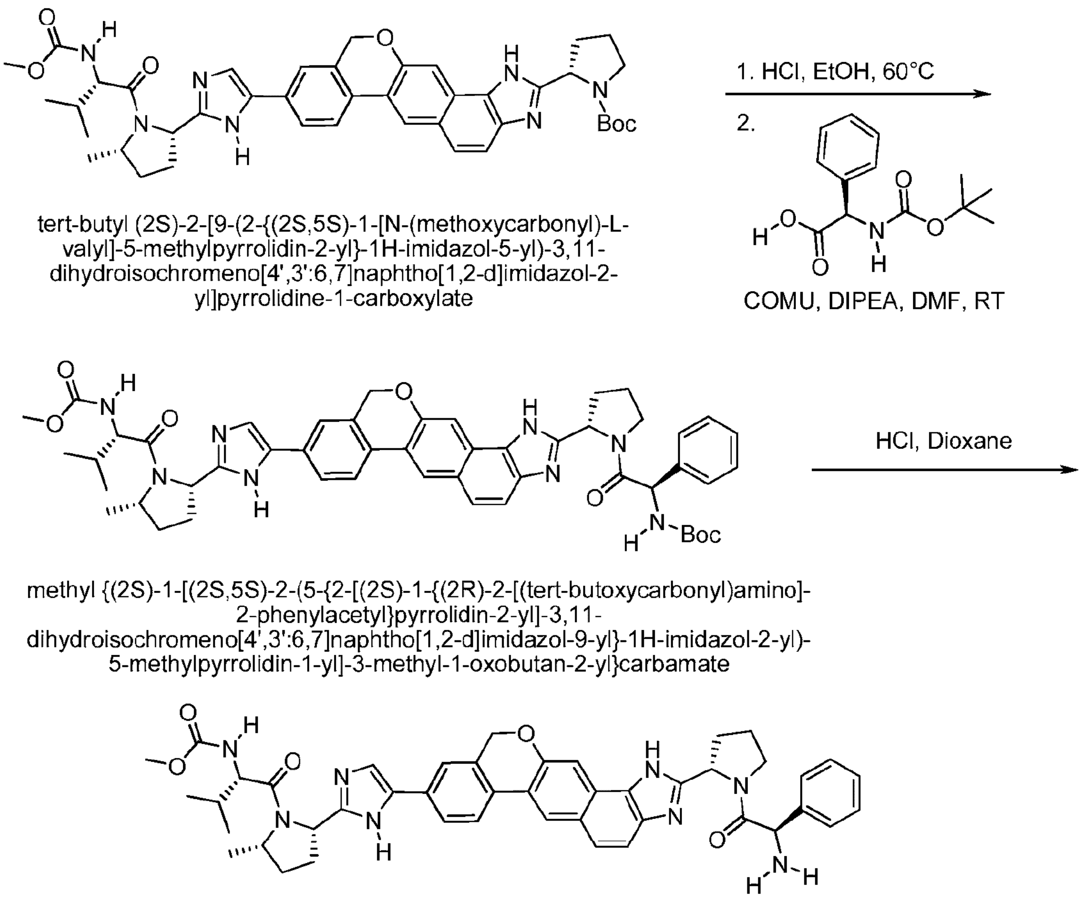
tert-butyl (2S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate

methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrol idin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**Methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate.** The synthesis of this compound was prepared according to the procedure of Example AA with the following modification. During the Suzuki coupling, (2S)-1-[(2S,5S)-2-(5-iodo-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-2-[(1-methoxyethenyl)amino]-3-methylbutan-1-one was used in lieu of (2S)-1-[(2S)-2-(5-bromo-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-[(1-methoxyethenyl)amino]-3-methylbutan-1-one. The crude material was purified by preparative HPLC to provide methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S)-1-{(2R)-2-

[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate as a white solid (110 mg, 0.131 mmol, 57 %). $^1$H NMR (400 MHz, cd$_3$od) δ 8.65 (s, 1H), 8.21 (d, 1H), 8.04 (m, 2H), 7.91 (s, 1H), 7.81 (m, 1H), 7.67 (m, 2H), 7.46 (m, 6H), 5.59 (s, 1H), 5.50 (dd, 1H), 5.33 (s, 2H), 5.22 – 5.09 (m, 1H), 4.14 (m, 2H), 3.74 (s, 1H), 3.65 (m, 6H), 3.52 – 3.37 (m, 2H), 2.60 – 1.89 (m, 11H), 1.56 (d, 3H), 1.29 (d, 1H), 0.99 (d, 3H), 0.88 (d, 3H).

## Example BM



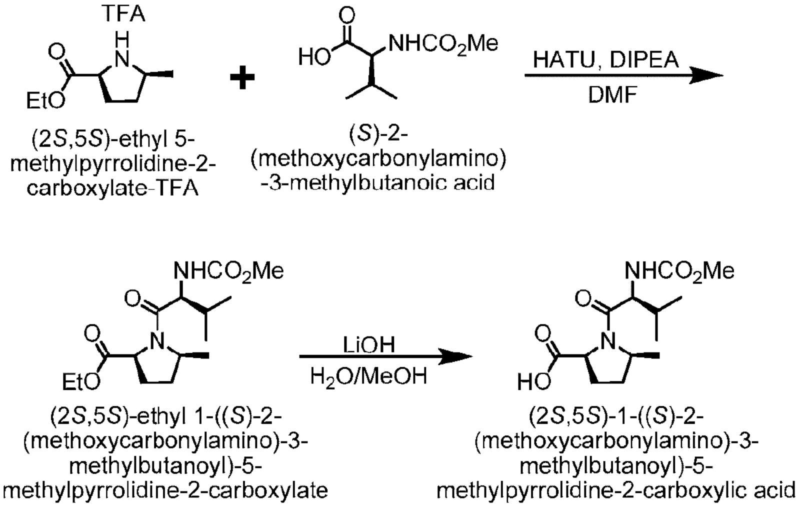
tert-butyl (2S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate

methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

methyl [(2S)-1-{(2S,5S)-2-[5-(2-{(2S)-1-[(2R)-2-amino-2-phenylacetyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-5-methylpyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

**Methyl [(2S)-1-{(2S,5S)-2-[5-(2-{(2S)-1-[(2R)-2-amino-2-phenylacetyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-5-methylpyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate.** The synthesis of this compound was prepared according to Example BL with the following modifications. During the amide coupling, (R)-2-(tert-butoxycarbonylamino)-2-phenylacetic acid was used in lieu of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid. This was then treated with an excess of hydrochloric acid (15 ml, 4.0 M in Dioxane) for 2 hours. The crude product was purified by HPLC to provide methyl [(2S)-1-{(2S,5S)-2-[5-(2-{(2S)-1-[(2R)-2-amino-2-phenylacetyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-5-methylpyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate as a white solid (153 mg, 0.196 mmol, 74%). $^1$H NMR (400 MHz, cd$_3$od) δ 8.63 (s, 1H), 8.20 (d, 1H), 7.99 (m, 1H), 7.93 (m, 2H), 7.80 (m, 2H), 7.72 – 7.64 (m, 2H), 7.63 – 7.52 (m, 5H), 5.52 (dd, 1H), 5.44 (m, 1H), 5.33 (s, 2H), 5.21 – 5.10 (m, 1H), 4.80 (m, 2H), 4.14 (m, 1H), 4.02 (m, 1H), 3.75 (s, 1H), 3.67 (s, 3H), 3.12 (dd, 1H), 2.72 – 2.13 (m, 7H), 2.00 (m, 3H), 1.56 (d, 3H), 1.30 (d, 1H), 0.98 (d, 3H), 0.88 (d, 3H).

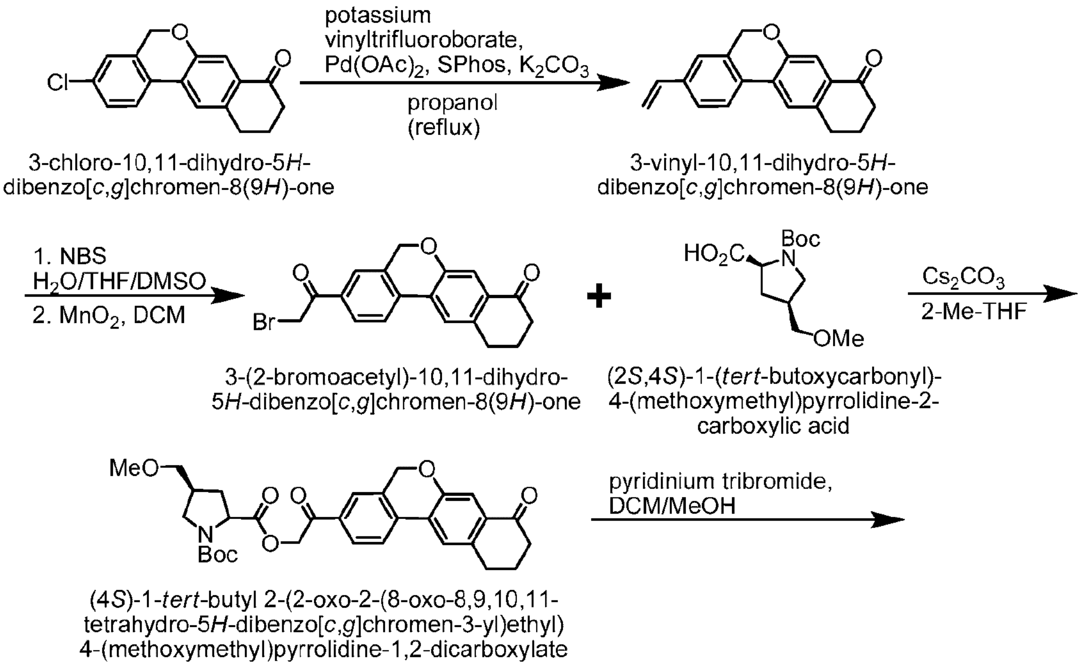
## Example BN



**(2S,5S)-Ethyl 1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylate:** (2S,5S)-Ethyl 5-methylpyrrolidine-2-carboxylate-TFA (10.0 g, 39.3 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (6.88 g, 39.3 mmol) and HATU (14.9 g, 39.3 mmol) were combined in DMF (100 mL) and DIPEA (15.0 mL, 86.5 mmol) was added. After stirring for 1 h at RT, the reaction mixture was diluted with EtOAc. The organic phase was washed successively with 10% HCl, saturated aqueous NaHCO$_3$ and brine, then dried over MgSO$_4$, filtered and concentrated under reduced pressure to afford (2S,5S)-ethyl 1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylate. The crude material was carried on without further purification.

**(2S,5S)-1-((S)-2-(Methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylic acid:** (2S,5S)-Ethyl 1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylate (39.3 mmol, assuming complete conversion from the previous transformation) was suspended in MeOH (200 mL) and aqueous LiOH (1.0 M, 100 mL, 100 mmol) was added. The reaction mixture was stirred o/n, then concentrated under reduced pressure to remove most of the MeOH. The aqueous solution was washed 2x with DCM before being acidified to pH~1-2 with 10% HCl. The acidic aqueous phase was then extracted 5x with EtOAc. The combined EtOAc extracts were dried over $MgSO_4$ filtered and concentrated under reduced pressure to afford (2S,5S)-1-((S)-2-(Methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylic acid (6.89 g, 56% over 2 steps).

## Example BO



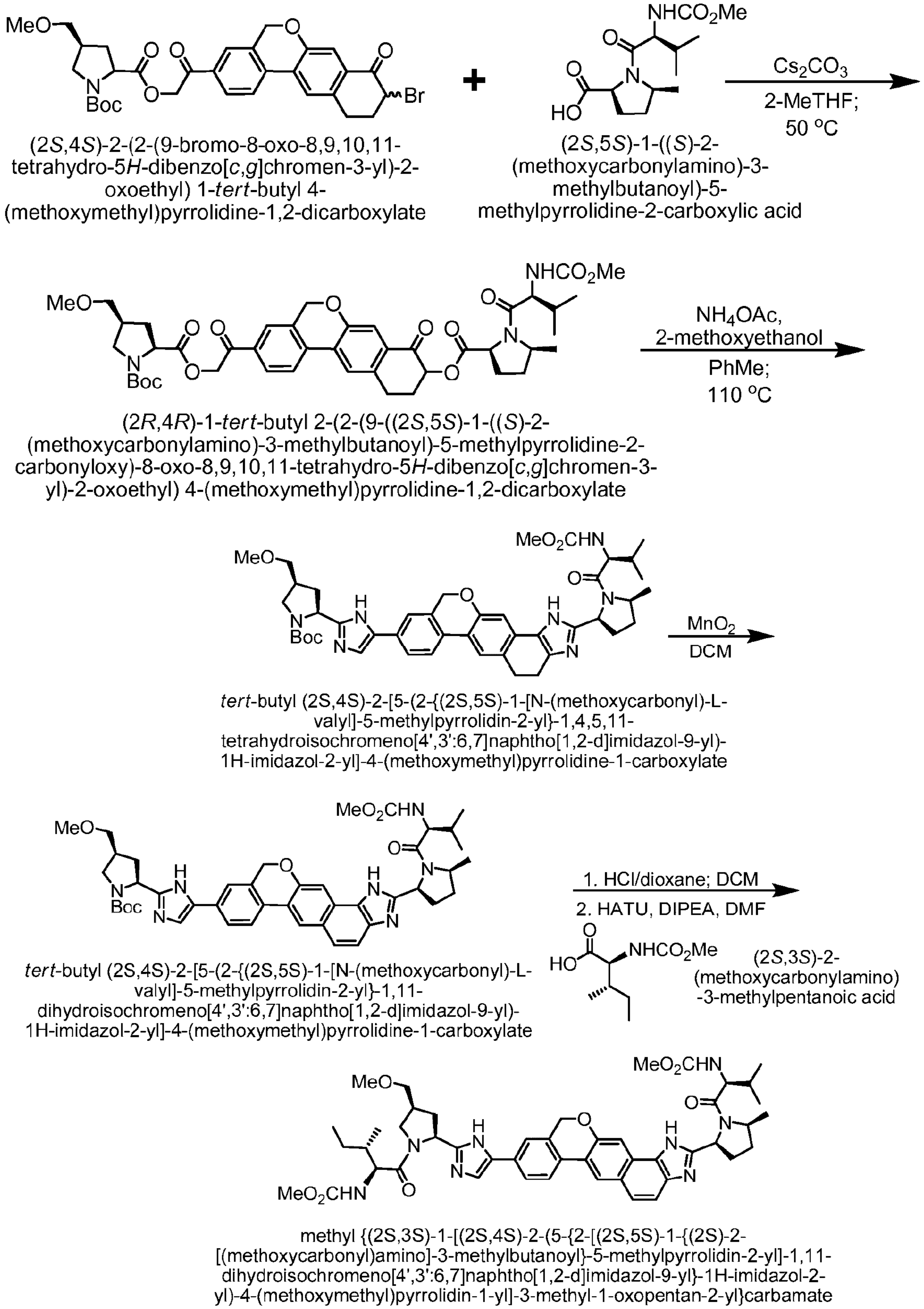
3-chloro-10,11-dihydro-5*H*-dibenzo[*c*,*g*]chromen-8(9*H*)-one

3-vinyl-10,11-dihydro-5*H*-dibenzo[*c*,*g*]chromen-8(9*H*)-one

3-(2-bromoacetyl)-10,11-dihydro-5*H*-dibenzo[*c*,*g*]chromen-8(9*H*)-one

(2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid

(4*S*)-1-*tert*-butyl 2-(2-oxo-2-(8-oxo-8,9,10,11-tetrahydro-5*H*-dibenzo[*c*,*g*]chromen-3-yl)ethyl) 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate



(2*S*,4*S*)-2-(2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5*H*-dibenzo[*c*,*g*]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate

(2*S*,5*S*)-1-((*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylic acid

(2*R*,4*R*)-1-*tert*-butyl 2-(2-(9-((2*S*,5*S*)-1-((*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5*H*-dibenzo[*c*,*g*]chromen-3-yl)-2-oxoethyl) 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate

*tert*-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

*tert*-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

(2*S*,3*S*)-2-(methoxycarbonylamino)-3-methylpentanoic acid

methyl {(2S,3S)-1-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate

**3-Vinyl-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one:** A 3-neck oven-dried 500 mL round-bottom flask was cooled under Ar, then charged with 3-Chloro-10,11-dihydro-5Hdibenzo[c,g]chromen-8(9H)-one (12.0 g, 42.1 mmol), potassium vinyltrifluoroborate (8.47 g, 6.32 mmol), $Pd(OAc)_2$ (473 mg, 2.11 mmol), SPhos (1.74 g, 4.25 mmol), $K_2CO_3$ (17.5 g, 126 mmol) and anhydrous propanol (120 mL). The reaction mixture was sparged with Ar for 16 min, then heated to reflux for 5.5 h. Upon completion, the reaction mixture was cooled to RT and concentrated under reduced pressure. The crude residue was suspended in DCM, then washed with $H_2O$ and brine. The organic solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was further purified via silica plug, eluting with DCM to afford 3-vinyl-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (10.2 g, 87%).

**3-(2-Bromoacetyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one:** 3-Vinyl-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (9.98 g, 36.1 mmol) was dissolved in a stirred solution of THF (70 mL), DMSO (70 mL) and $H_2O$ (35 mL). NBS (6.75 g, 37.9 mmol) was added in a single portion and the reaction mixture was stirred at RT for 33 min. Upon completion, the reaction medium was diluted with EtOAc and washed twice with $H_2O$ and once with brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude bromohydrin was suspended in DCM (200 mL) and treated with activated $MnO_2$ (62.7 g, 722 mmol). After stirring for 15 h at RT, the reaction mixture was filtered over celite and the filter cake was rinsed several times with DCM. The combined filtrate (~400 mL) was treated with MeOH (~100 mL) and the mixture was gradually concentrated under reduced pressure, causing solid material to precipitate from solution. When the liquid volume reached ~200 mL, the solid was filtered off and rinsed with MeOH. The concentration/precipitatation/filtration/rinsing sequence was performed 2x more, resulting in the collection of 3 crops of powdered 3-(2-bromoacetyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (7.49 g, 56% over 2 steps).

**(4S)-1-*tert*-Butyl 2-(2-oxo-2-(8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)ethyl) 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate:** 3-(2-Bromoacetyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (7.47 g, 20.1 mmol) and (2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid (5.22 g, 20.1 mmol) were suspended in 2-Me-THF (75 mL) and treated with $Cs_2CO_3$ (3.27 g, 10.1 mmol). After stirring 4 h at RT, the reaction mixture was diluted with diluted with DCM. The organic layer was washed with $H_2O$. The aqueous layer was then back extracted 2x with DCM. The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (10% to 50% EtOAc/DCM) to afford (4S)-1-*tert*-butyl 2-(2-oxo-2-(8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)ethyl) 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate (7.73 g, 70%).

**(2S,4S)-2-(2-(9-Bromo-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-tert-butyl 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate:** (4S)-1-*tert*-Butyl 2-(2-oxo-2-(8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)ethyl) 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate (7.66 g, 13.9 mmol) was dissolved in a solution of DCM (100 mL) and MeOH (40 mL), then treated with pyridinium tribromide (4.90 g, 15.3 mmol). After stirring at RT for 1.75 h, the reaction mixture was diluted with DCM and washed successively with 10% HCl, saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure and the crude material was carried on without further purification.

**(2R,4R)-1-*tert*-Butyl 2-(2-(9-((2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate:** (2S,4S)-2-(2-(9-Bromo-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-tert-butyl 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate (8.76 g, 13.94 mmol) was treated with a solution of (2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylic acid (6.85 g, 23.92 mmol) in 2-Me-THF (70 mL) and $Cs_2CO_3$ (3.63 g, 11.15 mmol). The stirred reaction mixture was heated to 50 °C for 20 h, then cooled to RT and diluted with EtOAc. The organic phase was washed with $H_2O$ and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0% to 30% MeOH/EtOAc) to afford (2R,4R)-1-*tert*-butyl 2-(2-(9-((2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate (10.47 g, 90%).

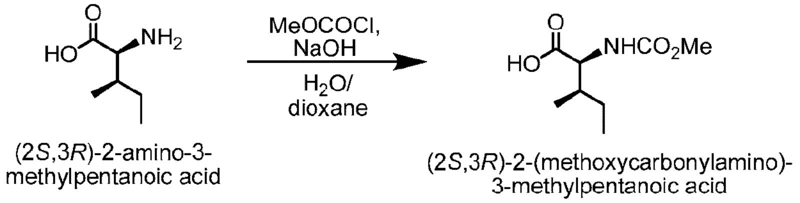
***tert*-Butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate:** (2R,4R)-1-*tert*-Butyl 2-(2-(9-((2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carbonyloxy)-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate (10.47 g, 12.56 mmol) and $NH_4OAc$ (50.9 g, 660 mmol) were suspended in a solution of 10:1 PhMe/2-methoxyethanol (132 mL). The stirred reaction mixture was heated to 110 °C for 4.5 h, then cooled to RT and diluted with EtOAc. The organic phase was washed 3x with saturated aqueous $NaHCO_3$, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (0% to 30% MeOH/EtOAc) to afford *tert*-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (8.33 g, 84%).

***tert*-Butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate:** *tert*-Butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (8.33 g, 1.049 mmol) was suspended in DCM and activated $MnO_2$ (55.0 g, 630 mmol) was added in a single portion. After 13 h, MeOH (200 mL) was added and the slurry was filtered over celite. The filter cake was washed with MeOH (600 mL) and the filtrate was concentrated under reduced pressure. The crude material was purified by silica column chromatography (0% to 45% MeOH/EtOAc) to afford *tert*-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (4.85 g, 58%).

**Methyl {(2S,3S)-1-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate:** *tert*-Butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (179 mg, 0.226 mmol) was dissolved in DCM (4 mL) and HCl (4.0 M in dioxane, 1 mL) was added. The reaction mixture was stirred for 1 h at RT then concentrated under reduced pressure. The resulting residue was treated with (2S,3S)-2-(methoxycarbonylamino)-3-methylpentanoic acid (51 mg, 0.27 mmol), HATU (95 mg, 0.25 mmol), DMF (2 mL) and DIPEA (0.39 mL, 2.3 mmol). After stirring for 6 min, the reaction was quenched with $H_2O$, filtered and purified by reverse phase HPLC to afford methyl {(2S,3S)-1-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-

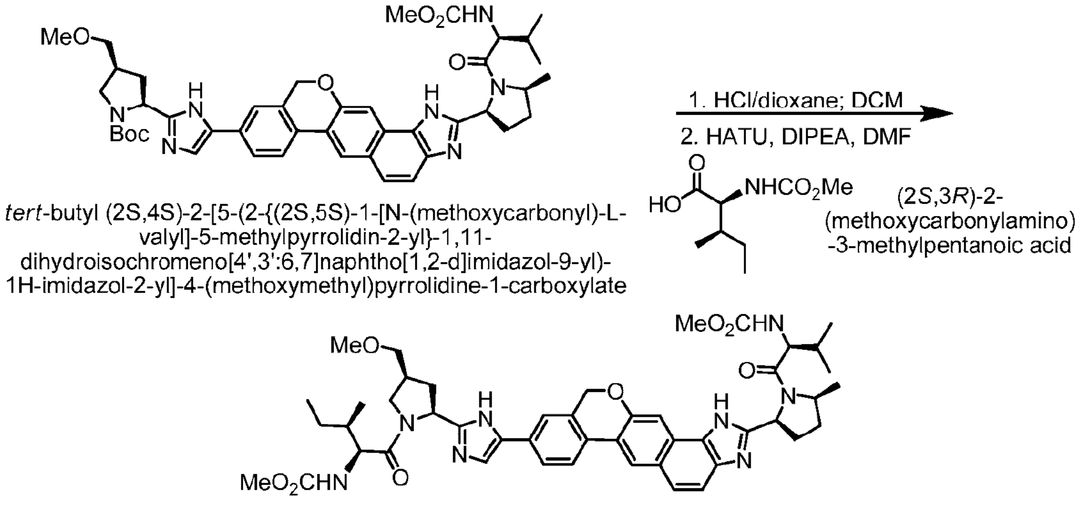
methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate (116 mg, 59%). MS (ESI) *m/z* 864 $[M + H]^+$. $^1H$ NMR (400 MHz, $cd_3od$) δ 8.57 (d, *J* = 14.7 Hz, 1H), 8.45 (s, 1H), 8.20 (d, *J* = 14.4 Hz, 1H), 8.15 – 7.98 (m, 2H), 7.91 (dd, *J* = 21.8, 14.1 Hz, 2H), 7.85 – 7.69 (m, 2H), 7.69 – 7.48 (m, 2H), 5.42 – 5.12 (m, 5H), 4.34 (dd, *J* = 22.3, 13.7 Hz, 1H), 4.30 – 4.10 (m, 2H), 3.87 – 3.73 (m, 1H), 3.73 – 3.63 (m, 7H), 3.62 – 3.48 (m, 2H), 3.48 – 3.38 (m, 4H), 3.35 (s, 3H), 2.95 – 2.70 (m, 1H), 2.70 – 2.55 (m, 2H), 2.55 – 2.20 (m, 2H), 2.20 – 1.91 (m, 3H), 1.77 (d, *J* = 42.0 Hz, 1H), 1.65 (d, *J* = 6.6 Hz, 3H), 1.43 (t, *J* = 24.6 Hz, 1H), 1.28 (d, *J* = 6.2 Hz, 1H), 1.23 – 1.01 (m, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.90 (dd, *J* = 13.1, 5.9 Hz, 10H).

## Example BP



(2*S*,3*R*)-2-amino-3-methylpentanoic acid

(2*S*,3*R*)-2-(methoxycarbonylamino)-3-methylpentanoic acid



*tert*-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

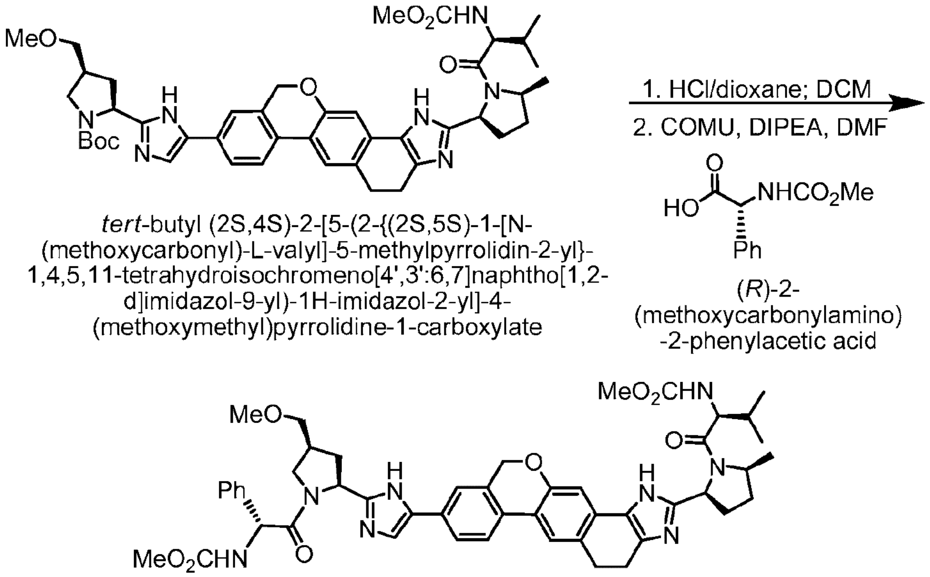
(2*S*,3*R*)-2-(methoxycarbonylamino)-3-methylpentanoic acid

methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-[N-(methoxycarbonyl)-L-alloisoleucyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**Methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-[N-(methoxycarbonyl)-L-alloisoleucyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate** was prepared from tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-

dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate by the same method employed in the synthesis of {(2S,3S)-1-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate, replacing (2S,3S)-2-(methoxycarbonylamino)-3-methylpentanoic acid with (2S,3R)-2-(methoxycarbonylamino)-3-methylpentanoic acid. MS (ESI) *m/z* 864 [M + H]$^+$. $^1$H NMR (400 MHz, cd$_3$od) δ 8.62 – 8.41 (m, 1H), 8.22 (s, 1H), 8.07 (dt, *J* = 20.1, 10.0 Hz, 1H), 7.89 (dt, *J* = 35.6, 15.6 Hz, 2H), 7.77 (dd, *J* = 20.3, 7.0 Hz, 2H), 7.68 – 7.48 (m, 2H), 5.95 (d, *J* = 5.0 Hz, 1H), 5.42 – 5.13 (m, 4H), 4.47 (t, *J* = 5.5 Hz, 1H), 4.40 – 4.09 (m, 2H), 3.80 – 3.73 (m, 1H), 3.73 – 3.62 (m, 6H), 3.57 (dt, *J* = 16.1, 9.7 Hz, 2H), 3.40 (s, 3H), 3.34 (d, *J* = 7.5 Hz, 1H), 2.81 (dd, *J* = 18.4, 12.5 Hz, 1H), 2.63 (td, *J* = 13.3, 6.8 Hz, 2H), 2.55 – 2.18 (m, 2H), 2.16 – 1.77 (m, 4H), 1.65 (d, *J* = 6.6 Hz, 3H), 1.50 – 1.31 (m, 1H), 1.26 (dd, *J* = 15.6, 6.7 Hz, 2H), 1.17 – 1.03 (m, 2H), 0.98 (dd, *J* = 6.7, 4.5 Hz, 5H), 0.89 (dd, *J* = 15.5, 7.8 Hz, 3H), 0.86 – 0.74 (m, 3H).

## Example BQ



*tert*-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

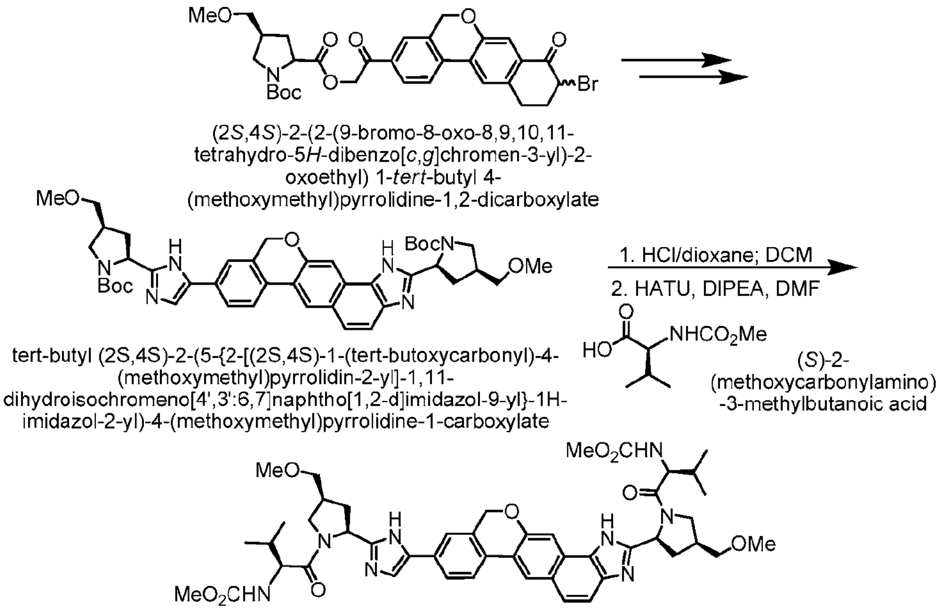
(*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid

methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**Methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-**

**(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate:** tert-Butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (102 mg, 0.128 mmol) was dissolved in DCM (4 mL) and HCl (4.0 M in dioxane, 2.0 mL, 8.0 mmol) was added. After stirring at RT for 30 min, the solution was concentrated under reduced pressure. The residue was treated with (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (29 mg, 0.141 mmol), COMU (60 mg, 0.141 mmol), DMF (3.0 mL) and DIPEA (0.223 mL, 1.28 mmol). After stirring at RT for 20 min, the reaction mixture was diluted with EtOAc. The organic solution was washed with saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by reverse-phase HPLC to afford methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate as the bis-TFA salt (82.4 mg, 60%). MS (ESI) *m/z* 866 $[M + H]^+$. $^1H$ NMR (400 MHz, $cd_3od$) δ 7.94 – 7.67 (m, 4H), 7.59 (d, *J* = 9.1 Hz, 1H), 7.52 (s, 1H), 7.48 – 7.33 (m, 4H), 7.11 (d, *J* = 18.7 Hz, 1H), 5.68 (d, *J* = 6.3 Hz, 1H), 5.48 – 5.33 (m, 1H), 5.23 (dd, *J* = 24.1, 15.7 Hz, 1H), 5.17 – 5.03 (m, 3H), 4.22 (dd, *J* = 17.0, 9.6 Hz, 1H), 4.16 – 4.01 (m, 1H), 3.91 (d, *J* = 24.1 Hz, 1H), 3.83 – 3.68 (m, 1H), 3.68 – 3.59 (m, 3H), 3.59 – 3.49 (m, 3H), 3.38 (ddd, *J* = 15.9, 9.6, 5.7 Hz, 2H), 3.28 – 3.14 (m, 5H), 3.10 (dd, *J* = 14.0, 8.2 Hz, 1H), 3.00 (dd, *J* = 17.8, 9.6 Hz, 1H), 2.92 (dd, *J* = 14.5, 6.7 Hz, 1H), 2.73 – 2.41 (m, 2H), 2.40 – 2.11 (m, 2H), 2.11 – 1.83 (m, 2H), 1.54 (t, *J* = 9.7 Hz, 2H), 1.24 (d, *J* = 6.2 Hz, 1H), 1.06 (t, *J* = 8.0 Hz, 1H), 0.99 (d, *J* = 6.8 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 2H), 0.85 (d, *J* = 6.7 Hz, 2H).

## Example BR



(2*S*,4*S*)-2-(2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5*H*-dibenzo[*c*,*g*]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate

tert-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate

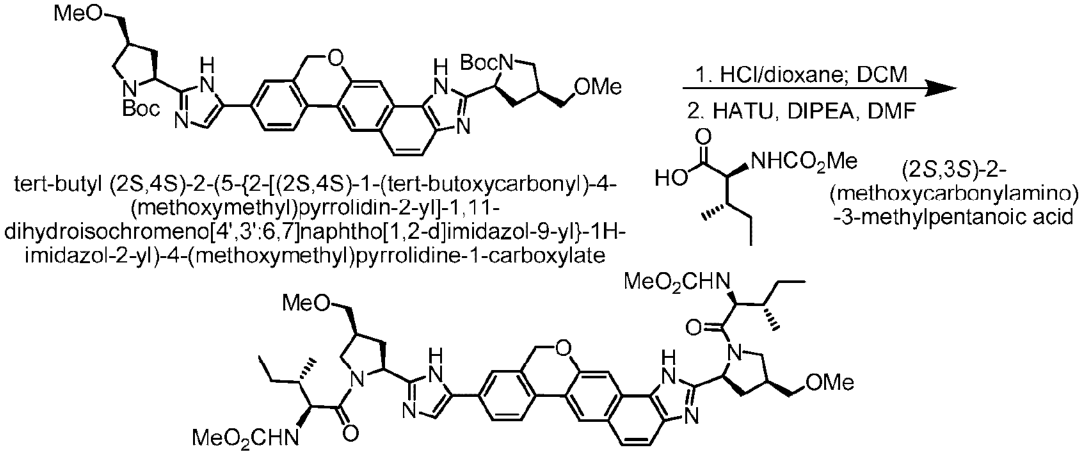
(*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid

methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**tert-Butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate** was prepared from (2S,4S)-2-(2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-tert-butyl 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate by the same method employed in the synthesis of tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate, replacing (2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylic acid with (2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid.

**Methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** tert-Butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (137 mg, 0.179 mmol) was dissolved in DCM (5 mL) and HCl (4.0 M in dioxane, 1 mL) was added. After stirring at RT for 1.5 h, the reaction mixture was concentrated under reduced pressure. The crude residue was treated with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (69 mg, 0.39 mmol), HATU (149 mg, 0.393 mmol), DMF (2.0 mL) and DIPEA (0.31 mL, 1.8 mmol). After stirring for 15 min at RT, the reaction mixture was quenched with water and purified by HPLC to provide methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (123 mg). MS (ESI) *m/z* 880 $[M + H]^+$. $^1H$ NMR (400 MHz, cd$_3$od) δ 8.48 (s, 1H), 8.05 (t, *J* = 11.2 Hz, 1H), 7.92 (dd, *J* = 19.7, 10.1 Hz, 2H), 7.74 (s, 2H), 7.59 – 7.44 (m, 2H), 5.49 (s, 1H), 5.40 (dt, *J* = 16.3, 8.1 Hz, 1H), 5.31 – 5.15 (m, 3H), 4.47 – 4.10 (m, 4H), 3.86 – 3.44 (m, 12H), 3.39 (dd, *J* = 13.2, 7.1 Hz, 6H), 2.94 – 2.57 (m, 4H), 2.25 – 1.94 (m, 4H), 1.02 – 0.82 (m, 12H).

## Example BS



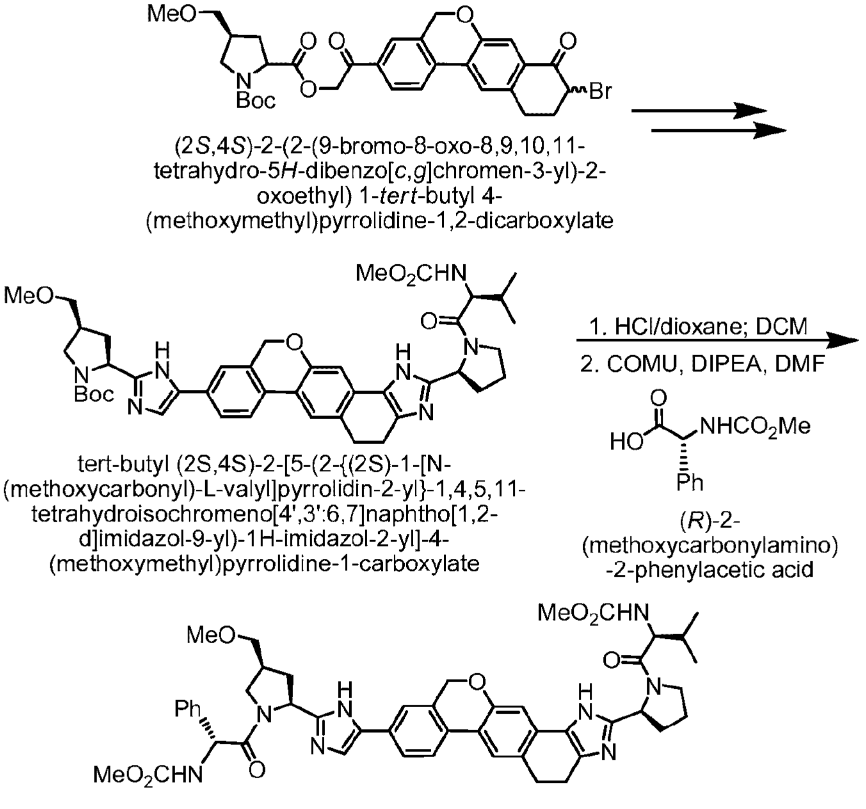
tert-butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate

(2*S*,3*S*)-2-(methoxycarbonylamino)-3-methylpentanoic acid

methyl {(2S,3S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S,3S)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate

**Methyl {(2S,3S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S,3S)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate** was prepared from tert-Butyl (2S,4S)-2-(5-{2-[(2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate using the same method employed in the synthesis of methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate, replacing with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid with (2S,3S)-2-(methoxycarbonylamino)-3-methylpentanoic acid. MS (ESI) *m/z* 908 $[M + H]^+$.

## Example BT



(2*S*,4*S*)-2-(2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5*H*-dibenzo[*c*,*g*]chromen-3-yl)-2-oxoethyl) 1-*tert*-butyl 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate

tert-butyl (2S,4S)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

(*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid

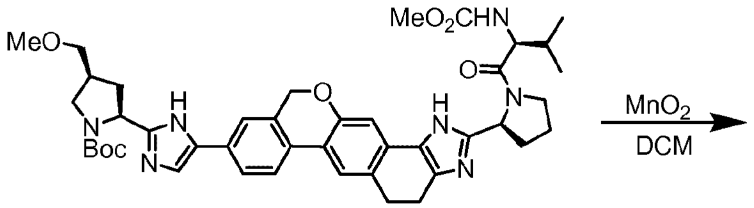
methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**tert-Butyl (2S,4S)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate** was synthesized from (2S,4S)-2-(2-(9-bromo-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-3-yl)-2-oxoethyl) 1-tert-butyl 4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate using the same methods described for the synthesis of tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-

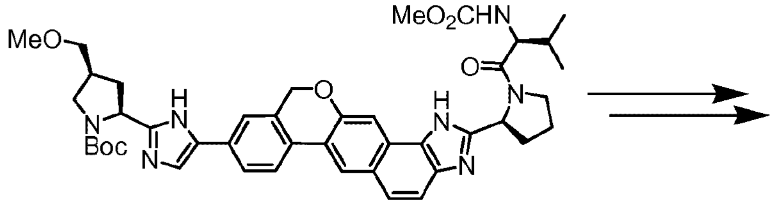
yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate, substituting (S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidine-2-carboxylic acid for (2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylic acid.

**Methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate** was synthesized from tert-butyl (2S,4S)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate using the same method employed for the synthesis of methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate substituting tert-butyl (2S,4S)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate for tert-Butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate. MS (ESI) $m/z$ 871 $[M + H]^+$. $^1H$ NMR (400 MHz, $cd_3od$) δ 7.87 (ddd, $J$ = 20.5, 15.3, 6.8 Hz, 4H), 7.65 (s, 1H), 7.50 – 7.38 (m, 5H), 7.17 (s, 1H), 5.41 (d, $J$ = 24.5 Hz, 1H), 5.28 (t, $J$ = 8.3 Hz, 1H), 5.20 (d, $J$ = 7.3 Hz, 3H), 4.24 (d, $J$ = 7.2 Hz, 1H), 4.12 (d, $J$ = 10.3 Hz, 1H), 4.03 – 3.94 (m, 1H), 3.89 (dd, $J$ = 15.4, 8.6 Hz, 1H), 3.77 (t, $J$ = 9.6 Hz, 1H), 3.72 – 3.64 (m, 4H), 3.63 – 3.52 (m, 4H), 3.43 (qd, $J$ = 9.5, 5.6 Hz, 3H), 3.30 (s, 3H), 3.24 – 3.08 (m, 2H), 2.97 (dd, $J$ = 11.6, 5.4 Hz, 2H), 2.59 (dt, $J$ = 21.1, 7.8 Hz, 3H), 2.29 (s, 1H), 2.24 – 2.14 (m, 2H), 2.11 – 1.85 (m, 2H), 0.92 (dd, $J$ = 15.8, 6.7 Hz, 6H).

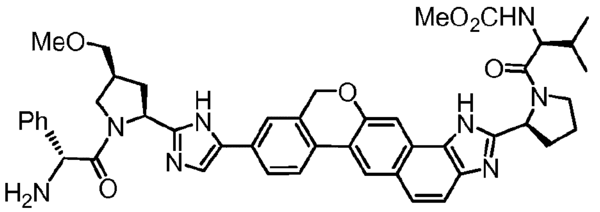
## Example BU



tert-butyl (2S,4S)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate



tert-butyl (2S,4S)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

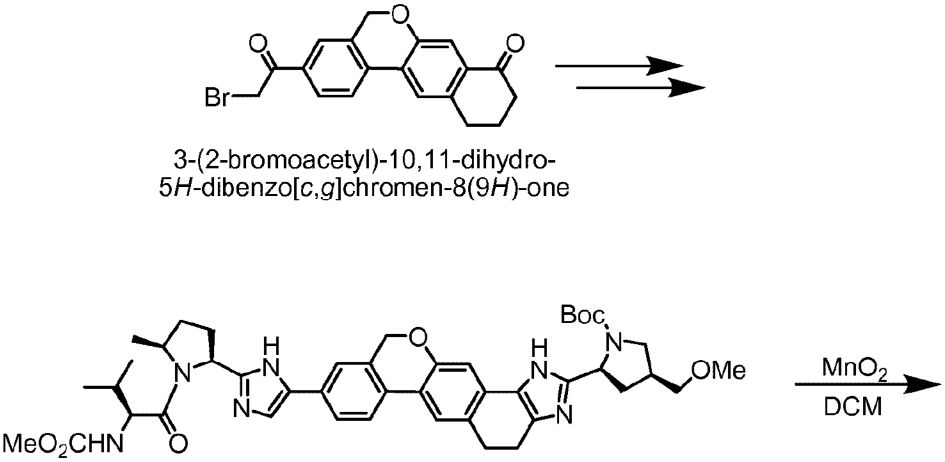


methyl {(2S)-1-[(2S)-2-(9-{2-[(2S,4S)-1-[(2R)-2-amino-2-phenylacetyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**tert-Butyl (2S,4S)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate** was prepared according to the method described for the synthesis of *tert*-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate, substituting tert-butyl (2S,4S)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate for *tert*-Butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate.

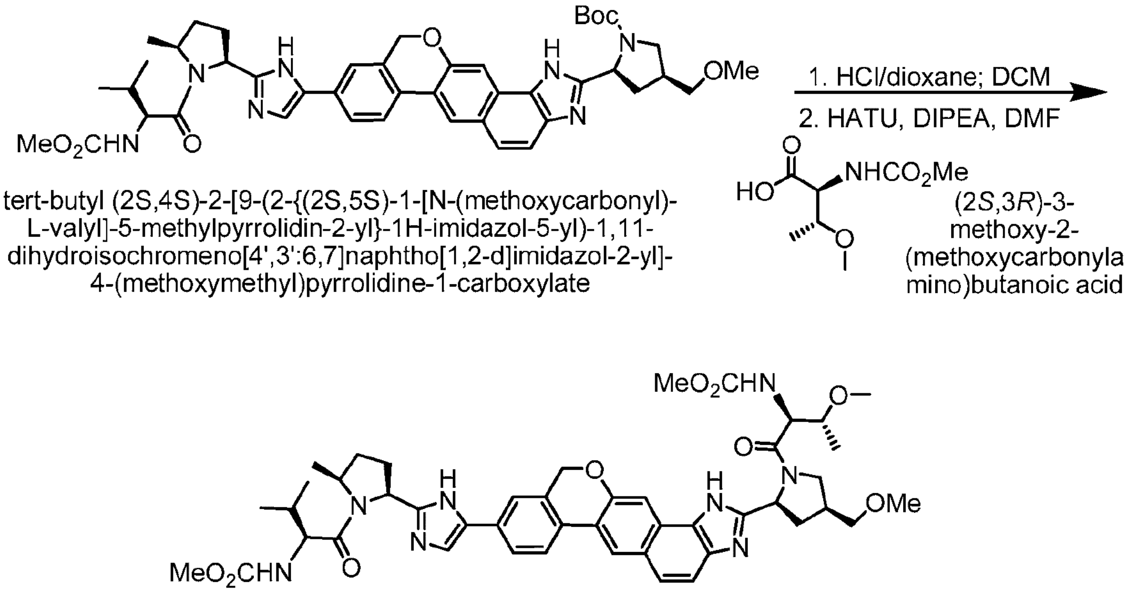
**Methyl {(2S)-1-[(2S)-2-(9-{2-[(2S,4S)-1-[(2R)-2-amino-2-phenylacetyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate** was prepared according to the method described for the synthesis of methyl (S)-1-((2S,4S)-2-(2'-((2S,4S)-1-((R)-2-amino-2-phenylacetyl)-4-(methoxymethyl)pyrrolidin-2-yl)-1H,1'H-7,7'-binaphtho[1,2-d]imidazol-2-yl)-4-methylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate, substituting methyl (S)-1-((2S,4S)-2-(2'-((2S,4S)-1-((R)-2-tert-butoxycarbonylamino-2-phenylacetyl)-4-(methoxymethyl)pyrrolidin-2-yl)-1H,1'H-7,7'-binaphtho[1,2-d]imidazol-2-yl)-4-methylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate with tert-butyl (2S,4S)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate. MS (ESI) *m/z* 811 $[M + H]^+$.

## Example BV



3-(2-bromoacetyl)-10,11-dihydro-5*H*-dibenzo[*c*,*g*]chromen-8(9*H*)-one

tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate



tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

(2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid

methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S,3R)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

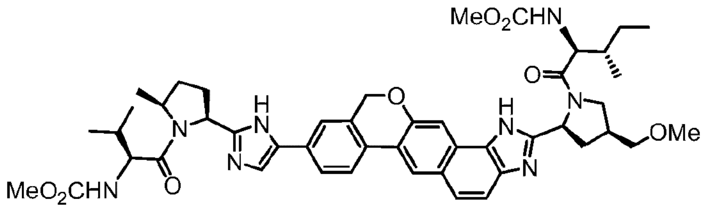
**tert-Butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate** was synthesized from 3-(2-bromoacetyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one, by the same methods employed in the synthesis of *tert*-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate, substituting (2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylic acid for (2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid and (2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid for (2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylic acid.

**tert-Butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate** was prepared according to the method described for the synthesis of tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-

9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate, substituting tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate for tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate.

**Methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S,3R)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate** was prepared from tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate according to the same method described for the synthesis of methyl (S)-1-((2S,4S)-2-(2'-((2S,4S)-1-((2S,3R)-2-methoxycarbonylamino-3-methoxybutanoyl)-4-(methoxymethyl)pyrrolidin-2-yl)-1H,1'H-7,7'-binaphtho[1,2-d]imidazol-2-yl)-4-methylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate, substituting (2S,4S)-tert-Butyl 2-(2'-((2S,4S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-4-methylpyrrolidin-2-yl)-1H,1'H-7,7'-binaphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate with tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate. MS (ESI) *m/z* 866 [M + H]$^{+}$. $^{1}$H NMR (400 MHz, cd$_3$od) δ 8.44 (d, *J* = 19.8 Hz, 1H), 8.02 (t, *J* = 8.6 Hz, 2H), 7.98 – 7.81 (m, 3H), 7.74 (dd, *J* = 22.2, 13.6 Hz, 2H), 7.63 – 7.41 (m, 2H), 5.79 (d, *J* = 6.0 Hz, 1H), 5.42 (dt, *J* = 43.3, 21.5 Hz, 2H), 5.31 – 5.10 (m, 5H), 4.85 – 4.70 (m, 1H), 4.52 (d, *J* = 3.8 Hz, 1H), 4.31 (t, *J* = 8.2 Hz, 1H), 4.17 (dd, *J* = 20.8, 8.8 Hz, 1H), 3.80 (dt, *J* = 19.0, 7.3 Hz, 2H), 3.73 – 3.63 (m, 7H), 3.63 – 3.49 (m, 3H), 3.39 (d, *J* = 9.7 Hz, 4H), 3.35 (s, 5H), 3.28 (d, *J* = 4.4 Hz, 3H), 2.84 (d, *J* = 8.8 Hz, 1H), 2.72 (dd, *J* = 12.5, 6.6 Hz, 1H), 2.59 – 2.45 (m, 1H), 2.45 – 2.11 (m, 4H), 2.11 – 1.82 (m, 2H), 1.56 (d, *J* = 6.6 Hz, 3H), 1.35 – 1.21 (m, 1H), 1.22 – 1.12 (m, 4H), 1.10 – 1.01 (m, 2H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H).

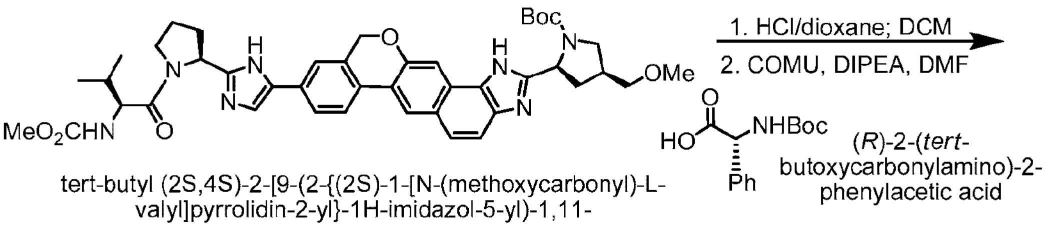
## Example BW



methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S,3S)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-(methoxymethyl)-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

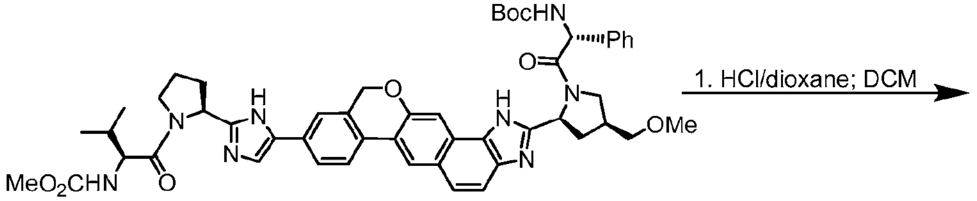
**Methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S,3S)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-(methoxymethyl)-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate** was prepared according to the method described for the synthesis of methyl {(2S,3S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S,3S)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate substituting tert-butyl (2S,4S)-2-[9-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate for *tert*-Butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate. MS (ESI) *m/z* 863 $[M + H]^+$. $^1H$ NMR (400 MHz, $cd_3od$) δ 8.43 (d, *J* = 24.6 Hz, 1H), 8.01 (dt, *J* = 16.1, 8.0 Hz, 1H), 7.95 – 7.78 (m, 2H), 7.77 – 7.64 (m, 2H), 7.59 – 7.41 (m, 2H), 5.79 (d, *J* = 5.8 Hz, 1H), 5.39 (dt, *J* = 46.2, 23.1 Hz, 1H), 5.27 – 5.07 (m, 3H), 4.85 – 4.72 (m, 1H), 4.42 (t, *J* = 8.6 Hz, 1H), 4.31 (d, *J* = 7.9 Hz, 1H), 4.17 (dd, *J* = 19.7, 8.7 Hz, 1H), 3.81 (dd, *J* = 23.6, 13.3 Hz, 1H), 3.69 (d, *J* = 10.0 Hz, 5H), 3.60 (dd, *J* = 14.7, 7.8 Hz, 2H), 3.42 (s, 3H), 3.17 (d, *J* = 6.1 Hz, 1H), 3.07 (s, 1H), 2.99 – 2.91 (m, 1H), 2.85 (s, 1H), 2.73 (dd, *J* = 12.5, 6.4 Hz, 1H), 2.62 – 2.48 (m, 1H), 2.45 – 2.14 (m, 3H), 2.10 – 1.91 (m, 2H), 1.83 (s, 1H), 1.57 (d, *J* = 6.6 Hz, 3H), 1.44 (d, *J* = 7.4 Hz, 1H), 1.34 – 1.23 (m, 1H), 1.20 – 0.96 (m, 5H), 0.90 (dt, *J* = 14.8, 6.7 Hz, 9H).

## Example BX

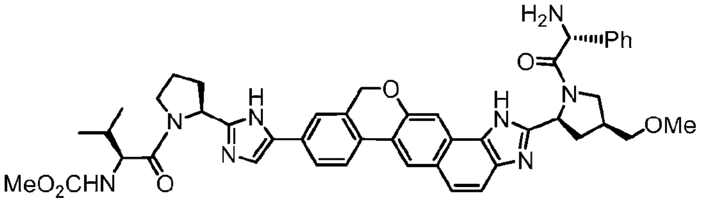


(*R*)-2-(*tert*-butoxycarbonylamino)-2-phenylacetic acid

tert-butyl (2S,4S)-2-[9-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate



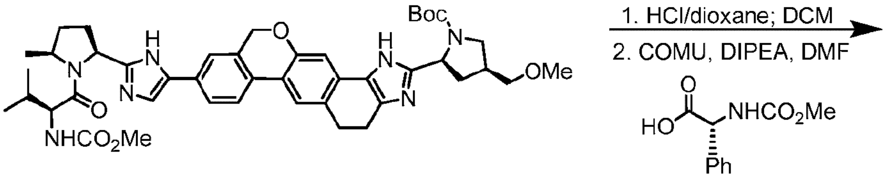
methyl {(2S)-1-[(2S)-2-(5-{2-[(2S,4S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate



methyl {(2S)-1-[(2S)-2-(5-{2-[(2S,4S)-1-[(2R)-2-amino-2-phenylacetyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

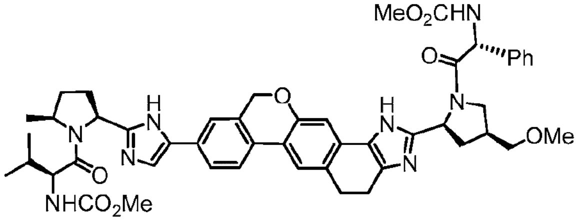
**Methyl {(2S)-1-[(2S)-2-(5-{2-[(2S,4S)-1-[(2R)-2-amino-2-phenylacetyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate** was prepared according to the method described for the synthesis of methyl (S)-1-((2S,4S)-2-(2'-((2S,4S)-1-((R)-2-amino-2-phenylacetyl)-4-(methoxymethyl)pyrrolidin-2-yl)-1H,1'H-7,7'-binaphtho[1,2-d]imidazol-2-yl)-4-methylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate, substituting tert-butyl (2S,4S)-2-[9-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate for (2S,4S)-tert-butyl 2-(2'-((2S,4S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-4-methylpyrrolidin-2-yl)-1H,1'H-7,7'-binaphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate. MS (ESI) *m/z* 811 $[M + H]^+$.

## Example BY



tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

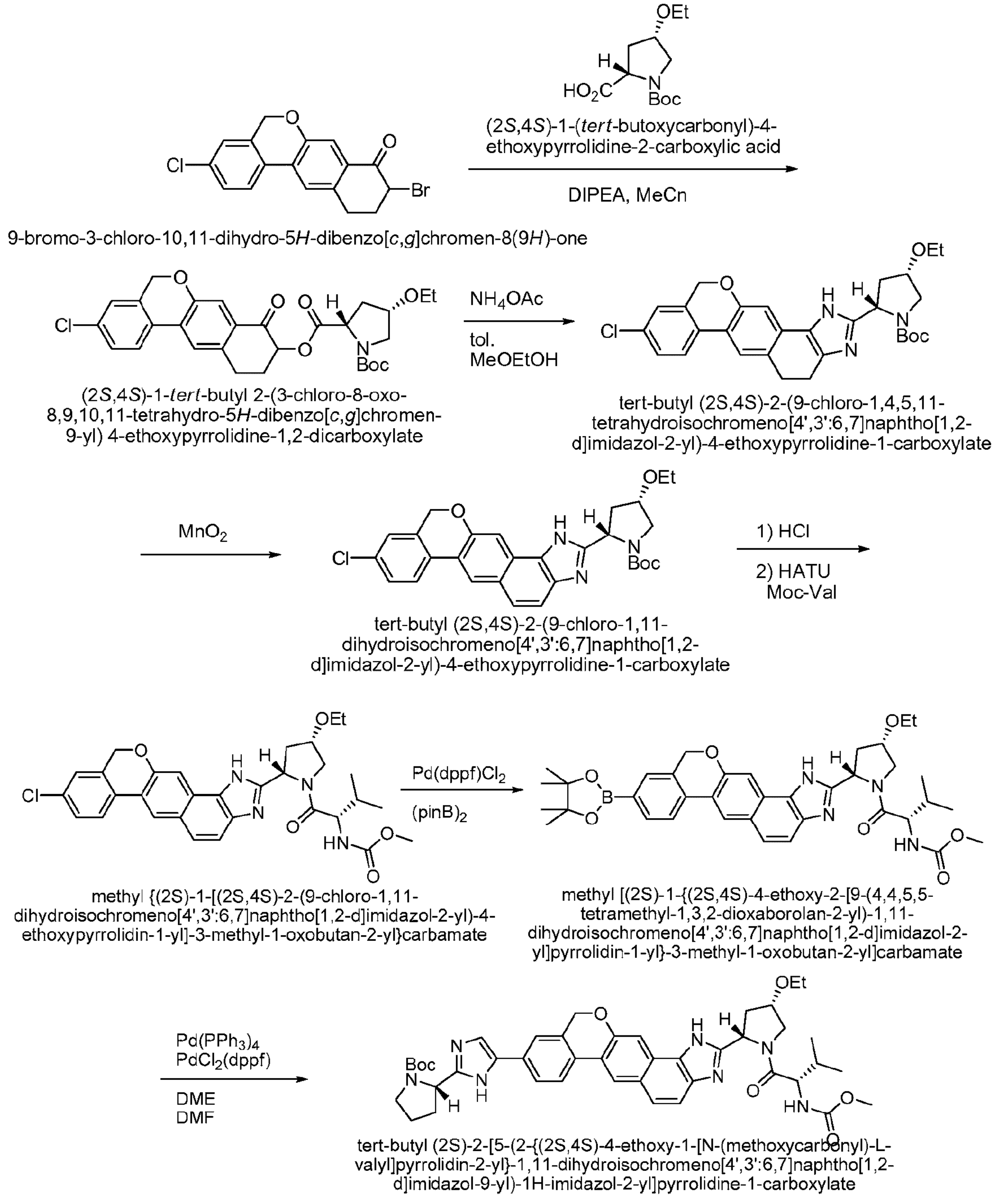
(*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid

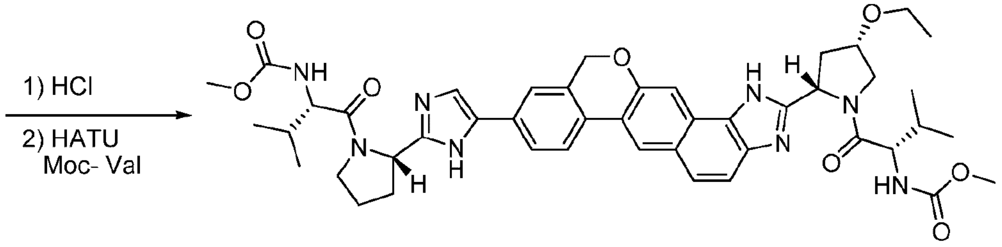


methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**Methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate** was synthesized according to the protocol described for the preparation of methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate, substituting tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate for tert-butyl (2S,4S)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,4,5,11 tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate. MS (ESI) *m/z* 886 $[M + H]^+$. $^1$H NMR (400 MHz, $cd_3od$) δ 8.02 – 7.85 (m, 2H), 7.85 – 7.68 (m, 2H), 7.58 (d, *J* = 21.5 Hz, 1H), 7.55 – 7.35 (m, 4H), 7.31 (d, *J* = 13.6 Hz, 1H), 5.43 (d, *J* = 19.1 Hz, 1H), 5.28 (t, *J* = 8.3 Hz, 1H), 5.25 – 5.10 (m, 3H), 4.13 (t, *J* = 9.5 Hz, 1H), 3.93 – 3.54 (m, 7H), 3.42 (qd, *J* = 9.5, 5.5 Hz, 2H), 3.34 (d, *J* = 7.9 Hz, 1H), 3.28 (s, 3H), 3.19 (t, *J* = 7.8 Hz, 2H), 3.00 (t, *J* = 7.8 Hz, 2H), 2.74 – 2.46 (m, 3H), 2.44 – 2.15 (m, 2H), 2.12 – 1.86 (m, 2H), 1.56 (d, $J$ = 6.7 Hz, 2H), 1.29 (d, $J$ = 6.3 Hz, 1H), 1.15 – 1.01 (m, 1H), 0.98 (d, $J$ = 6.7 Hz, 2H), 0.88 (d, $J$ = 6.8 Hz, 2H).

## Example BZ





methyl {(2S)-1-[(2S)-2-(5-{2-[(2S,4S)-4-ethoxy-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**(2S,4S)-1-Tert-butyl 2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-9-yl) 4-ethoxypyrrolidine-1,2-dicarboxylate.** To a slurry of 9-bromo-3-chloro-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (2.50 g, 6.8 mmol) in MeCN (20 mL) was added (2S,4S)-1-(tert-butoxycarbonyl)-4-ethoxypyrrolidine-2-carboxylic acid (2.68 g, 10.3 mmol) and DIPEA (1.3 mL, 7.5 mmol). The reaction was heated with stirring to 50 °C for 18 h. The reaction was then cooled to room temperature and diluted with EtOAc. The solution was washed with HCl (1N) and brine. The aqueous layers were backextracted with EtOAc and the resulting organic layers were combined, dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (15% to 50 % EtOAc/Hexanes) to afford (2S,4S)-1-tert-butyl 2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-9-yl) 4-ethoxypyrrolidine-1,2-dicarboxylate (2.08 g, 56%).

**Tert-butyl (2S,4S)-2-(9-chloro-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-ethoxypyrrolidine-1-carboxylate.** To a solution of (2S,4S)-1-tert-butyl 2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-9-yl) 4-ethoxypyrrolidine-1,2-dicarboxylate (2.08 g, 3.8 mmol) in a mixture of toluene (30 mL) and methoxyethanol (4 mL) was added ammonium acetate (2.90 g, 37.7 mmol). The solution was heated with stirring to 80 °C for 18 h. The reaction was then cooled to room tmeperature and diluted with EtOAc. The solution was washed with brine, and the resulting aquous layer was backextracted with EtOAc. The resulting organic layers were combined, dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (10% to 75 % EtOAc(w/5% MeOH)/Hexanes) to afford tert-butyl (2S,4S)-2-(9-chloro-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-ethoxypyrrolidine-1-carboxylate (0.99 g, 50%).

**Tert-butyl (2S,4S)-2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-ethoxypyrrolidine-1-carboxylate.** To a solution of (2S,4S)-2-(9-chloro-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-ethoxypyrrolidine-

1-carboxylate (0.99 g, 1.9 mmol) in $CH_2Cl_2$ (18 mL) was added $MnO_2$ (4.52 g, 52.0 mmol). The resulting slurry was stirred at room temperature for 18 h. The reaction was filtered through celite, washed with $CH_2Cl_2$, and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (10% to 75 % EtOAc(w/5% MeOH)/Hexanes) to afford tert-butyl (2S,4S)-2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-ethoxypyrrolidine-1-carboxylate (0.71 g, 72%)

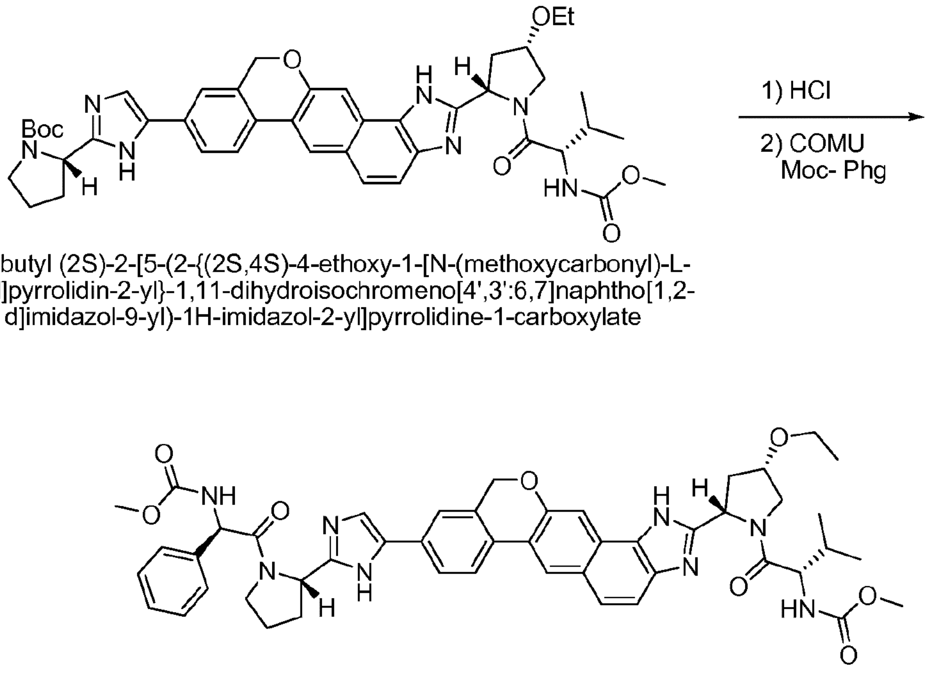
**Methyl {(2S)-1-[(2S,4S)-2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-ethoxypyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate.** To a solution of (2S,4S)-2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-ethoxypyrrolidine-1-carboxylate (0.46 g, 0.9 mmol) in a mixture of $CH_2Cl_2$ (9.0 mL) and MeOH (1.5 mL) was added HCl (in dioxanes, 4M, 6.5 mL, 26.0 mmol). The resulting solution was stirred at room temperature for 2 h. The solution was concentrated to dryness under reduced pressure. To the crude intermediate in $CH_2Cl_2$ (10.0 mL) was added (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.17 g, 0.9 mmol), HATU (0.41 g, 1.1 mmol), and DIPEA (0.5 mL, 2.9 mmol). The resulting solution was stirred at room temperature for 48 h and diluted with $CH_2Cl_2$. The solution was washed with aqueous HCl (1N) and brine. The aqueous layers were backextracted with $CH_2Cl_2$ (2x). The resulting organic layers were combined, dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (20% to 100 % EtOAc(w/5% MeOH)/Hexanes to 80% MeOH/EtOAc) to afford methyl {(2S)-1-[(2S,4S)-2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-ethoxypyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (0.46 g, 90%).

**Methyl [(2S)-1-{(2S,4S)-4-ethoxy-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate.** To a solution of methyl {(2S)-1-[(2S,4S)-2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-ethoxypyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (0.46 g, 0.84 mmol) in dioxane (8.5 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.32 g, 1.3 mmol), potassium acetate (0.25 g, 2.5 mmol), bis(dibenzylideneacetone)palladium (0.032 g, 0.035 mmol), and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos, 0.032 g, 0.067 mmol). The resulting solution was degassed with argon for 5 min and heated, with stirring, to 90 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc, and filtered through celite. The crude residue was purified by silica column chromatography (20% to 100 % EtOAc(w/5% MeOH)/Hexanes to 90% MeOH/EtOAc) to afford methyl [(2S)-1-{(2S,4S)-4-ethoxy-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate (0.41 g, 73%).

**Tert-butyl (2S)-2-[5-(2-{(2S,4S)-4-ethoxy-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate.** To a solution of methyl [(2S)-1-{(2S,4S)-4-ethoxy-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate (0.41 g, 0.61 mmol) in a mixture of DME (6.1 mL) and DMF (1.0 mL) was added (S)-tert-butyl 2-(5-bromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (0.39 g, 1.2 mmol), tetrakis(triphenylphosphine)palladium (0.021 g, 0.018 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium (0.030 g, 0.041 mmol), and aqueous potassium carbonate (2M, 1.0 mL, 2.0 mmol). The solution was degasses with argon for 5 min and heted, with stirring, to 85 °C for 6 h. The solution was cooled to room temperature and diluted with EtOAc. The organic layer was washed with water and brine. The aqueous layers were backextracted with EtOAc (3x). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (20% to 100 % EtOAc(w/5% MeOH)/Hexanes to 80% MeOH/EtOAc) to afford tert-butyl (2S)-2-[5-(2-{(2S,4S)-4-ethoxy-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate (0.16 g, 33%).

**Methyl {(2S)-1-[(2S)-2-(5-{2-[(2S,4S)-4-ethoxy-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate.** To a solution of tert-butyl (2S)-2-[5-(2-{(2S,4S)-4-ethoxy-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate (0.048 g, 0.062 mmol) in a mixture of $CH_2Cl_2$ (1.0 mL) and MeOH (0.25 mL) was added HCl (in dioxanes, 4M, 0.47 mL, 1.9 mmol). The solution was stirred at room temperature for 3 h, and then concentrated to dryness under reduced pressure. To the crude intermediate suspended in $CH_2Cl_2$ (1.5 mL) was added (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.012 g, 0.069 mmol), HATU (0.029 g, 0.076 mmol), and DIPEA (0.050 mL, 0.28 mmol). The resulting solution was stirred at room temperature for 1.5 h. The reaction was diluted with DMF and aqueous LiOH (2.5 M, 4 drops) was added. The solution was concentrated to remove the $CH_2Cl_2$ and the crude residue was purified by preparative reverse phase HPLC (10% to 52 % MeCN/water with 0.1% TFA). The desired fractions were combined and concentrated under reduced pressure to remove volitle organics. The addition of aqueous sodium bicarbonate with stirring resulted in precipitation of a white solid. The precipitate was filtered through a membrane filter and washed with water. Drying under reduced pressure afforded methyl {(2S)-1-[(2S)-2-(5-{2-[(2S,4S)-4-ethoxy-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (0.008 g, 17%). 1H-NMR: 400 MHz, (MeOD) δ: (Mixture of rotomers) 8.37 (s, 1H), 7.97 (s, 2H), 7.37-7.76 (m, 5H), 5.38-5.54 (m, 1H), 5.18 (s, 2H), 5.14-5.16 (m, 1H), 4.21-4.31 (m, 4H), 3.87-4.09 (m, 1H), 3.79-3.85 (m, 2H), 3.66 (s, 3H), 3.64 (s, 3H), 3.46-3.55 (m, 2H), 2.30-2.35 (m, 3H), 2.04-2.06 (m, 3H), 1.11 (m, 2H), 0.95 (d, 3H), 0.88 (d, 3H). MS (ESI) *m/z* 836.02 $[M + H]^+$.

## Example CA

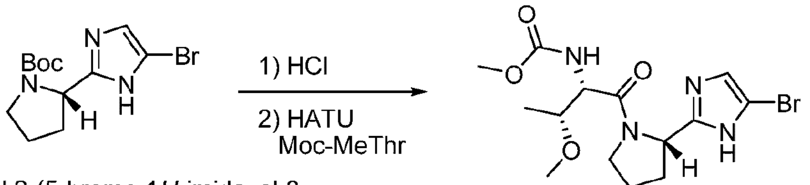


tert-butyl (2S)-2-[5-(2-{(2S,4S)-4-ethoxy-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate

methyl {(1R)-2-[(2S)-2-(5-{2-[(2S,4S)-4-ethoxy-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**Methyl {(1R)-2-[(2S)-2-(5-{2-[(2S,4S)-4-ethoxy-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate.** To a solution of tert-butyl (2S)-2-[5-(2-{(2S,4S)-4-ethoxy-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate (0.11 g, 0.14 mmol) in a mixture of $CH_2Cl_2$ (2.0 mL) and MeOH (0.5 mL) was added HCl (in dioxanes, 4M, 1.0 mL, 4.0 mmol). The solution was stirred at room temperature for 3 h, and then concentrated to dryness under reduced pressure. To the crude intermediate suspended in $CH_2Cl_2$ (1.5 mL) was added (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (0.044 g, 0.21 mmol) and DIPEA (0.075 mL, 0.43 mmol). The resulting solution was cooled to -40 °C and COMU (0.096 g, 0.22 mmol) was added. The reaction was allowed to slowly warm to 0 °C over 1 h. The reaction was diluted with DMF. The solution was concentrated to remove the $CH_2Cl_2$ and the crude residue was purified by preparative reverse phase HPLC (10% to 55% MeCN/water with 0.1% TFA). The desired fractions were combined and concentrated under reduced pressure to remove volatile organics. The addition of aqueous sodium bicarbonate with stirring resulted in precipitation of a white solid. The precipitate was filtered through a membrane filter and washed with water. Drying under reduced pressure afforded methyl {(1R)-2-[(2S)-2-(5-{2-[(2S,4S)-4-ethoxy-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (0.022 g, 18%). 1H-NMR: 400 MHz, (MeOD) δ: (Mixture of rotomers) 8.28 (d, 1H), 7.88 (d, 1H), 7.52-7.70 (m, 3H), 7.28-7.38 (m, 5H), 6.90-6.96 (m, 2H), 5.44-5.47 (m, 1H), 5.31 (s, 1H), 5.12 (s, 2H), 4.16-4.48 (m, 3H), 3.81-3.19 (m, 1H), 3.62-3.76 (m, 2H), 3.58 (s, 3H), 2.56 (s, 3H), 2.42-2.57 (m, 1H), 2.31 (m, 1H), 1.81-2.41 (m, 5H), 1.04 (t, 3H), 0.87 (d, 3H), 0.81 (d, 3H). MS (ESI) *m/z* 869.55 $[M + H]^+$.

## Example CB

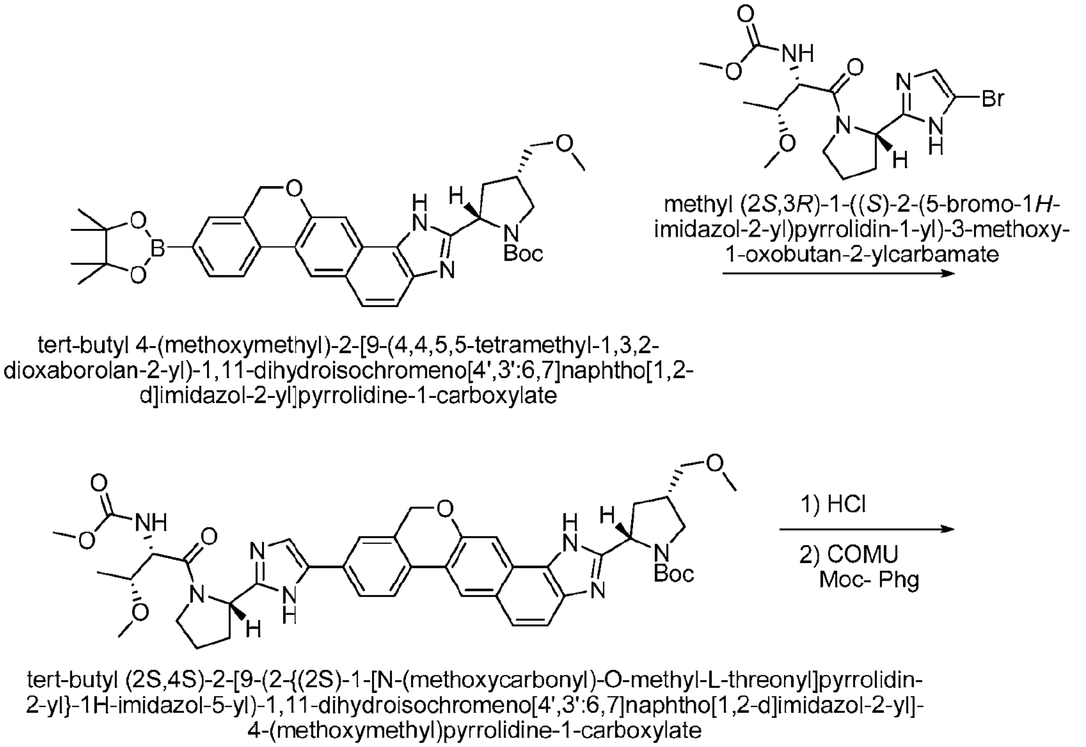


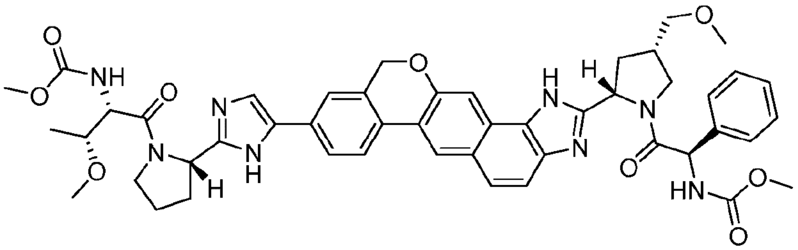
(*S*)-*tert*-butyl 2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate

methyl (2*S*,3*R*)-1-((*S*)-2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methoxy-1-oxobutan-2-ylcarbamate

**Methyl (2S,3R)-1-((S)-2-(5-bromo-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methoxy-1-oxobutan-2-ylcarbamate.** To a solution of (S)-tert-butyl 2-(5-bromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (1.00 g, 3.2 mmol) in a mixture of $CH_2Cl_2$ (30 mL) and MeOH (5 mL) was added HCl (in dioxane, 4 M, 11.5 mL, 46.0 mmol). The solution was stirred at 40 °C for 1h, cooled to room temperature, and concentrated to dryness under reduced pressure. To the crude intermediate suspended in $CH_2Cl_2$ (30 mL) was added (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (0.67 g, 3.5 mmol), HATU (1.47 g, 3.8 mmol), and DIPEA (1.00 mL, 6.0 mmol), The resulting solution was stirred at room temperature for 24 h. DMF (2 mL) and aqueous LiOH (2.5 M, 1 mL) were added and the reaction was concentrated to dryness under reduced pressure. The crude material was diluted with EtOAc and washed with $H_2O$ and brine. The aqueous layers were backextracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (20% to 100 % EtOAc(w/5% MeOH)/$CH_2Cl_2$) to afford methyl (2S,3R)-1-((S)-2-(5-bromo-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methoxy-1-oxobutan-2-ylcarbamate (1.2g, 100%).

## Example CC





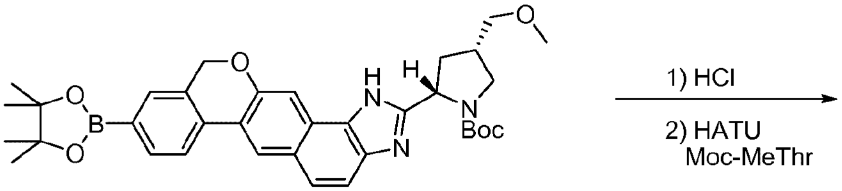
methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S)-1-{(2S,3R)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**Tert-butyl (2S,4S)-2-[9-(2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate.** To a solution of tert-butyl 4-(methoxymethyl)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate (1.0 g, 3.2 mmol) in a mixture of DMSO (2.0 mL) and dioxanes (2.0 mL) was added methyl (2S,3R)-1-((S)-2-(5-bromo-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methoxy-1-oxobutan-2-ylcarbamate (0.24 g, 0.62 mmol), tetrakis(triphenylphosphine)palladium (0.050 g, 0.043 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium (0.030 g, 0.041 mmol), and aqueous potassium carbonate (2M, 0.65 mL, 1.3 mmol). The solution was degasses with argon for 5 min and heated, with stirring, to 85 °C for 6 h. The solution was cooled to room temperature and diluted with EtOAc. The organic layer was washed with water and brine. The aqueous layers were backextracted with EtOAc (3x). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (20% to 100 % EtOAc(w/5% MeOH)/Hexanes to 60% MeOH/EtOAc) to afford tert-butyl (2S,4S)-2-[9-(2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (0.20 g, 63%).

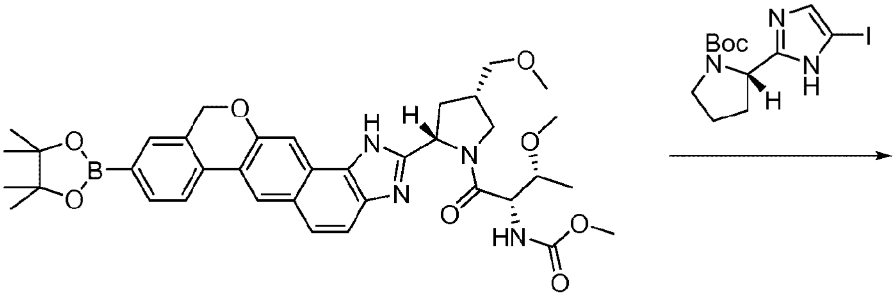
**Methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S)-1-{(2S,3R)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate.** To a solution of tert-butyl (2S,4S)-2-[9-(2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-

(methoxymethyl)pyrrolidine-1-carboxylate (0.20 g, 0.26 mmol) in a mixture of $CH_2Cl_2$ (3.0 mL) and MeOH (0.5 mL) was added HCl (in dioxanes, 4M, 2.0 mL, 8.0 mmol). The solution was stirred at 40 °C for 1 h, and then cooled to room temperature and concentrated to dryness under reduced pressure. To the crude intermediate suspended in $CH_2Cl_2$ (3.0 mL) was added (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (0.081 g, 0.39 mmol) and DIPEA (0.150 mL, 0.86 mmol). The resulting solution was cooled to -40 °C and COMU (0.180 g, 0.42 mmol) was added. The reaction was allowed to slowly warm to room temperature over 30 min and maintained for 1.5 h. The solution was diluted with $CH_2Cl_2$ and washed with aqueous bicarb. The aqueous layer was backextracted with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude residue was purified by preparative reverse phase HPLC (10% to 50% MeCN/water with 0.1% TFA). The desired fractions were combined and concentrated under reduced pressure to remove volatile organics. The addition of aqueous sodium bicarbonate with stirring resulted in precipitation of a white solid. The precipitate was filtered through a membrane filter and washed with water. Drying under reduced pressure afforded methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S)-1-{(2S,3R)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (0.10 g, 46%). 1H-NMR: 400 MHz, (MeOD) δ: (Mixture of rotomers) 8.34 (s, 1H), 7.92-7.97 (m, 2H), 7.33-7.69 (m, 10H), 5.53 (s, 1H), 5.36-5.39 (m, 1H), 5.15-5.21 (m, 3H), 4.44 (d, 1H), 3.86-3.93 (m, 2H), 3.68-3.75 (m, 2H), 3.66 (s, 3H), 3.65 (s, 3H), 3.46-3.57 (m, 2H), 3.28 (s, 3H), 3.19 (s, 3H), 2.47-2.60 (m, 3H), 2.22-2.36 (m, 4H), 1.99-2.08 (m, 3H), 1.15 (d, 3H). MS (ESI) *m/z* 886.19 $[M + H]^+$.

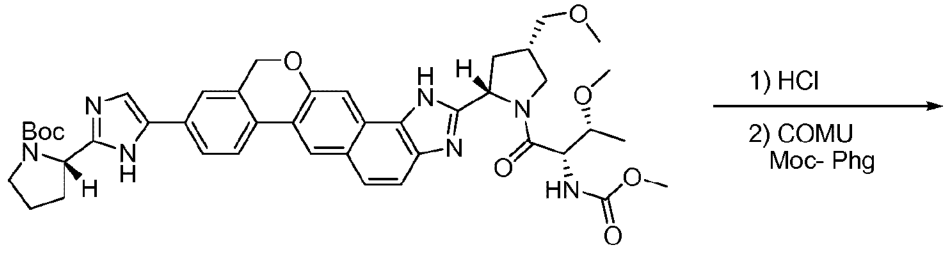
## Example CD



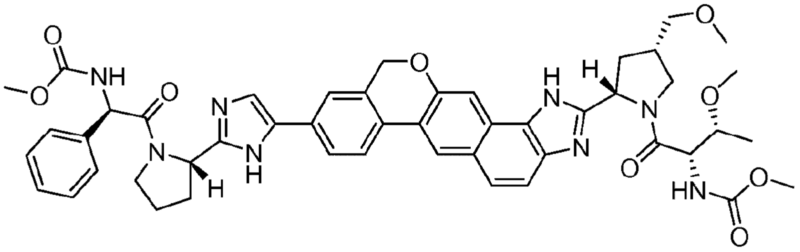
tert-butyl 4-(methoxymethyl)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate



methyl (1-{4-(methoxymethyl)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-3-methoxy-1-oxobutan-2-yl)carbamate



tert-butyl (2S)-2-(5-{2-[(2S,4S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidine-1-carboxylate



methyl {(1R)-2-[(2S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methoxybutanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

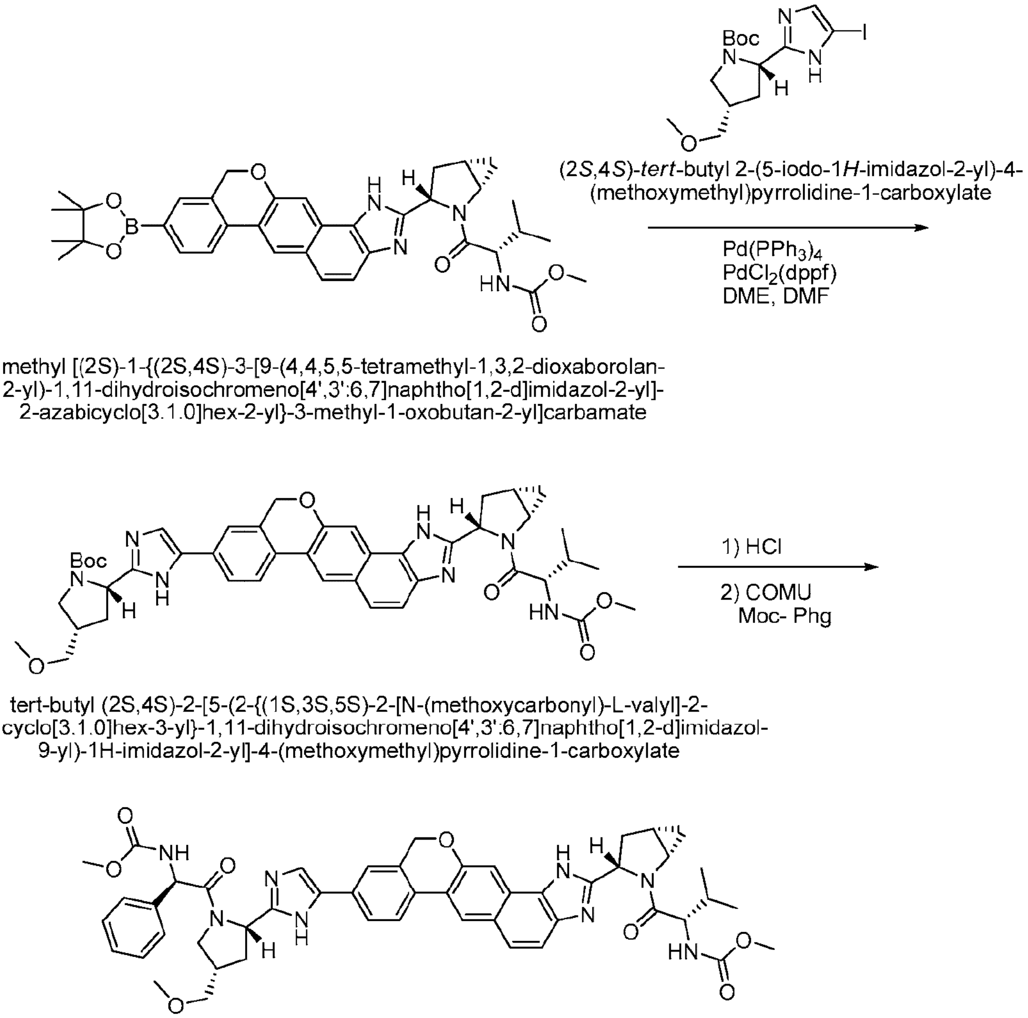
**Methyl (1-{4-(methoxymethyl)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-3-methoxy-1-oxobutan-2-yl)carbamate.** To a solution of tert-butyl 4-(methoxymethyl)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-

d]imidazol-2-yl]pyrrolidine-1-carboxylate (0.25 g, 0.41 mmol) in a mixture of $CH_2Cl_2$ (4.0 mL) and MeOH (1.0 mL) was added HCl (in dioxanes, 4M, 3.0 mL, 12.0 mmol). The resulting solution was stirred at 40 °C for 45 min. The solution was cooled to room temperature and concentrated to dryness under reduced pressure. To the crude intermediate in $CH_2Cl_2$ (4.0 mL) was added (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (0.08 g, 0.42 mmol), HATU (0.17 g, 0.45 mmol), and DIPEA (0.4 mL, 2.3 mmol). The resulting solution was stirred at room temperature for 48 h and diluted with $CH_2Cl_2$. The solution was washed with brine. The aqueous layer was backextracted with $CH_2Cl_2$ (2x). The resulting organic layers were combined, dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (30% to 100 % EtOAc(w/5% MeOH)/Hexanes to 80% MeOH/EtOAc) to afford methyl (1-{4-(methoxymethyl)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-3-methoxy-1-oxobutan-2-yl)carbamate (0.24 g, 92%).

**Tert-butyl (2S)-2-(5-{2-[(2S,4S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidine-1-carboxylate.** To a solution of methyl (1-{4-(methoxymethyl)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-3-methoxy-1-oxobutan-2-yl)carbamate (0.15 g, 0.22 mmol) in a mixture of DMSO (2.0 mL) and dioxane (2.0 mL) was added (S)-tert-butyl 2-(5-iodo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (0.15 g, 0.40 mmol), tetrakis(triphenylphosphine)palladium (0.028 g, 0.024 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium (0.018 g, 0.025 mmol), and aqueous potassium carbonate (2M, 0.35 mL, 0.70 mmol). The solution was degasses with argon for 5 min and heted, with stirring, to 90 °C for 6 h. The solution was cooled to room temperature and diluted with EtOAc. The organic layer was washed with water and brine. The aqueous layers were backextracted with EtOAc (3x). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude residue was purified by preparative reverse phase HPLC (10% to 55% MeCN/water with 0.1% TFA). The desired fractions were combined and concentrated under reduced pressure to remove volatile organics. The remaining solution was basified with aqueous bicarbonate and extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure to provide tert-butyl (2S)-2-(5-{2-[(2S,4S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (0.013 g, 7%).

**Methyl {(1R)-2-[(2S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methoxybutanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate.** To a solution of tert-butyl (2S)-2-(5-{2-[(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (0.013 g, 0.016 mmol) in a mixture of $CH_2Cl_2$ (0.5 mL) and MeOH (0.02 mL) was added HCl (in dioxanes, 4M, 0.20 mL, 0.80 mmol). The solution was stirred at room temperature for 1 h, and then concentrated to dryness under reduced pressure. To the crude intermediate suspended in $CH_2Cl_2$ (0.5 mL) was added (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (0.006 g, 0.029 mmol) and DIPEA (0.05 mL, 0.28 mmol). The resulting solution was cooled to 0 °C and COMU (0.012 g, 0.028 mmol) was added. The reaction was stirred at 0 °C for 30 min. The solution was diluted with DMF and aqueous LiOH (2.5 M, 2 drops) and concentrated under reduced pressure to remove the $CH_2Cl_2$. The crude residue was purified by preparative reverse phase HPLC (10% to 55% MeCN/water with 0.1% TFA). The desired fractions were combined and concentrated under reduced pressure to remove volatile organics. The addition of aqueous sodium bicarbonate with stirring resulted in precipitation of a white solid. The precipitate was filtered through a membrane filter and washed with water. Drying under reduced pressure afforded methyl {(1R)-2-[(2S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methoxybutanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (0.008 g, 61%). $^1H$-NMR: 400 MHz, (MeOD) δ: (Mixture of rotomers) 8.37 (m, 1H), 7.96-7.98 (m, 2H), 7.60-7.79 (m, 3H), 7.35-7.52 (m, 6H), 6.98-7.03 (m, 1H), 5.52 (s, 1H), 5.26-5.39 (m, 2H), 5.20 (s, 2H), 4.44 (m, 1H), 4.27 (m, 1H), 3.64 (s, 6H), 3.50-3.57 (m, 3H), 3.37 (s, 3H), 3.29-3.44 (m, 3H), 3.20 (s, 3H), 2.68-2.72 (m, 2H), 2.57-2.62 (m, 2H), 1.89-2.15 (m, 6H), 1.18 (d, 3H). MS (ESI) *m/z* 885.73 $[M + H]^+$.

## Example CE



methyl [(2S)-1-{(2S,4S)-3-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-2-azabicyclo[3.1.0]hex-2-yl}-3-methyl-1-oxobutan-2-yl]carbamate

tert-butyl (2S,4S)-2-[5-(2-{(1S,3S,5S)-2-[N-(methoxycarbonyl)-L-valyl]-2-azabicyclo[3.1.0]hex-3-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(1S,3S,5S)-2-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[3.1.0]hex-3-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol -2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

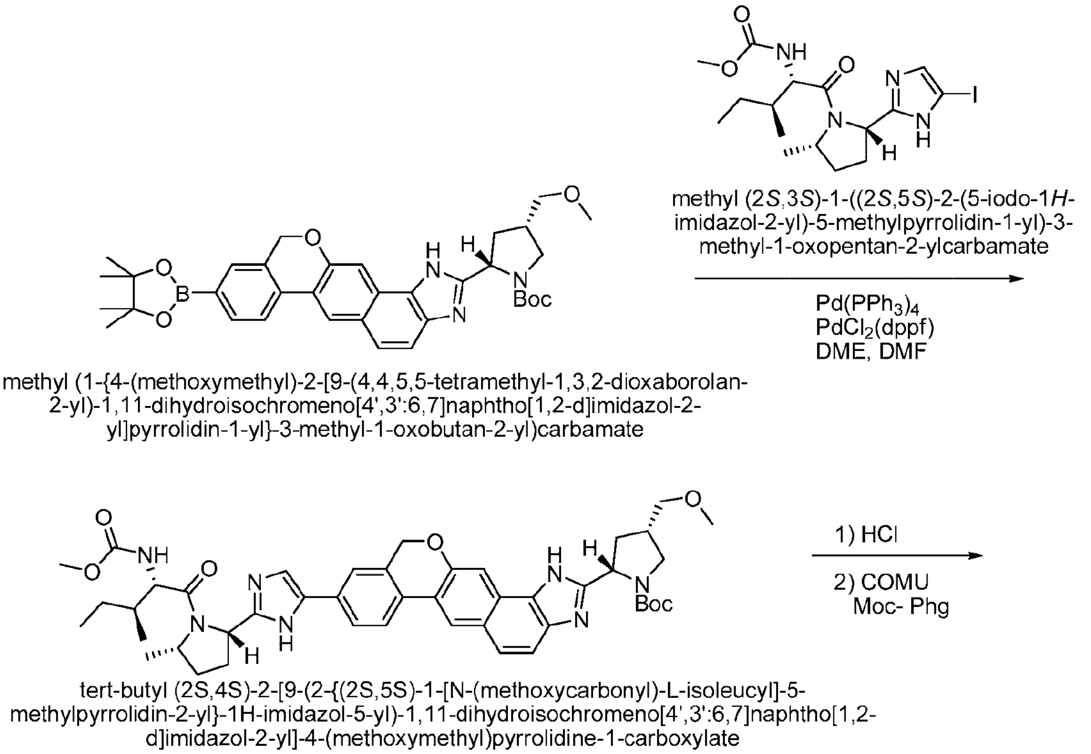
**Methyl [(2S)-1-{(2S,4S)-3-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-2-azabicyclo[3.1.0]hex-2-yl}-3-methyl-1-oxobutan-2-yl]carbamate.** Methyl [(2S)-1-{(2S,4S)-3-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-2-azabicyclo[3.1.0]hex-2-yl}-3-methyl-1-oxobutan-2-yl]carbamate was prepared following the procedure for methyl [(2S)-1-{(2S,4S)-4-ethoxy-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate by substitution of (1S,3S,5S)-2-(tert-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid for (2S,4S)-1-(tert-butoxycarbonyl)-4-ethoxypyrrolidine-2-carboxylic acid.

**Tert-butyl (2S,4S)-2-[5-(2-{(1S,3S,5S)-2-[N-(methoxycarbonyl)-L-valyl]-2-azabicyclo[3.1.0]hex-3-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate.** To a solution of methyl [(2S)-1-{(2S,4S)-3-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-2-azabicyclo[3.1.0]hex-2-yl}-3-methyl-1-oxobutan-2-yl]carbamate (0.19 g, 0.30 mmol) in a mixture of DMSO (2.0 mL) and dioxane (2.0 mL) was added (2S,4S)-tert-butyl 2-(5-iodo-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (0.20 g, 0.55 mmol), tetrakis(triphenylphosphine)palladium (0.035 g, 0.030 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (0.025 g, 0.034 mmol), and aqueous potassium carbonate (2M, 0.5 mL, 1.0 mmol). The solution was degasses with argon for 5 min and heated, with stirring, to 90 °C for 6 h. The solution was cooled to room temperature, diluted with EtOAc, and filtered through celite. The filtrate was concentrated under reduced pressure and purified by silica column chromatography (2% to 25 % $CH_2Cl_2$/MeOH) and preparative reverse phase HPLC (10% to 55% MeCN/water with 0.1% TFA). The desired fractions were combined and concentrated under reduced pressure to remove volatile organics. The aqueous layer was basified with aqueous sodium bicarbonate and extracted with $CH_2Cl_2$ (3x). The organic layers were combine, dried over $Na_2SO_4$, and concentrated under reduced pressure to afford tert-butyl (2S,4S)-2-[5-(2-{(1S,3S,5S)-2-[N-(methoxycarbonyl)-L-valyl]-2-azabicyclo[3.1.0]hex-3-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (0.025 g, 11%).

**Methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(1S,3S,5S)-2-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[3.1.0]hex-3-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol -2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate.** To a solution of tert-butyl (2S,4S)-2-[5-(2-{(1S,3S,5S)-2-[N-(methoxycarbonyl)-L-valyl]-2-azabicyclo[3.1.0]hex-3-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (0.025 g, 0.032 mmol) in a mixture of $CH_2Cl_2$ (1.0 mL) and MeOH (0.25 mL) was added HCl (in dioxanes, 4M, 0.50 mL, 2.0 mmol). The solution was stirred at room temperature for 12 h, and then concentrated to dryness under reduced pressure. To the crude intermediate suspended in $CH_2Cl_2$ (0.5 mL) was added (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (0.012 g, 0.057 mmol) and

DIPEA (0.05 mL, 0.28 mmol). The resulting solution was cooled to 0 °C and COMU (0.023 g, 0.054 mmol) was added. The reaction was stirred at 0 °C for 30 min. The solution was diluted with DMF and aqueous LiOH (2.5 M, 2 drops) and concentrated under reduced pressure to remove the $CH_2Cl_2$. The crude residue was purified by preparative reverse phase HPLC (10% to 55% MeCN/water with 0.1% TFA). The desired fractions were combined and concentrated under reduced pressure to remove volatile organics. The addition of aqueous sodium bicarbonate with stirring resulted in precipitation of a white solid. The precipitate was filtered through a membrane filter and washed with water. Drying under reduced pressure afforded methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(1S,3S,5S)-2-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[3.1.0]hex-3-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (0.015 g, 55%). $^1$H-NMR: 400 MHz, (MeOD) δ: (Mixture of rotomers) 8.35 (m, 1H), 7.94-7.96 (m, 2H), 7.54-7.78 (m, 6H), 6.93-7.00 (m, 1H), 5.72 (m, 1H), 5.46 (s, 1H), 5.19 (s, 2H), 5.14-5.16 (m, 1H), 3.95 (m, 1H), 3.67 (s, 3H), 3.63 (s, 3H), 3.42-3.49 (m, 2H), 3.24 (s, 3H), 2.67-2.78 (m, 2H), 2.41-2.62 (m, 3H), 2.01-2.13 (m, 2H), 1.86-1.99 (m, 3H), 0.99-1.03 (m, 2H), 0.90 (d, 3H). MS (ESI) *m/z* 882.23 $[M + H]^+$.

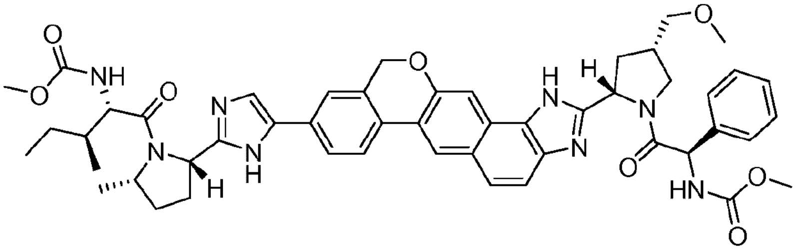
## Example CF



methyl (2*S*,3*S*)-1-((2*S*,5*S*)-2-(5-iodo-1*H*-imidazol-2-yl)-5-methylpyrrolidin-1-yl)-3-methyl-1-oxopentan-2-ylcarbamate

methyl (1-{4-(methoxymethyl)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl)carbamate

tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-isoleucyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate



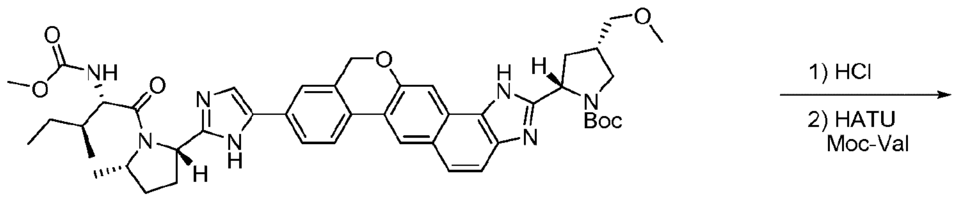
methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S,5S)-1-{(2S,3S)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**Tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-isoleucyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate.** To a solution of methyl (1-{4-(methoxymethyl)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl)carbamate (0.47 g, 0.78 mmol) in a mixture of DMSO (4.0 mL) and dioxane (4.0 mL) was added methyl (2S,3S)-1-((2S,5S)-2-(5-iodo-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl)-3-methyl-1-oxopentan-2-ylcarbamate (0.26 g, 0.72 mmol), tetrakis(triphenylphosphine)palladium (0.090 g, 0.078 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium (0.061g, 0.083 mmol), and aqueous potassium carbonate (2M, 1.2 mL, 2.4 mmol). The solution was degasses with argon for 5 min and heated, with stirring, to 90 °C for 6 h. The solution was cooled to room temperature, diluted with EtOAc, and filtered through celite. The filtrate was concentrated under reduced pressure and diluted with EtOAc. The organic solution was washed water and brine and the aqueous layers were backextracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (10% to 100% EtOAc (5% MeOH)/$CH_2Cl_2$) to afford tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-isoleucyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (0.25 g, 40%).

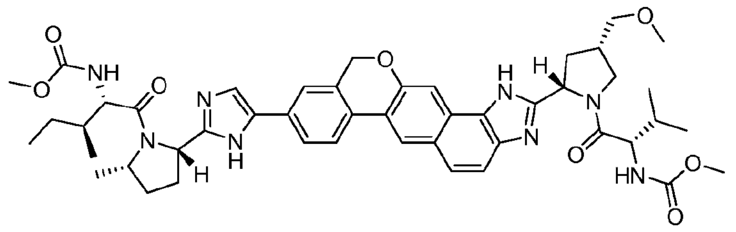
**Methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S,5S)-1-{(2S,3S)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate.** To a solution of tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-isoleucyl]-5-methylpyrrolidin-2-

yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (0.175 g, 0.21 mmol) in a mixture of $CH_2Cl_2$ (2.0 mL) and MeOH (0.5 mL) was added HCl (in dioxanes, 4M, 1.6 mL, 6.4 mmol). The solution was stirred at 40 °C for 1 h, cooled to room temperature, and then concentrated to dryness under reduced pressure. To the crude intermediate suspended in $CH_2Cl_2$ (3.0 mL) was added (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (0.070 g, 0.34 mmol) and DIPEA (0.15 mL, 0.86 mmol). The resulting solution was cooled to -40 °C and COMU (0.15 g, 0.35 mmol) was added. The reaction was warmed to room temperature over 30 min and diluted with $CH_2Cl_2$. The solution was washed with saturated aqueous sodium bicarbonate. The aqueous layer was backextracted with $CH_2Cl_2$, and the combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude residue was purified by preparative reverse phase HPLC (10% to 58% MeCN/water with 0.1% TFA). The desired fractions were combined and concentrated under reduced pressure to remove volatile organics. The addition of aqueous sodium bicarbonate with stirring resulted in precipitation of a white solid. The precipitate was filtered through a membrane filter and washed with water. Drying under reduced pressure afforded methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S,5S)-1-{(2S,3S)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (0.079 g, 41%). $^1$H-NMR: 400 MHz, (MeOD) δ: (Mixture of rotomers) 8.36 (m, 1H), 7.93-7.98 (m, 2H), 7.66-7.84 (m, 3H), 7.35-7.48 (m, 7H), 5.53 (s, 1H), 5.36-5.39 (m, 1H), 5.17 (d, 2H), 5.08 (m, 1H), 4.14-4.35 (m, 1H), 3.74 (m, 4H), 3.64 (s, 3H), 3.62 (s, 3H), 3.46 (m, 1H), 3.19 (s, 3H), 2.76 (m, 1H), 2.46-2.60 (m, 3H), 2.24-2.35 (m, 1H), 2.08-2.18 (m, 2H), 1.91 (m, 1H), 1.61-1.87 (m, 2H), 1.48 (d, 3H), 1.13-1.21 (m, 3H), 0.80-0.97 (m, 3H). MS (ESI) *m/z* 898.24 $[M + H]^+$.

## Example CG



tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-isoleucyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

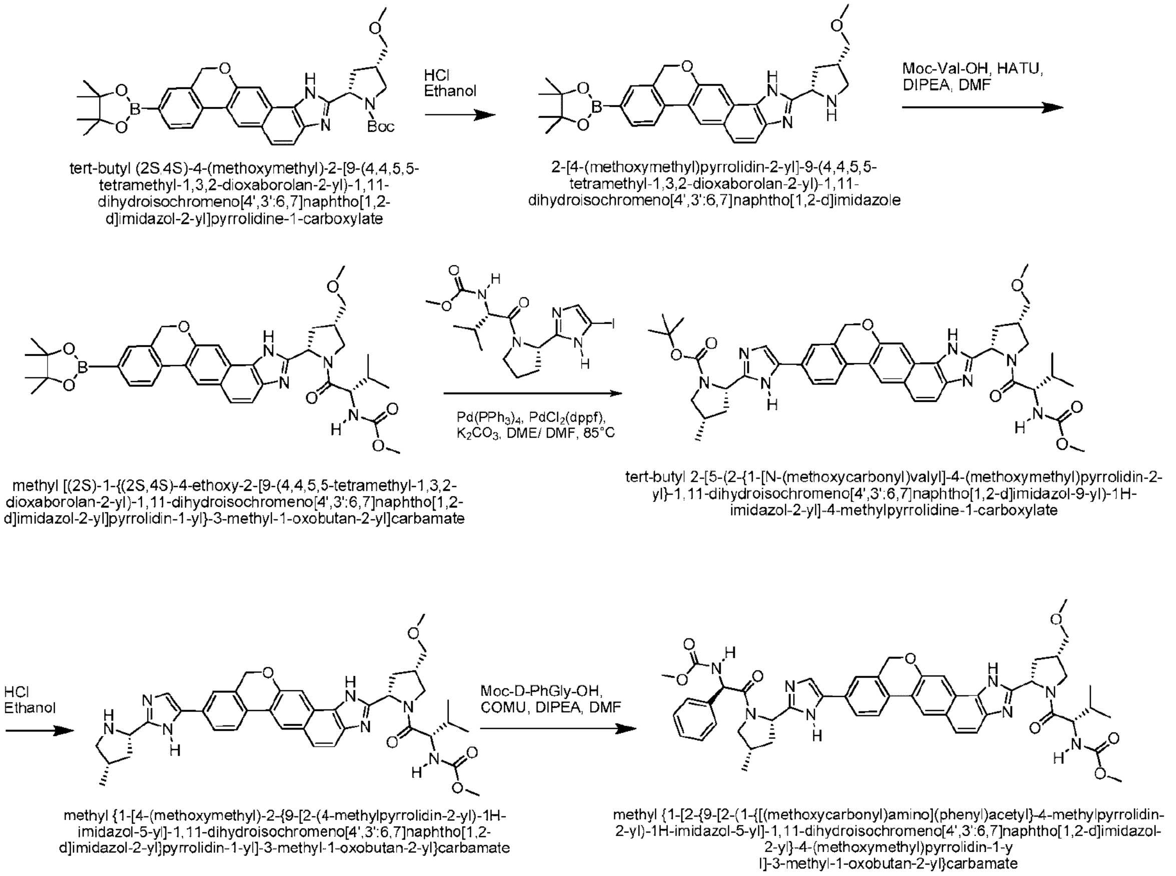


methyl {(2S)-1-[(2S,4S)-2-(9-{2-[(2S,5S)-1-{(2S,3S)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**Methyl {(2S)-1-[(2S,4S)-2-(9-{2-[(2S,5S)-1-{(2S,3S)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate.** To a solution of tert-butyl (2S,4S)-2-[9-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-isoleucyl]-5-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (0.075 g, 0.09 mmol) in a mixture of $CH_2Cl_2$ (1.0 mL) and MeOH (0.25 mL) was added HCl (in dioxanes, 4M, 0.7 mL, 2.8 mmol). The solution was stirred at 40 °C for 1 h, cooled to room temperature, and then concentrated to dryness under reduced pressure. To the crude intermediate suspended in $CH_2Cl_2$ (3.0 mL) was added (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.020 g, 0.14 mmol), HATU (0.043 g, 0.11 mmol) and DIPEA (0.10 mL, 0.57 mmol). The reaction was stirred at room temperature for 2 h. The reaction was diluted with DMF and aqueous LiOH (2.5 M, 3 drops) and the $CH_2Cl_2$ was removed under reduced pressure. The crude residue was purified by preparative reverse phase HPLC (10% to 58% MeCN/water with 0.1% TFA). The desired fractions were combined and concentrated under reduced pressure to remove volatile organics. The addition of aqueous sodium bicarbonate with stirring resulted in precipitation of a white solid. The precipitate was filtered through a membrane filter and washed with water. Drying under reduced pressure afforded methyl {(2S)-1-

[(2S,4S)-2-(9-{2-[(2S,5S)-1-{(2S,3S)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (0.031 g, 38%). $^1$H-NMR: 400 MHz, (MeOD) δ: (Mixture of rotomers) 8.34 (m, 1H), 7.91-9.97 (m, 2H), 7.50-7.81 (m, 3H), 7.35-7.38 (m, 2H), 5.17-5.26 (m, 3H), 5.08 (m, 1H), 4.14-4.33 (m, 4H), 3.64 (s, 3H), 3.63 (s, 3H), 3.51- 3.59 (m, 3H), 3.37 (s, 3H), 2.71 (m, 1H), 2.55-2.59 (m, 1H), 2.23-2.33 (m, 1H), 1.92-2.10 (m, 2H), 1.77-1.89 (m, 1H), 1.60 (m, 1H), 1.48 (d, 1H), 1.11-1.22 (m, 2H), 0.81-0.98 (m, 12H). MS (ESI) *m/z* 864.27 [M + H]$^+$.

## Example CH



tert-butyl (2S,4S)-4-(methoxymethyl)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate

2-[4-(methoxymethyl)pyrrolidin-2-yl]-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazole

methyl [(2S)-1-{(2S,4S)-4-ethoxy-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

tert-butyl 2-[5-(2-{1-[N-(methoxycarbonyl)valyl]-4-(methoxymethyl)pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate

methyl {1-[4-(methoxymethyl)-2-{9-[2-(4-methylpyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

methyl {1-[2-{9-[2-(1-{[(methoxycarbonyl)amino](phenyl)acetyl}-4-methylpyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**tert-butyl (2S,4S)-4-(methoxymethyl)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate:** The title compound was obtained as in Example AA but using (2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid in place of (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid.

**2-[4-(methoxymethyl)pyrrolidin-2-yl]-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazole:** Tert-butyl (2S,4S)-4-(methoxymethyl)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate ( 310mg, 0.507mmol) was treated with 2mL 1.25N HCl in ethanol and stirred at room temperature for 2h then at $50^0$C for 2h. The reaction mixture was concentrated under reduced pressure to give a dark yellow solid that was directly in the next step.

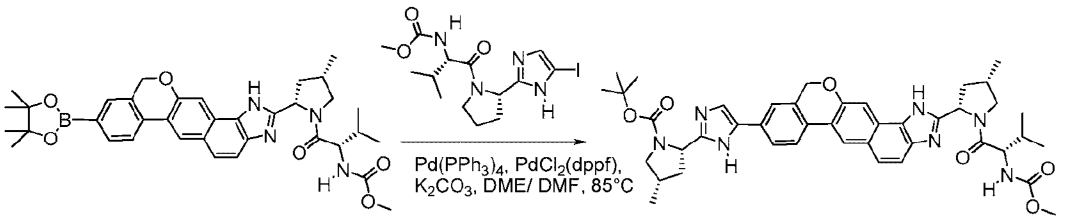
**methyl [(2S)-1-{(2S,4S)-4-ethoxy-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate:** A mixture of (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (107mg, 0.608mmol), HATU (231mg, 0.608mmol) and 6mL 10% DIPEA in DMF was pre-activated for 5 minutes, then it was added to the amine salt from the step above and allowed to stir overnight. The reaction mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic phase was concentrated and purified by silica gel chromatography. (103mg)

**tert-butyl 2-[5-(2-{1-[N-(methoxycarbonyl)valyl]-4-(methoxymethyl)pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate:** the title compound was obtained as in Example AA but using methyl [(2S)-1-{(2S,4S)-4-ethoxy-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate (103mg, 0.154mmol) in place of tert-butyl 2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate and methyl (S)-1-((S)-2-(5-iodo-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (58mg, 0.154mmol)in place of methyl (S)-1-((S)-2-(5-bromo-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate. (50.0mg)

**methyl {1-[4-(methoxymethyl)-2-{9-[2-(4-methylpyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** tert-butyl 2-[5-(2-{1-[N-(methoxycarbonyl)valyl]-4-(methoxymethyl)pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (50mg, 0.063mmol) was treated with 2mL 1.25N HCl in ethanol and heated at $60^0$C for 2h, then it was concentrated under reduced pressure and pumped dry under high vacuum and used directly in the next step.

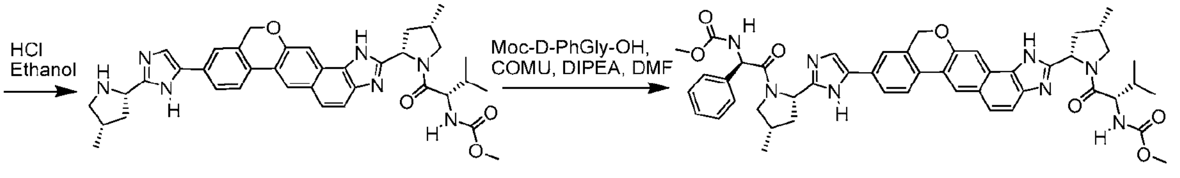
**methyl {1-[2-{9-[2-(1-{[(methoxycarbonyl)amino](phenyl)acetyl}-4-methylpyrrolidin-2-yl)-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl}-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate :** A mixture of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (13mg, 0.063mmol), COMU (30mg, 0.069mmol) in 0.500mL DMF and DIPEA (0.033mL, 0.189mmol) was allowed to preactivate for 15 minutes before it was added to the solid crude amine salt from the previous step and stirred overnight. The product was purified by reverse phase HPLC. The product was converted to the free base by dissolution in 2mL 1:1 acetonitrile:methanol and passage through a prepacked cartridge of polymer supported carbonate. Concentration and drying gave an off white powder. (23.3mg). MS (ESI) *m/z* 883.8 $[M + H]^+$ $^1H$ NMR ($CD_3CN$) 8.176 (s, 1H), 7.778 (m, 1H), 7.596-7.521 (m, 4H), 7.455-7.347 (m, 6H), 7.218 (s, 1H), 5.482 (s, 1H), 5.310 (m, 1H), 5.192 (m, 1H), 4.999 (q, 2H, *J*= 14 Hz), 4.372 (d, 1H, *J*= 6.4 Hz), 4.279 (m, 1H), 3.800-3.697 (m, 2H), 3.632 (s, 3H) 3.597-3.445 (m, 7H), 3.355 (s, 3H), 2.876 (m, 2H), 2.761 (m, 1H), 2.583 (m, 2H), 2.220 (m, 2H), 1.764 (m, 1H), 1.070 (d, 3H, *J* = 6.4 Hz), 1.020 (d, 3H, *J* = 6.4 Hz), 0.898 (d, 3H, *J* = 6.4 Hz).

## Example CI



methyl [(2S)-3-methyl-1-{(2S,4S)-4-methyl-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate

tert-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate



methyl {(2S)-3-methyl-1-[(2S,4S)-4-methyl-2-(9-{2-[(2S,4S)-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1-yl]-1-oxobutan-2-yl}carbamate

methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

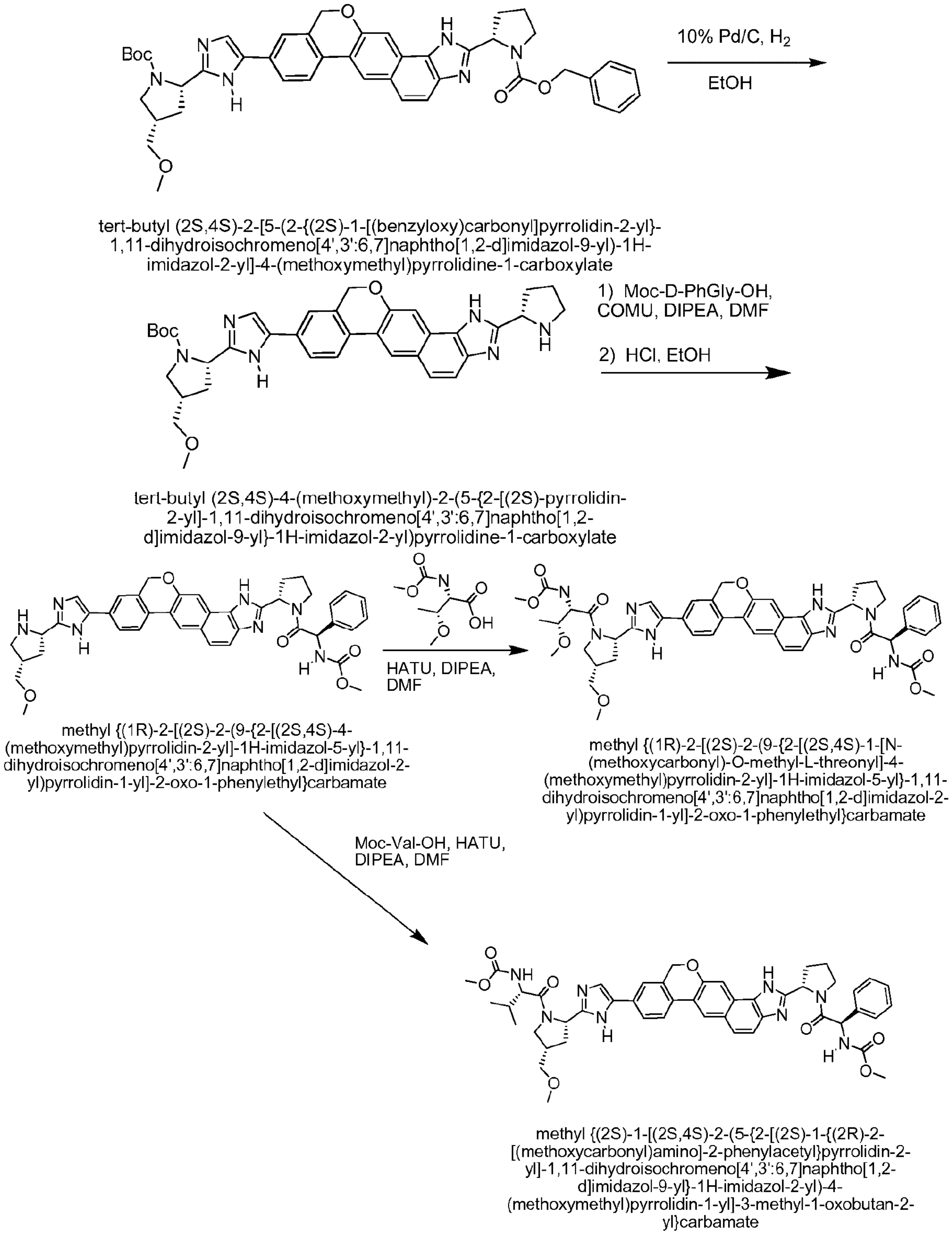
**tert-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate:** The title compound was obtained as in Example AA but using methyl [(2S)-3-methyl-1-{(2S,4S)-4-methyl-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate (307mg, 0.481mmol) in place of tert-butyl 2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidine-1-carboxylate and methyl (S)-1-((S)-2-(5-iodo-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (181mg, 0.481mmol)in place of methyl (S)-1-((S)-2-(5-bromo-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate. (200.8mg)

**methyl {(2S)-3-methyl-1-[(2S,4S)-4-methyl-2-(9-{2-[(2S,4S)-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1-yl]-1-oxobutan-2-yl}carbamate:** Tert-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (200mg, 0.262mmol) was treated with 2mL 1.25N HCl in ethanol and heated at 60$^0$C for 2h, then it was concentrated under reduced pressure and pumped dry under high vacuum and used directly in the next step.

**methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate:** A mixture of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (13mg, 0.063mmol), COMU (30mg, 0.069mmol) in 1.5mL DMF was allowed to preactivate for 5 minutes before it was added to a solution of the amine from the previous salt in 1.5mL DMF and DIPEA (0.137mL, 0.786mmol) and stirred overnight. The product was purified by reverse phase HPLC. The product was converted to the free base by dissolution in 2mL 1:1 acetonitrile:methanol and passage through a prepacked cartridge of polymer supported carbonate. Concentration and drying gave an off white powder. (25.8mg). MS (ESI) *m/z* 853.8 $[M + H]^+$. $^1$H NMR ($CD_3CN$) 8.164 (s, 1H), 7.781 (m, 1H), 7.609 (m, 2H), 7.535 (m, 2H), 7.433-7.305 (m, 6H), 7.229 (s, 1H), 5.482 (s, 1H), 5.290 (m, 1H), 5.191 (m, 1H), 4.997 (m, 2H), 4.372 (d, 1H, *J*= 6.4 Hz), 4.267 (m, 1H), 3.735-3.445 (m, 10H), 2.573 (m, 4H), 2.197 (m, 2H), 2.017 (m, 1H), 1.760

(m, 1H), 1.204 (d, 3H, *J*= 6.4 Hz), 1.068 (d, 3H, *J* = 6.4 Hz), 1.010 (d, 3H, *J* = 6.8 Hz), 0.887 (d, 3H, *J* = 6.8 Hz).

## Example CJ



tert-butyl (2S,4S)-2-[5-(2-{(2S)-1-[(benzyloxy)carbonyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

tert-butyl (2S,4S)-4-(methoxymethyl)-2-(5-{2-[(2S)-pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

methyl {(1R)-2-[(2S)-2-(9-{2-[(2S,4S)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

methyl {(1R)-2-[(2S)-2-(9-{2-[(2S,4S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**tert-butyl (2S,4S)-2-[5-(2-{(2S)-1-[(benzyloxy)carbonyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate:** The title compound was obtained as in Example BO (compound tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate) but using (S)-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid in place of (2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylic acid in step 6

**tert-butyl (2S,4S)-4-(methoxymethyl)-2-(5-{2-[(2S)-pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidine-1-carboxylate:** A mixture of tert-butyl (2S,4S)-2-[5-(2-{(2S)-1-[(benzyloxy)carbonyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (724mg, 0.96mmol) and 70mg 10%Pd/C in 20mL ethanol was hydrogenated at 1atm overnight. Additional 10%Pd/C (300mg) and a portion of solid NaHCO3 was added and hydrogenation continued for 4 hours. Filtration through celite and concentration of the filtrate under reduced pressure gave the product as a dark brown solid, 454mg. Purification by reverse phase HPLC gave 65mg purified product.

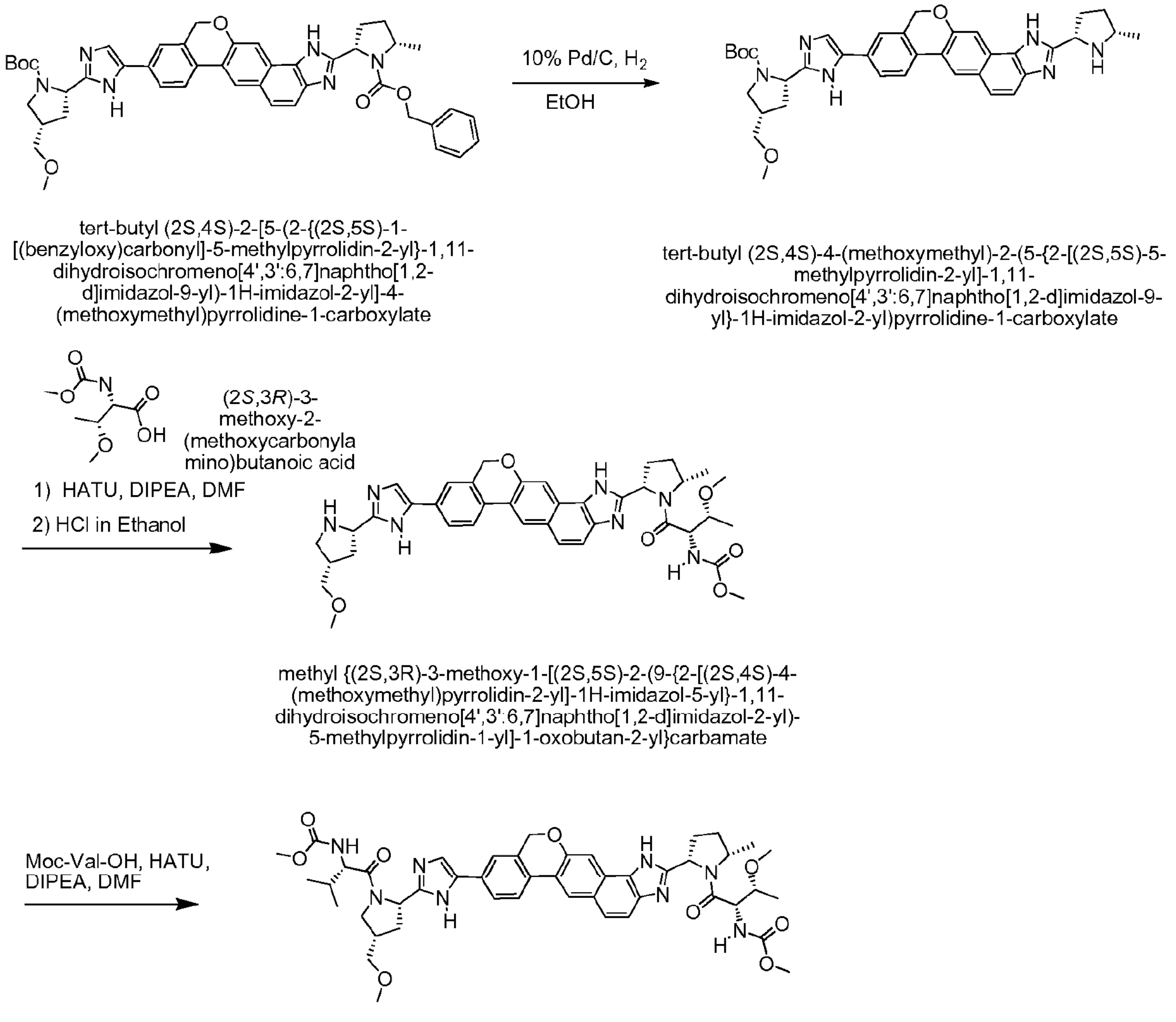
**methyl {(1R)-2-[(2S)-2-(9-{2-[(2S,4S)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate:** A mixture of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (22mg, 0.105mmol), COMU (45mg, 0.069mmol), and tert-butyl (2S,4S)-4-(methoxymethyl)-2-(5-{2-[(2S)-pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (65mg, 0.105mmol) in 1.5mL 10% DIPEA in DMF was stirred for 1.5h. The reaction mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic phase was dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude intermediate was treated with 8mL 1.25N HCl in ethanol at $50^0$C for 4h. Added saturated sodium bicarbonate and extracted the free base into dichloromethane. (106mg)

**methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-**

**oxobutan-2-yl}carbamate:** A mixture of methyl {(1R)-2-[(2S)-2-(9-{2-[(2S,4S)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (55mg, 0.077mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (14mg, 0.077mmol), HATU (32mg, 0.085mmol) and 0.4mL 10% DIPEA in DMF was stirred at room temperature for 1 hour. The product was purified by reverse phase HPLC. The product was converted to the free base by dissolution in 2mL 1:1 acetonitrile:methanol and passage through a prepacked cartridge of polymer supported carbonate. The eluent was concentrated, the taken up in 1%TFA in 1:1 acetonitrile:water, frozen, and lyophilized to give the product as a trifluoroacetate salt. (30.7mg) MS (ESI) *m/z* 869.9 $[M + H]^+$.

**methyl {(1R)-2-[(2S)-2-(9-{2-[(2S,4S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate:** A mixture of methyl {(1R)-2-[(2S)-2-(9-{2-[(2S,4S)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (51mg, 0.072mmol), (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (14mg, 0.072mmol), HATU (30mg, 0.079mmol) and 0.4mL 10% DIPEA in DMF was stirred at room temperature for 1 hour. The product was purified by reverse phase HPLC. The product was converted to the free base by dissolution in 2mL 1:1 acetonitrile:methanol and passage through a prepacked cartridge of polymer supported carbonate. The eluent was concentrated, the taken up in 1%TFA in 1:1 acetonitrile:water, frozen, and lyophilized to give the product as a trifluoroacetate salt. (24mg). MS (ESI) *m/z* 885.8 $[M + H]^+$; $^1$H NMR ($CD_3CN$) 7.635 (s, 1H), 7.434 (m, 3H), 7.330 (m, 4H), 7.233 (m, 1H), 7.164 (m, 1H), 6.983 (m, 1H), 6.747 (m, 2H), 6.127 (m, 1H), 5.584 (d, 1H, *J* = 6.4 Hz), 5.431 (m, 1H), 5.145 (m, 1H), 4.729 (s, 2H), 4.442 (m, 1H), 4.029 (m, 2H), 3.838 (m, 1H), 3.662-3.534 (m, 2H), 3.572 (s, 3H) 3.552 (s, 3H), 3.444-3.310 (m, 3H), 3.240 (s, 3H), 3.225 (s, 3H), 2.618 (m, 1H), 2.464 (m, 1H), 2.304 (m, 1H), 2.129 (m, 1H), 2.041 (m, 1H), 1.899 (m, 2H), 1.107 (d, 3H, *J* = 6.4 Hz).

## Example CK



tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[(benzyloxy)carbonyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

tert-butyl (2S,4S)-4-(methoxymethyl)-2-(5-{2-[(2S,5S)-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

methyl {(2S,3R)-3-methoxy-1-[(2S,5S)-2-(9-{2-[(2S,4S)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-1-oxobutan-2-yl}carbamate

methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S,3R)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

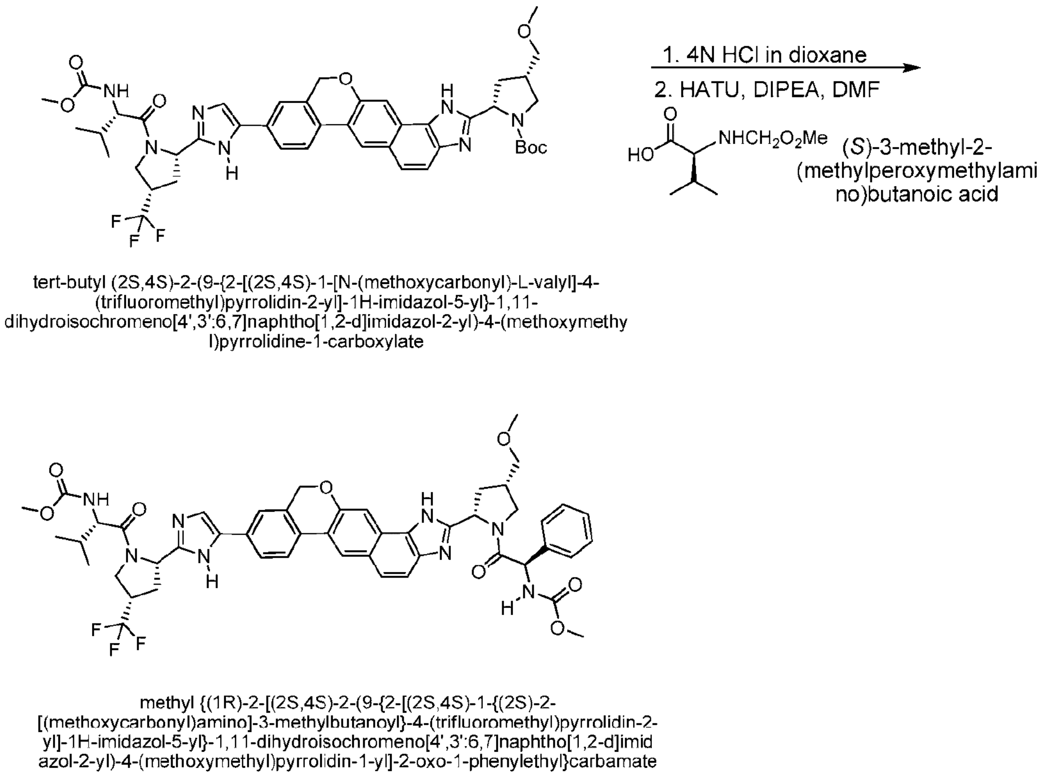
**tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[(benzyloxy)carbonyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate:** The title compound was obtained as in Example BO (compound tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate) but using (2S,5S)-1-(benzyloxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid in place of (2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylic acid.

**tert-butyl (2S,4S)-4-(methoxymethyl)-2-(5-{2-[(2S,5S)-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidine-1-carboxylate:** A mixture of 683A (830mg, 1.08mmol) and 100mg 10%Pd/C in 20mL ethanol was hydrogenated at 1atm overnight. Additional 10%Pd/C (300mg) and a portion of solid NaHCO3 was added and hydrogenation continued for 4 hours. Filtration through celite and concentration of the filtrate under reduced pressure gave the product as a dark brown solid, 722mg. Purification by reverse phase HPLC gave 100mg purified product.

**tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate:** A mixture of tert-butyl (2S,4S)-4-(methoxymethyl)-2-(5-{2-[(2S,5S)-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (101mg, 0.159mmol), (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (30mg, 0.159mmol), HATU (61mg, 0.159mmol) and 2mL 10% DIPEA in DMF was stirred at room temperature for 1.5 hours. Saturated sodium bicarbonate was added and the product was extracted into dichloromethane, dried over sodium sulphate, filtered and concentrated under reduced pressure. This crude product was treated with 5mL 1.25N HCl in ethanol at $50^0$C for 4h and then it was concentrated under reduced pressure. Saturated sodium bicarbonate was added and the product was extracted into dichloromethane, dried over sodium sulphate, filtered and concentrated under reduced pressure. (74.6mg)

**methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S,3R)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** A mixture of methyl {(2S,3R)-3-methoxy-1-[(2S,5S)-2-(9-{2-[(2S,4S)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-1-oxobutan-2-yl}carbamate (74.6mg, 0.105mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (18.5mg, 0.105mmol), HATU (44mg, 0.116mmol) and 0.6mL 10% DIPEA in DMF was stirred at room temperature for 1 hour. The product was purified by reverse phase HPLC. (48.1mg) MS (ESI) *m/z* 866.1 $[M + H]^+$.

## Example CL



tert-butyl (2S,4S)-2-(9-{2-[(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-(trifluoromethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate

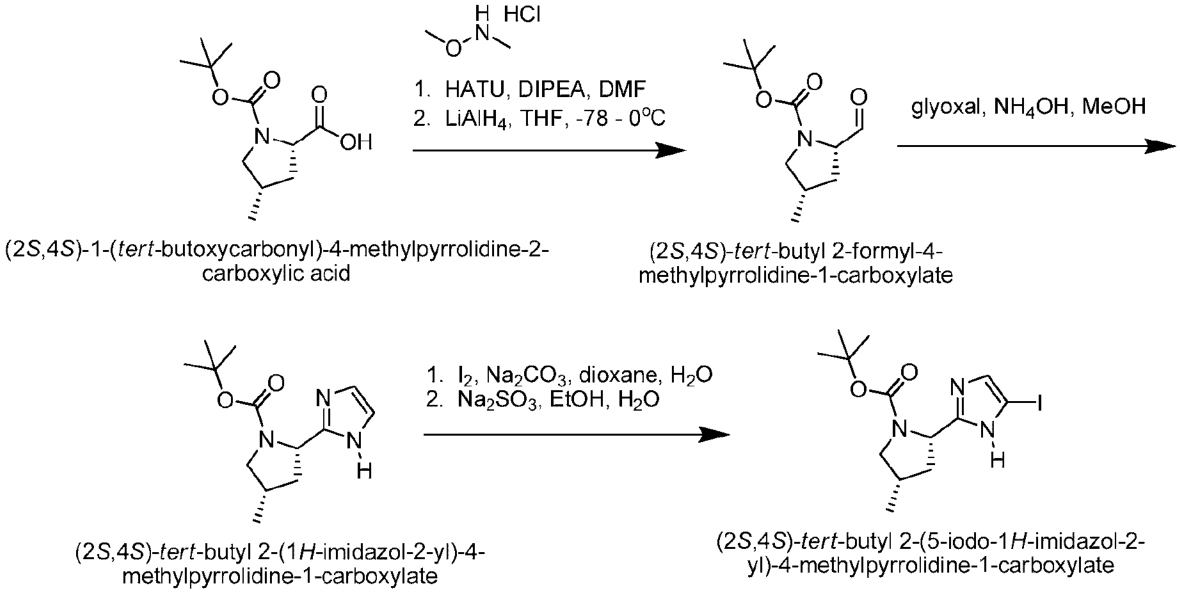
methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-(trifluoromethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**tert-butyl (2S,4S)-2-(9-{2-[(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-(trifluoromethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate:** the title compound was prepared as in Example BO for compound tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate, by using (2S,4S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-4-(trifluoromethyl)pyrrolidine-2-carboxylic acid in place of (2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid and (2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid in place of (2S,5S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-5-methylpyrrolidine-2-carboxylic acid.

**methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-(trifluoromethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate:** tert-butyl (2S,4S)-2-

(9-{2-[(2S,4S)-1-[N-(methoxycarbonyl)-L-valyl]-4-(trifluoromethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate (<0.412mmol, crude from previous step) was treated with 6mL 4N HCl in dioxane at room temperature overnight and then at 50$^{O}$C for 1 hour. Diethyl ether (20mL) was added and the precipitate of hydrochloride salt was collected by vacuum filtration. (126mg, 0.16mmol). This material was combined with (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (34mg, 0.16mmol), COMU (70mg, 0.16mmol), and 1.6mL of 10% DIPEA in DMF. After 1 hour at room temperature, the mixture was added dropwise into 25mL saturated sodium bicarbonate, with stirring and the resulting precipitate was collected by vacuum filtration and washed with 2mL water. The product was purified, then re-purified by reverse phase HPLC. (3.5mg). MS (ESI) *m/z* 938.1 $[M + H]^+$.

## Example CM



(2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid

(2*S*,4*S*)-*tert*-butyl 2-formyl-4-methylpyrrolidine-1-carboxylate

(2*S*,4*S*)-*tert*-butyl 2-(1*H*-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate

(2*S*,4*S*)-*tert*-butyl 2-(5-iodo-1*H*-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate

**(2S,4S)-tert-butyl 2-formyl-4-methylpyrrolidine-1-carboxylate:** A mixture of (2S,4S)-1-(tert-butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid (5.2g, 22.7 mmol), O,N-dimethylhydroxylamine hydrochloride (2.4g, 24.9mmol), HATU (10.4g, 27.2mmol) and DIPEA (9.5mL, 54.5mmol) in 114mL DMF was stirred at room temperature overnight. The mixture was extracted into ethyl acetate and washed with saturated bicarbonate and water, dried over sodium sulphate, filtered, and concentrated. It was then dissolved in diethyl ether (100mL) and washed with water to remove residual DMF, dried, filtered, and concentrated to a pale yellow oil (5.30g, 19.5mmol) of (2S,4S)-tert-butyl 2-(methoxy(methyl)carbamoyl)-4-methylpyrrolidine-1-carboxylate.

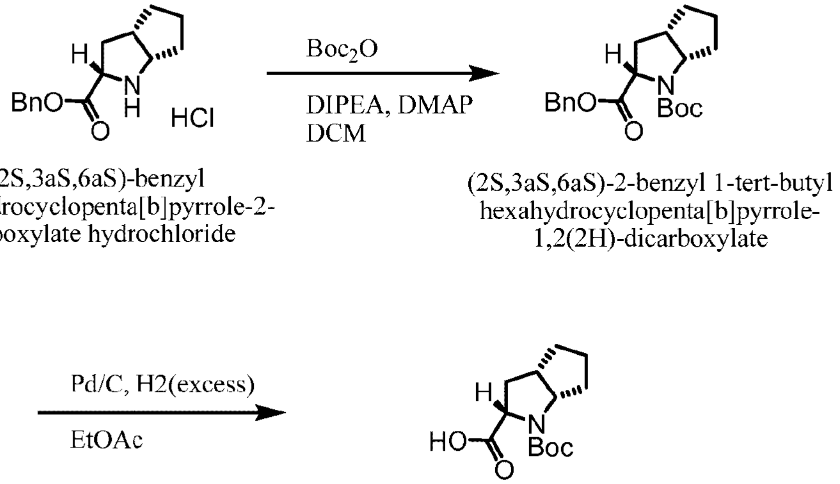
(2S,4S)-tert-butyl 2-(methoxy(methyl)carbamoyl)-4-methylpyrrolidine-1-carboxylate (5.30g, 19.5mmol) was dissolved in 120mL THF, cooled to -78$^{O}$C and treated with lithium aluminium hydride (1M in THF, 19.5mL, 19.5mmol) dropwise *via* addition funnel. After 1 hour, the mixture was brought to 0$^{O}$C and kept at that temperature for 2 hours. It was quenched by dropwise addition of a 50mL solution of 3.0g KHSO4 in water, removed from the ice bath, and stirred 15 minutes at room temperature. The product was extracted with three 75mL portions of ethyl acetate and washed with brine. The organic phase was dried over sodium sulphate, filtered, and concentrated to give crude (2S,4S)-tert-butyl 2-formyl-4-methylpyrrolidine-1-carboxylate. (4.89g)

**(2S,4S)-tert-butyl 2-(1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate:** To a solution of (2S,4S)-tert-butyl 2-formyl-4-methylpyrrolidine-1-carboxylate (4.89g, 22.9mmol), ammonium hydroxide (17mL) and water (17mL) was added, dropwise, glyoxal (40% in water, 14.6mL, 128mmol) and the resulting mixture was stirred at room temperature overnight. Saturated sodium bicarbonate (100mL) was added and the mixture was extracted with four 75mL portions of dichloromethane. The organic phase was washed with water, dried over sodium sulphate, filtered and concentrated, and then purified by silica gel chromatography to give a total of 3.76g product.

**(2S,4S)-tert-butyl 2-(5-iodo-1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate:** A mixture of (2S,4S)-tert-butyl 2-(1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (1.0g, 3.97mmol), iodine (2.22g, 8.75mmol) and sodium carbonate (1.3g, 12.31mmol) in 20mL dioxane and 13.25mL water was covered in foil and stirred at room temperature overnight. The mixture was diluted with ethyl acetate and treated with 10% sodium thiosulfate (5mL) and stirred for 10 minutes. The organic phase was washed with brine, and then the aqueous phase was back extracted with ethyl acetate. The combined organic phases were dried over sodium sulphate, filtered and concentrated to provide crude (2S,4S)-tert-butyl 2-(4,5-diiodo-1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (2.25g) as a pale yellow solid.

A solution of (2S,4S)-tert-butyl 2-(4,5-diiodo-1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (2.25g, 4.4mmol) in 18mL ethanol and 18mL water was treated with sodium sulfite (5.59g, 44.4 mmol) and heated at 90 $^{O}$C overnight. The mixture was partitioned between ethyl acetate and water. The aqueous phase was extracted with more ethyl acetate and the combined organic phase was washed with brine, dried over sodium sulphate, filtered, concentrated, and purified by silica gel chromatography to give 766mg (2S,4S)-tert-butyl 2-(5-iodo-1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate.

### Example CN



(2S,3aS,6aS)-benzyl octahydrocyclopenta[b]pyrrole-2-carboxylate hydrochloride

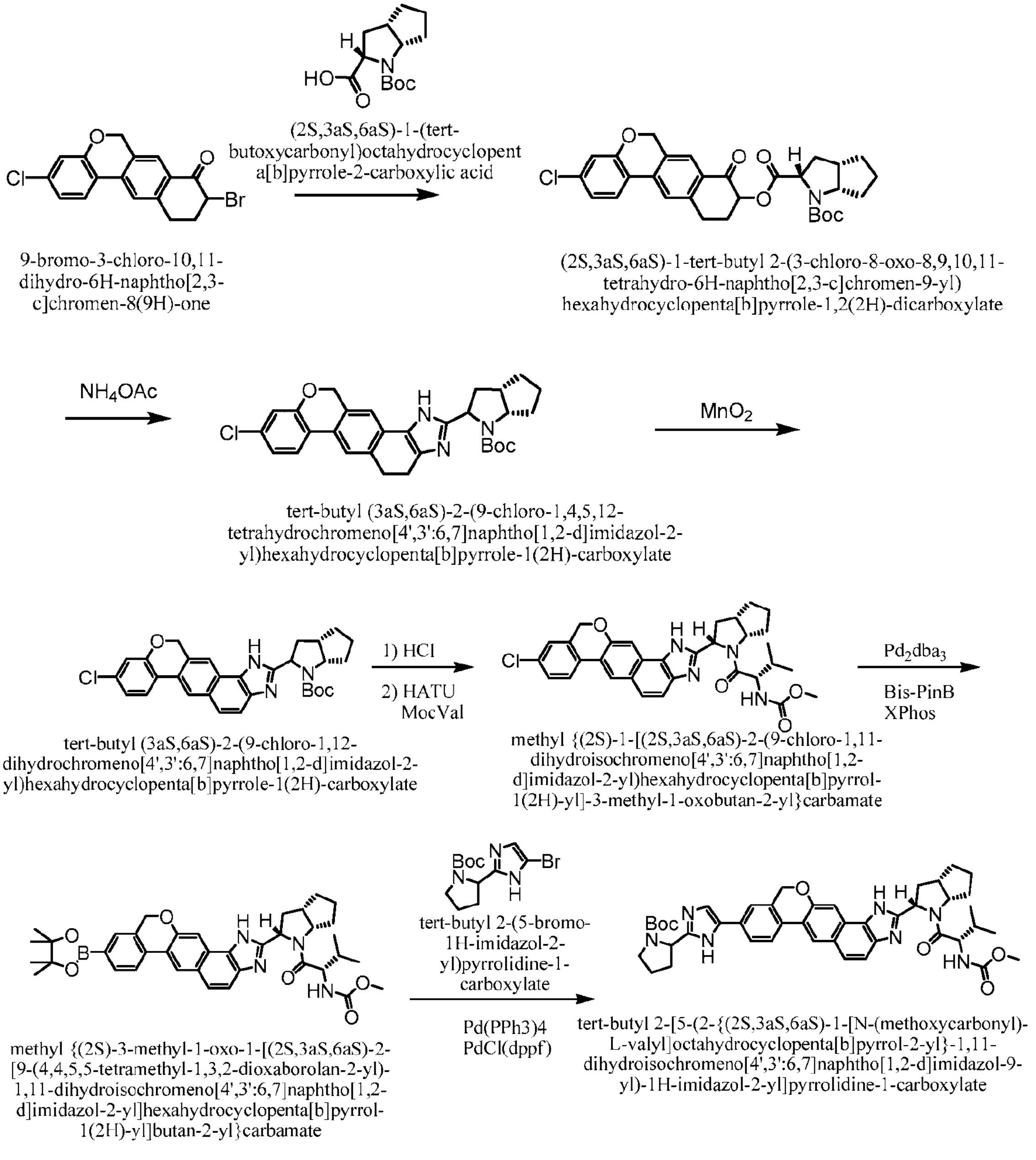
(2S,3aS,6aS)-2-benzyl 1-tert-butyl hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate

(2S,3aS,6aS)-1-(tert-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid

**(2S,3aS,6aS)-2-benzyl 1-tert-butyl hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate**: To a solution of comercially avaliable (2S,3aS,6aS)-2-benzyl 1-tert-butyl hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate (4.70 g, 16.68 mmol) in methylene chloride (42 mL) was added Di-tert-butyl dicarbonate (7.28 g, 33.36 mmol) N,N-diisopropylethylamine (5.82 mL, 33.36 mmol) and 4-(Dimethylamino)pyridine (0.20 g, 1.67 mmol). The solution was sirred under air for 16 hours. Upon completion, the reaction was concentrated in vacuo, diluted in ethyl acetate, and washed with 1N HCl. The aqueous layers were backextracted twice with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel chromatrography (5-40% ethyl acetate in hexanes) to afford (2S,3aS,6aS)-2-benzyl 1-tert-butyl hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate which was used without further purification. MS (ESI) *m/z* 368.47 $[M + Na]^+$.

**(2S,3aS,6aS)-1-(tert-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid**: To a 250mL round bottom flask charged with a stirbar and (2S,3aS,6aS)-2-benzyl 1-tert-butyl hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate (5.76 g, 16.68 mmol) was added 10% Palladium on carbon (1.77g). Ethanol was poured over the mixture and the reaction mixture was evacuated and flushed with hydrogen gas three times. The suspension was sitrred at room temperature under and atmosphere of hydrogen for 24 hours. Upon completion, the reaction mixture was filtered through celite and concentrated to give (2S,3aS,6aS)-1-(tert-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid (4.45g, >99%). MS (ESI) *m/z* 256.21 $[M + H]^+$.

## Example CO



(2S,3aS,6aS)-1-(tert-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid

9-bromo-3-chloro-10,11-dihydro-6H-naphtho[2,3-c]chromen-8(9H)-one

(2S,3aS,6aS)-1-tert-butyl 2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-6H-naphtho[2,3-c]chromen-9-yl) hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate

$NH_4OAc$

tert-butyl (3aS,6aS)-2-(9-chloro-1,4,5,12-tetrahydrochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate

$MnO_2$

tert-butyl (3aS,6aS)-2-(9-chloro-1,12-dihydrochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate

1) HCl

2) HATU MocVal

methyl {(2S)-1-[(2S,3aS,6aS)-2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)hexahydrocyclopenta[b]pyrrol-1(2H)-yl]-3-methyl-1-oxobutan-2-yl}carbamate

$Pd_2dba_3$

Bis-PinB

XPhos

methyl {(2S)-3-methyl-1-oxo-1-[(2S,3aS,6aS)-2-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]hexahydrocyclopenta[b]pyrrol-1(2H)-yl]butan-2-yl}carbamate

tert-butyl 2-(5-bromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

Pd(PPh3)4

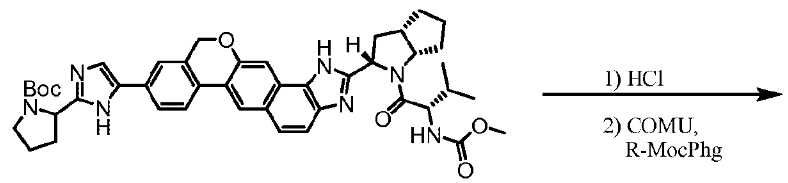
PdCl(dppf)

tert-butyl 2-[5-(2-{(2S,3aS,6aS)-1-[N-(methoxycarbonyl)-L-valyl]octahydrocyclopenta[b]pyrrol-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate

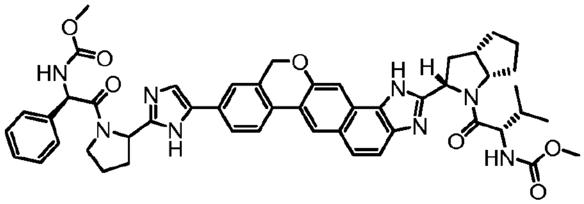
**tert-butyl 2-[5-(2-{(2S,3aS,6aS)-1-[N-(methoxycarbonyl)-L-valyl]octahydrocyclopenta[b]pyrrol-2-yl}-1,11-**

**dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate**: This compound was made in an analogous manner to tert-butyl (2R)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate subsitituing (2S,3aS,6aS)-1-(tert-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid for the innitial alkylation of 9-bromo-3-chloro-10,11-dihydro-6H-naphtho[2,3-c]chromen-8(9H)-one. Reactions in the synthesis of tert-butyl 2-[5-(2-{(2S,3aS,6aS)-1-[N-(methoxycarbonyl)-L-valyl]octahydrocyclopenta[b]pyrrol-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate gave similar product yields as in the synthesis of tert-butyl (2R)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate. MS (ESI) *m/z* 774.1 $[M + H]^+$.

## Example CP



tert-butyl 2-[5-(2-{(2S,3aS,6aS)-1-[N-(methoxycarbonyl)-L-valyl]octahydrocyclopenta[b]pyrrol-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate

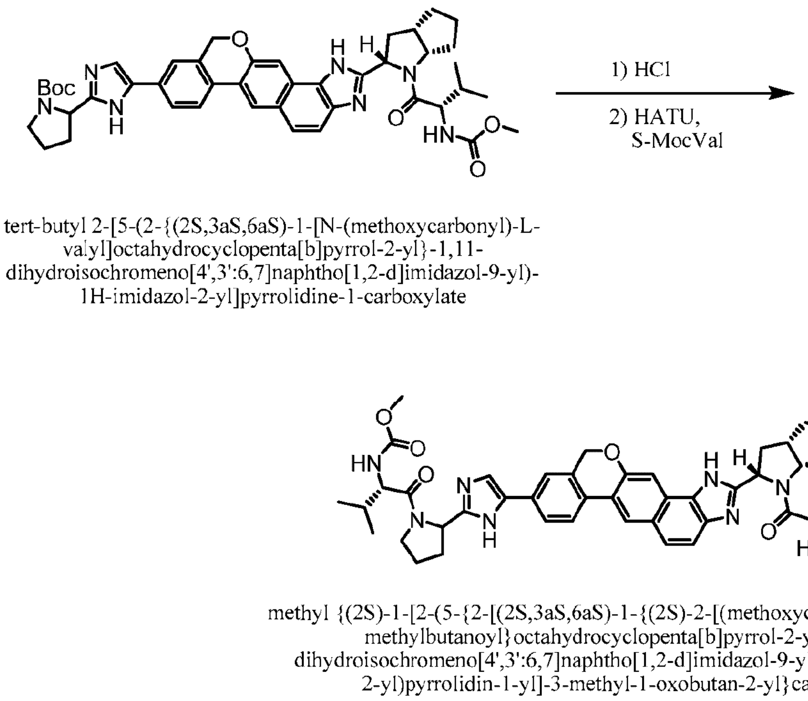


methyl {(1R)-2-[2-(5-{2-[(2S,3aS,6aS)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[b]pyrrol-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**methyl {(1R)-2-[2-(5-{2-[(2S,3aS,6aS)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[b]pyrrol-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate**: To a solution of tert-butyl 2-[5-(2-{(2S,3aS,6aS)-1-[N-(methoxycarbonyl)-L-valyl]octahydrocyclopenta[b]pyrrol-2-yl}-1,11-

dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate (0.128 g, 0.165 mmol) in a mixture of $CH_2Cl_2$ (1.6 mL) and MeOH (0.33 mL) was added HCl (4M in 1,4-dioxane, 1.24 mL, 4.9 mmol). The solution was stirred at room temperature for 1.5 h and concentrated to dryness. The intermediate was dissolved in $CH_2Cl_2$ (1.6 mL). (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (0.052 g, 0.25 mmol) and DIPEA (0.087 mL, 0.496 mmol) were then added to the solution. The reaction mixture was cooled to -40 °C (external temperature, MeCN/$CO_2$(s) bath). COMU (0.113 g, 0.265 mmol) was then added and solution was allowed to warm to 0 °C over 1.5 h. Upon completion by LCMS, the solution was diluted with DMF and concentrated. The crude product was purified by preperative HPLC (Gemini column, 10-47% MeCN/$H_2O$ with 0.1% TFA) and the desired fractions were combined. The solution was concentrated until the aqueous layer remained and aqueous bicarbonate (sat.) was slowly added until the solution was basic. The resulting slurry was stirred at room temperature for 2h and filtered. The resulting solid was dried *in vacuo* to provide methyl {(1R)-2-[2-(5-{2-[(2S,3aS,6aS)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[b]pyrrol-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (0.068 g, 48%). MS (ESI) *m/z* 865.7 $[M + H]^+$. $^1H$ NMR (400 MHz, $cd_3od$) δ 8.44 – 8.30 (m, 1H), 8.02 – 7.82 (m, 2H), 7.81 – 7.58 (m, 4H), 7.50 – 7.11 (m, 6H), 7.09 – 6.83 (m, 2H), 5.72 – 5.45 (m, 2H), 5.41 (s, 1H), 5.34 – 5.28 (m, 1H), 5.22 (s, 3H), 4.69 – 4.64 (m, 1H), 4.26 – 4.19 (m, 1H), 4.03 – 3.98 (m, 1H), 3.96 – 3.91 (m, 1H), 3.66 (d, 4H), 2.98 – 2.91 (m, 1H), 2.88 – 2.83 (m, 1H), 2.58 – 2.48 (m, 1H), 2.27 – 2.12 (m, 4H), 2.11 – 2.00 (m, 3H), 2.00 – 1.89 (m, 2H), 1.77 – 1.72 (m, 1H), 1.31 – 1.04 (m, 3H), 0.93 (d, 6H).

## Example CQ



tert-butyl 2-[5-(2-{(2S,3aS,6aS)-1-[N-(methoxycarbonyl)-L-valyl]octahydrocyclopenta[b]pyrrol-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate

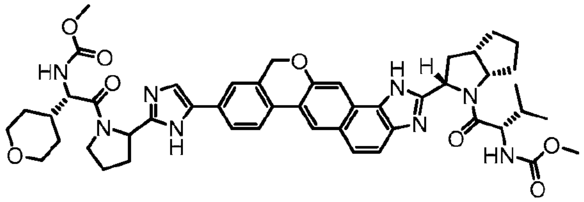
methyl {(2S)-1-[2-(5-{2-[(2S,3aS,6aS)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[b]pyrrol-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**methyl {(2S)-1-[2-(5-{2-[(2S,3aS,6aS)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[b]pyrrol-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate**: To a solution of tert-butyl 2-[5-(2-{(2S,3aS,6aS)-1-[N-(methoxycarbonyl)-L-valyl]octahydrocyclopenta[b]pyrrol-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate (0.030 g, 0.039 mmol) in a mixture of $CH_2Cl_2$ (0.39 mL) and MeOH (0.078 mL) was added HCl (4M in 1,4-dioxane, 0.29 mL, 1.16 mmol). The solution was stirred at room temperature for 1.5 h and concentrated to dryness.

The intermediate was dissolved in $CH_2Cl_2$ (0.39 mL). (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.007 g, 0.043 mmol) and DIPEA (0.020 mL, 0.116 mmol) were then added to the solution. HATU (0.018 g, 0.047 mmol) was added and solution was allowed to stir at room temp. Upon completion, the solution was diluted with DMF and concentrated. The crude product was purified by preperative HPLC (Gemini column, 10-47% MeCN/$H_2O$ with 0.1% TFA) and the desired fractions were combined and lyophilized to provide methyl {(2S)-1-[2-(5-{2-[(2S,3aS,6aS)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[b]pyrrol-2-yl]-1,11-

dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (0.010g, 31%). MS (ESI) *m/z* 832.2 $[M + H]^+$.

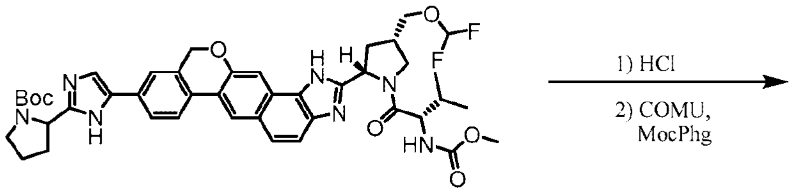
## Example CR



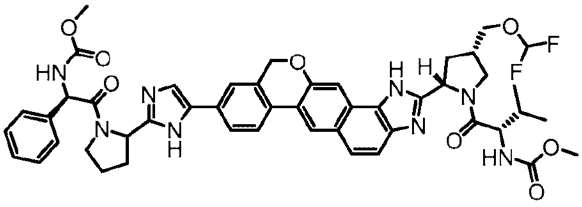
methyl [(1S)-2-[2-(5-{2-[(2S,3aS,6aS)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[b]pyrrol-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl]carbamate

**methyl [(1S)-2-[2-(5-{2-[(2S,3aS,6aS)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[b]pyrrol-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl]carbamate:** This compound was made in an analogous manner to methyl {(2S)-1-[2-(5-{2-[(2S,3aS,6aS)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[b]pyrrol-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate, substituting (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid for (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid to give methyl [(1S)-2-[2-(5-{2-[(2S,3aS,6aS)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[b]pyrrol-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl]carbamate (0.039, 56%). MS (ESI) *m/z* 874.34 $[M + H]^+$. $^1$H NMR (400 MHz, $cd_3od$) δ 8.58 (s, 2H), 8.26 – 8.08 (m, 2H), 7.96 – 7.75 (m, 4H), 7.65 – 7.54 (m, 5H), 5.36 – 5.11 (m, 4H), 4.34 – 4.04 (m, 4H), 3.97 – 3.79 (m, 4H), 3.65 (s, 4H), 3.53 – 3.44 (m, 2H), 2.68 – 2.47 (m, 4H), 2.32 – 2.02 (m, 7H), 1.95 – 1.82 (m, 3H), 1.77 – 1.54 (m, 4H), 1.49 – 1.24 (m, 5H), 1.10 – 0.99 (m, 3H), 0.92 – 0.85 (m, 4H).

## Example CS



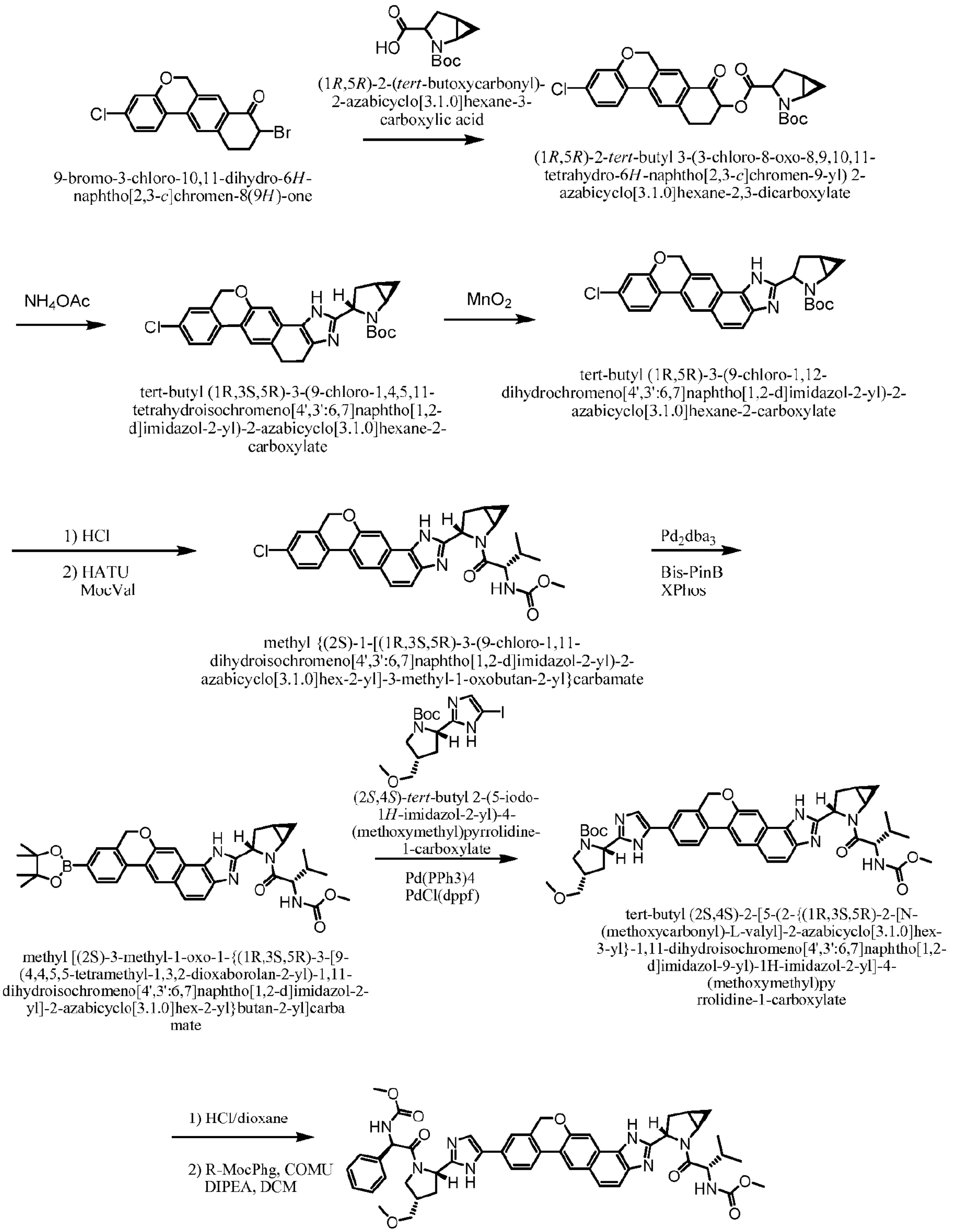
tert-butyl 2-[5-(2-{(2S,4S)-4-[(difluoromethoxy)methyl]-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate



methyl {(1R)-2-[2-(5-{2-[(2S,4S)-4-[(difluoromethoxy)methyl]-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**tert-butyl 2-[5-(2-{(2S,4S)-4-[(difluoromethoxy)methyl]-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate**: This compound was made in an analogous manner to tert-butyl 2-[5-(2-{(2S,3aS,6aS)-1-[N-(methoxycarbonyl)-L-valyl]octahydrocyclopenta[b]pyrrol-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate subsitituing (2S,4S)-1-(tert-butoxycarbonyl)-4-((difluoromethoxy)methyl)pyrrolidine-2-carboxylic acid for the innitial alkylation of 9-bromo-3-chloro-10,11-dihydro-6H-naphtho[2,3-c]chromen-8(9H)-one. Reactions in the synthesis of tert-butyl 2-[5-(2-{(2S,4S)-4-[(difluoromethoxy)methyl]-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate gave similar product yields as in the synthesis of tert-butyl 2-[5-(2-{(2S,3aS,6aS)-1-[N-(methoxycarbonyl)-L-valyl]octahydrocyclopenta[b]pyrrol-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate. MS (ESI) *m/z* 815.04 $[M + H]^+$. $^1$H NMR (400 MHz, cd$_3$od) δ 8.58 (s, 1H), 8.18 (d, 1H), 7.96 – 7.85 (m, 3H), 7.70 (s, 1H), 7.60 (d, 1H), 7.50 – 7.38 (m, 4H), 7.10 (s, 1H), 6.46 (t, 1H), 5.51 (s, 1H), 5.39 – 5.36 (m, 1H), 5.31 – 5.28 (m, 2H), 4.43 – 4.36 (m, 1H), 4.24 (d, 1H), 4.13 – 4.02 (m, 3H), 3.75 – 3.62 (m, 7H), 3.51 – 3.47 (m, 1H), 3.18 – 3.11 (m, 2H), 2.93 – 2.83 (m, 2H), 2.75 – 2.69 (m, 1H), 2.47 – 2.36 (m, 2H), 2.23 – 2.09 (m, 3H), 2.01 – 1.94 (m, 2H), 0.87 (dd, 6H).

# Example CT



9-bromo-3-chloro-10,11-dihydro-6*H*-naphtho[2,3-*c*]chromen-8(9*H*)-one

(1*R*,5*R*)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid

(1*R*,5*R*)-2-*tert*-butyl 3-(3-chloro-8-oxo-8,9,10,11-tetrahydro-6*H*-naphtho[2,3-*c*]chromen-9-yl) 2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate

tert-butyl (1R,3S,5R)-3-(9-chloro-1,4,5,11-tetrahydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

tert-butyl (1R,5R)-3-(9-chloro-1,12-dihydrochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate

methyl {(2S)-1-[(1R,3S,5R)-3-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl]-3-methyl-1-oxobutan-2-yl}carbamate

(2*S*,4*S*)-*tert*-butyl 2-(5-iodo-1*H*-imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate

methyl [(2S)-3-methyl-1-oxo-1-{(1R,3S,5R)-3-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-2-azabicyclo[3.1.0]hex-2-yl}butan-2-yl]carbamate

tert-butyl (2S,4S)-2-[5-(2-{(1R,3S,5R)-2-[N-(methoxycarbonyl)-L-valyl]-2-azabicyclo[3.1.0]hex-3-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(1R,3S,5R)-2-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[3.1.0]hex-3-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

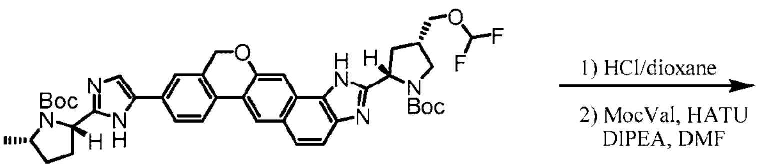
**tert-butyl (2S,4S)-2-[5-(2-{(1R,3S,5R)-2-[N-(methoxycarbonyl)-L-valyl]-2-azabicyclo[3.1.0]hex-3-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate**: This compound was made in an analogous manner to tert-butyl (2R)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate subsitituing (1R,5R)-2-(tert-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid for the innitial alkylation of 9-bromo-3-chloro-10,11-dihydro-6H-naphtho[2,3-c]chromen-8(9H)-one, and subsituting (2S,4S)-tert-butyl 2-(5-iodo-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidine-1-carboxylate for the Suzuki-Miyara couping. Reactions in the synthesis of tert-butyl (2S,4S)-2-[5-(2-{(1R,3S,5R)-2-[N-(methoxycarbonyl)-L-valyl]-2-azabicyclo[3.1.0]hex-3-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylategave similar product yields as in the synthesis of tert-butyl (2R)-2-[5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-3,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate. MS (ESI) *m/z* 791.0 $[M + H]^+$.

**methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(1R,3S,5R)-2-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[3.1.0]hex-3-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate**: To a solution of tert-butyl (2S,4S)-2-[5-(2-{(1R,3S,5R)-2-[N-(methoxycarbonyl)-L-valyl]-2-azabicyclo[3.1.0]hex-3-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (0.060 g, 0.076 mmol) in a mixture of $CH_2Cl_2$ (0.76 mL) and MeOH (0.15 mL) was added HCl (4M in 1,4-dioxane, 0.570 mL, 2.28 mmol). The solution was stirred at room temperature for 2 h and concentrated to dryness.

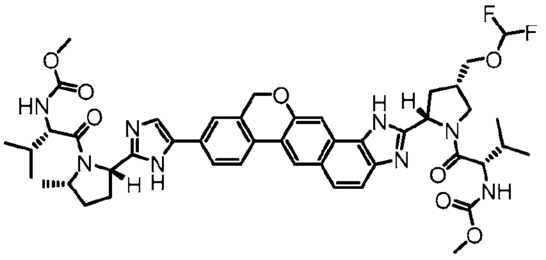
The intermediate was dissolved in $CH_2Cl_2$ (0.76 mL). (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (0.024 g, 0.114 mmol) and DIPEA (0.040 mL, 0.228 mmol) were then added to the solution. The reaction mixture was cooled to -40 °C (external temperature, $MeCN/CO_2(s)$ bath). COMU (0.052 g, 0.122 mmol) was then added and solution was allowed to warm to 0 °C over 1.5 h. Upon completion by LCMS, the solution was diluted with DMF and concentrated. The crude product was purified by preperative HPLC (Gemini column, 10-45% $MeCN/H_2O$ with 0.1% TFA) and lyophilized to provide methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(1R,3S,5R)-2-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-

azabicyclo[3.1.0]hex-3-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate (0.028 g, 42%). MS (ESI) *m/z* 881.8 $[M + H]^+$. $^1$H NMR (400 MHz, cd₃od) δ 8.45 – 8.33 (m, 1H), 8.02 – 7.94 (m, 1H), 7.91 – 7.75 (m, 2H), 7.72 – 7.67 (m, 1H), 7.61 (s, 1H), 7.59 – 7.34 (m, 6H), 7.09 – 6.91 (m, 2H), 5.62 – 5.38 (m, 2H), 5.29 (t, 1H), 5.24 – 5.09 (m, 3H), 4.61 (d, 1H), 4.37 – 4.26 (m, 1H), 3.83 – 3.73 (m, 1H), 3.69 – 3.56 (m, 6H), 3.50 – 3.40 (m, 1H), 3.20 – 3.11 (m, 1H), 2.99 (s, 1H), 2.83 (d, 1H), 2.63 – 2.50 (m, 2H), 2.47 – 2.34 (m, 2H), 2.29 – 2.13 (m, 2H), 2.10 – 1.95 (m, 2H), 1.37 – 1.23 (m, 3H), 1.19 – 1.10 (m, 1H), 1.03 – 0.78 (m, 7H).

## Example CU



tert-butyl (2S,4S)-2-(9-{2-[(2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-[(difluoromethoxy)methyl]pyrrolidine-1-carboxylate



methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-4-[(difluoromethoxy)methyl]-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**tert-butyl (2S,4S)-2-(9-{2-[(2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-[(difluoromethoxy)methyl]pyrrolidine-1-carboxylate**: This compound was made in an analogous manner to tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate subsitituing (2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid for the innitial alkylation of 3-(2-

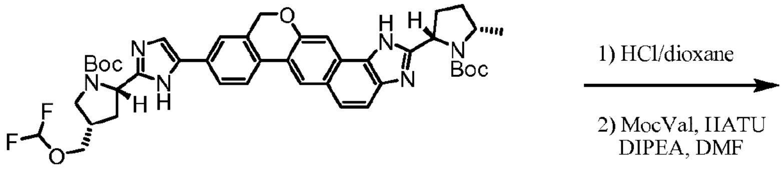
bromoacetyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one, and subsituting (2S,4S)-1-(tert-butoxycarbonyl)-4-((difluoromethoxy)methyl)pyrrolidine-2-carboxylic acid for the other alkylation in the sequence. Reactions in the synthesis of tert-butyl (2S,4S)-2-(9-{2-[(2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-[(difluoromethoxy)methyl]pyrrolidine-1-carboxylategave similar product yields as in the synthesis of tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate. MS (ESI) *m/z* 772.03 $[M + H]^+$.

**methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-4-[(difluoromethoxy)methyl]-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate** To a solution of tert-butyl (2S,4S)-2-(9-{2-[(2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-[(difluoromethoxy)methyl]pyrrolidine-1-carboxylate (0.081 g, 0.105 mmol) in a mixture of $CH_2Cl_2$ (1.05 mL) and MeOH (0.210 mL) was added HCl (4M in 1,4-dioxane, 0.788 mL, 3.15 mmol). The solution was stirred at room temperature for 2 h and concentrated to dryness.

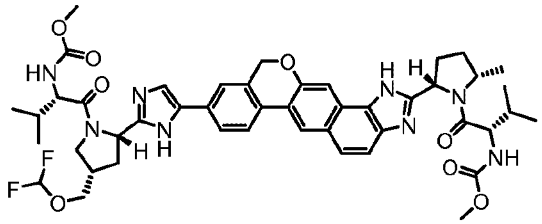
The intermediate was dissolved in $CH_2Cl_2$ (1.05 mL). (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.040 g, 0.231 mmol) and DIPEA (0.055 mL, 0.315 mmol) were then added to the solution. HATU (0.176 g, 0.462 mmol) was added and solution was allowed to stir at room temp. Upon completion, the solution was diluted with DMF and concentrated. The crude product was purified by preperative HPLC (Gemini column, 10-45% MeCN/$H_2O$ with 0.1% TFA) and the desired fractions were combined. The solution was concentrated until the aqueous layer remained and aqueous bicarbonate (sat.) was slowly added until the solution was basic. The resulting slurry was stirred at room temperature for 2h and filtered. The resulting solid was dried *in vacuo* to provide methyl {(2S)-1-[(2S,5S)-2-(5-{2-[(2S,4S)-4-[(difluoromethoxy)methyl]-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (0.025 g, 27%). MS (ESI) *m/z* 886.1 $[M + H]^+$. $^1H$ NMR (400 MHz, $cd_3od$) δ 8.49 – 8.25

(m, 2H), 8.08 – 7.82 (m, 2H), 7.79 – 7.27 (m, 5H), 6.45 (t, 1H), 5.36 – 5.26 (m, 1H), 5.22 – 5.07 (m, 3H), 4.78 – 4.49 (m, 2H), 4.45 – 4.19 (m, 3H), 4.16 – 4.05 (m, 2H), 3.99 – 3.92 (m, 1H), 3.85 – 3.71 (m, 2H), 3.66 (s, 3H), 2.88 – 2.70 (m, 2H), 2.69 – 2.49 (m, 2H), 2.42 – 2.26 (m, 2H), 2.23 – 2.10 (m, 2H), 2.07 – 1.87 (m, 3H), 1.51 (d, 2H), 1.34 – 1.20 (m, 2H), 1.17 – 0.76 (m, 12H).

## Example CV



tert-butyl (2S,4S)-2-(5-{2-[(2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-[(difluoromethoxy)methyl]pyrrolidine-1-carboxylate



methyl {(2S)-1-[(2S,4S)-4-[(difluoromethoxy)methyl]-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

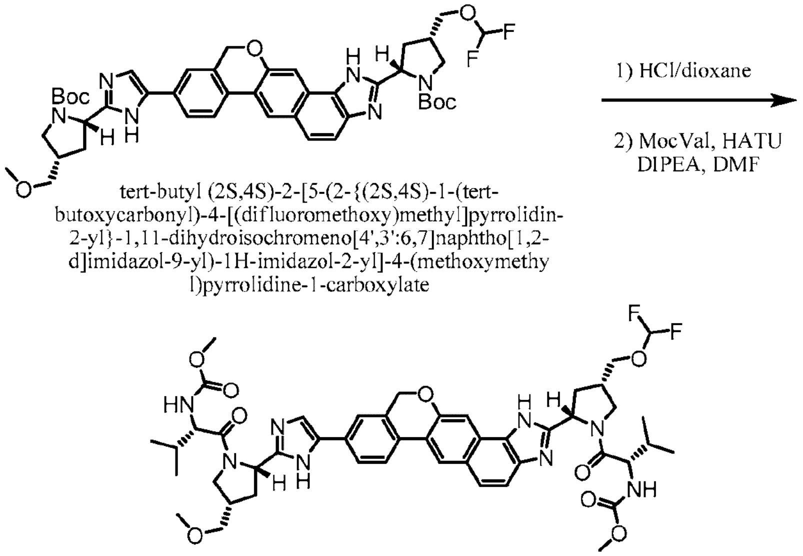
**methyl {(2S)-1-[(2S,4S)-4-[(difluoromethoxy)methyl]-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate**: This compound was made in an analogous manner to tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate subsitituing (2S,4S)-1-(tert-butoxycarbonyl)-4-((difluoromethoxy)methyl)pyrrolidine-2-carboxylic acid for the innitial alkylation of 3-(2-bromoacetyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one, and subsituting (2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid for the other alkylation in the sequence. Reactions in the synthesis of tert-butyl (2S,4S)-2-(5-{2-[(2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-

[(difluoromethoxy)methyl]pyrrolidine-1-carboxylategave similar product yields as in the synthesis of tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate. MS (ESI) *m/z* 772.31 $[M + H]^+$.

**methyl {(2S)-1-[(2S,4S)-4-[(difluoromethoxy)methyl]-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** To tert-butyl (2S,4S)-2-(5-{2-[(2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-[(difluoromethoxy)methyl]pyrrolidine-1-carboxylate (0.057 g, 0.074 mmol) in a mixture of $CH_2Cl_2$ (0.739 mL) and MeOH (0.148 mL) was added HCl (4M in 1,4-dioxane, 0.555 mL, 2.218 mmol). The solution was stirred at room temperature for 2 h and concentrated to dryness.

The intermediate was dissolved in $CH_2Cl_2$ (0.739 mL). (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.028 g, 0.163 mmol) and DIPEA (0.039 mL, 0.222 mmol) were then added to the solution. HATU (0.124 g, 0.325 mmol) was added and solution was allowed to stir at room temp. Upon completion, the solution was diluted with DMF and concentrated. The crude product was purified by preparative HPLC (Gemini column, 10-46% MeCN/$H_2O$ with 0.1% TFA) and the desired fractions were combined and lyophilized to provide methyl {(2S)-1-[(2S,4S)-4-[(difluoromethoxy)methyl]-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (0.011 g, 17%). MS (ESI) *m/z* 886.1 $[M + H]^+$. $^1H$ NMR (400 MHz, $cd_3od$) $\delta$ 8.67 – 8.51 (m, 1H), 8.26 – 8.11 (m, 1H), 8.04 – 7.75 (m, 3H), 7.69 – 7.58 (m, 2H), 6.43 (t, 1H), 5.41 – 5.15 (m, 4H), 4.48 – 3.90 (m, 6H), 3.82 (s, 1H), 3.71 – 3.57 (m, 5H), 3.53 – 3.43 (m, 1H), 3.20 – 3.01 (m, 2H), 2.92 – 2.63 (m, 3H), 2.60 – 2.25 (m, 4H), 2.15 – 1.86 (m, 4H), 1.57 (d, 3H), 1.24 (d, 2H), 1.07 (dd, 2H), 0.98 – 0.77 (m, 9H).

## Example CW



tert-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-(tert-butoxycarbonyl)-4-[(difluoromethoxy)methyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

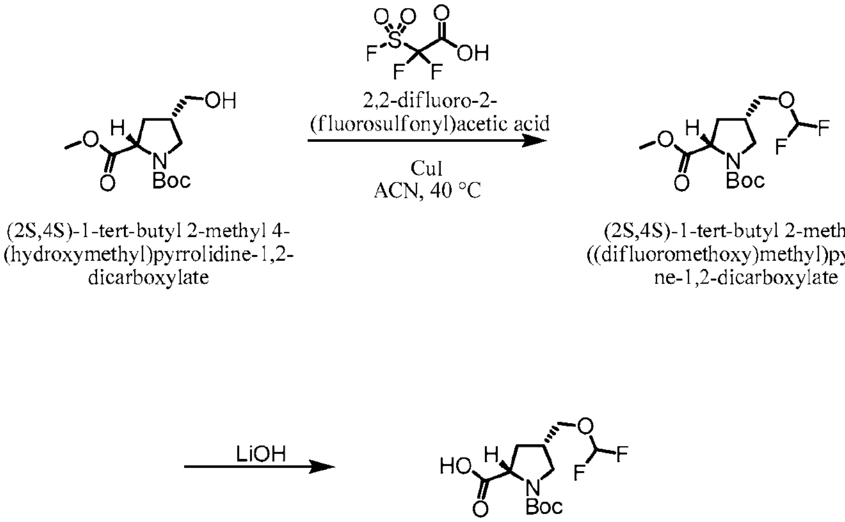
methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-4-[(difluoromethoxy)methyl]-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**tert-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-(tert-butoxycarbonyl)-4-[(difluoromethoxy)methyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate**: This compound was made in an analogous manner to tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate subsitituing (2S,4S)-1-(tert-butoxycarbonyl)-4-(methoxymethyl)pyrrolidine-2-carboxylic acid for the innitial alkylation of 3-(2-bromoacetyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one, and subsituting (2S,4S)-1-(tert-butoxycarbonyl)-4-((difluoromethoxy)methyl)pyrrolidine-2-carboxylic acid for the other alkylation in the sequence. Reactions in the synthesis of tert-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-(tert-butoxycarbonyl)-4-[(difluoromethoxy)methyl]pyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate gave similar product yields as in the synthesis of tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate. MS (ESI) *m/z* 801.1 $[M + H]^+$.

**methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-4-[(difluoromethoxy)methyl]-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** To tert-butyl (2S,4S)-2-[5-(2-{(2S,4S)-1-(tert-butoxycarbonyl)-4-[(difluoromethoxy)methyl]pyrrolidin-2-yl}-1,11 dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (0.092 g, 0.115 mmol) in a mixture of $CH_2Cl_2$ (1.15 mL) and MeOH (0.230 mL) was added HCl (4M in 1,4-dioxane, 0.862 mL, 3.446 mmol). The solution was stirred at room temperature for 2 h and concentrated to dryness.

The intermediate was dissolved in $CH_2Cl_2$ (1.149 mL). (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.044 g, 0.253 mmol) and DIPEA (0.060 mL, 0.345 mmol) were then added to the solution. HATU (0.192 g, 0.505 mmol) was added and solution was allowed to stir at room temp. Upon completion, the solution was diluted with DMF and concentrated. The crude product was purified by preparative HPLC (Gemini column, 10-45% MeCN/$H_2O$ with 0.1% TFA) and the desired fractions were combined. The solution was concentrated until the aqueous layer remained and aqueous bicarbonate (sat.) was slowly added until the solution was basic. The resulting slurry was stirred at room temperature for 2h and filtered. The resulting solid was dried *in vacuo* to provide methyl {(2S)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-4-[(difluoromethoxy)methyl]-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (0.042 g, 40%). MS (ESI) *m/z* 916.30 $[M + H]^+$. $^1$H NMR (400 MHz, $cd_3od$) δ 8.55 – 8.25 (m, 1H), 8.15 – 7.85 (m, 2H), 7.83 – 7.26 (m, 5H), 6.44 (t, 1H), 5.37 – 5.02 (m, 4H), 4.47 – 4.35 (m, 1H), 4.33 – 4.18 (m, 3H), 4.15 – 3.90 (m, 3H), 3.81 – 3.45 (m, 11H), 3.39 (s, 3H), 2.90 – 2.27 (m, 5H), 2.22 – 1.92 (m, 4H), 1.12 – 0.73 (m, 13H).

## Example CX



(2S,4S)-1-tert-butyl 2-methyl 4-(hydroxymethyl)pyrrolidine-1,2-dicarboxylate

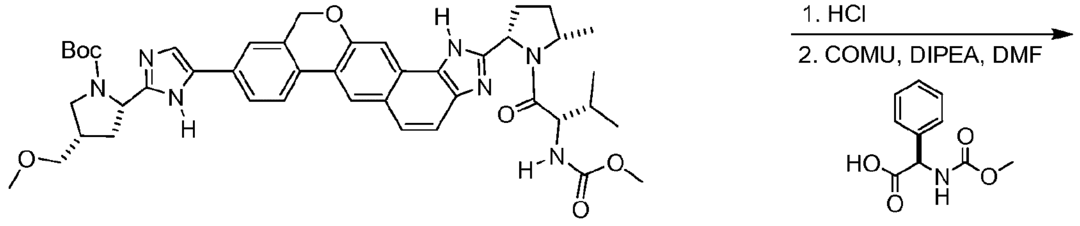
(2S,4S)-1-tert-butyl 2-methyl 4-((difluoromethoxy)methyl)pyrrolidine-1,2-dicarboxylate

(2S,4S)-1-(tert-butoxycarbonyl)-4-((difluoromethoxy)methyl)pyrrolidine-2-carboxylic acid

**(2S,4S)-1-tert-butyl 2-methyl 4-((difluoromethoxy)methyl)pyrrolidine-1,2-dicarboxylate:** A 100 mL round-bottom flask was charged with (2S,4S)-1-tert-butyl 2-methyl 4-(hydroxymethyl)pyrrolidine-1,2-dicarboxylate (3.33 g, 12.84 mmol), CuI (0.489 g, 2.56 mmol), and anhydrous acetonitrile (57.1 mL). The reaction was heated to 45 °C (ext. oil bath). 2,2-difluoro-2-(fluorosulfonyl)acetic acid (2.655 mL, 25.68 mmol) was added at 45 °C over 30 minutes via syringe pump. The reaction was heated for 30 minutes. Upon completion as monitored by TLC, the reaction mixture was cooled to room temperature and concentrated in vacuo. The crude residue was diluted in EtOAc and washed with sodium bicarbonate (aq). The bicarbonate layer was back extracted with ethyl acetate twice. Combined organic layers were washed with brine, dried over sodium sulphate, filtered and concentrated. The resulting residue was further purified via silica gel chromatography (10 to 40 % EtOAc/Hexanes) to afford (2S,4S)-1-tert-butyl 2-methyl 4-((difluoromethoxy)methyl)pyrrolidine-1,2-dicarboxylate (2.41 g, 61%). MS (ESI) *m/z* 210.21 $[M + H - Boc]^+$.

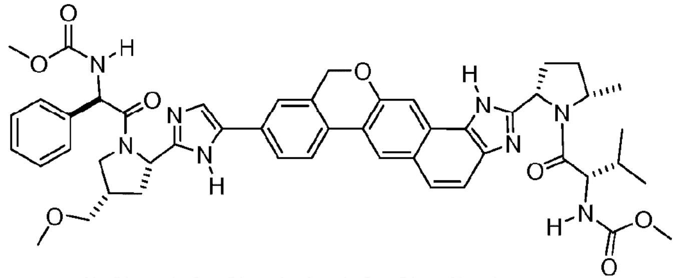
**(2S,4S)-1-(tert-butoxycarbonyl)-4-((difluoromethoxy)methyl)pyrrolidine-2-carboxylic acid:** To a solution of (2S,4S)-1-tert-butyl 2-methyl 4-((difluoromethoxy)methyl)pyrrolidine-1,2-dicarboxylate (2.41 g, 7.79 mmol) in a mixture of THF (39 mL) and MeOH (15.6 mL) was added LiOH (2.5 M aqueous, 15.6 mL, 38.9 mmol). The resulting solution was stirred at room temperature for 1h. Upon completion by TLC the reaction mixture was and acidified with aqueous HCl (1N). The desired product was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried over $Na_2SO_4$ and concentrated to provide (2S,4S)-1-(tert-butoxycarbonyl)-4-((difluoromethoxy)methyl)pyrrolidine-2-carboxylic acid (2.4 g, 99%). MS (ESI) *m/z* 294.96 [M - H]$^-$. $^1$H-NMR: 400 MHz, (acetone-$d_6$) δ (mixture of rotomers): 6.50 (t, 1H), 4.36-4.17 (m, 1H), 3.93 (d, 2H), 3.77-3.67 (m, 1H), 3.63-3.59 (m, 1H), 3.26-3.12 (m, 1H), 2.72-2.41 (m, 2H), 1.89-1.73 (m, 2H), 1.41 (s, 9H).

## Example CY



tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

(*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid

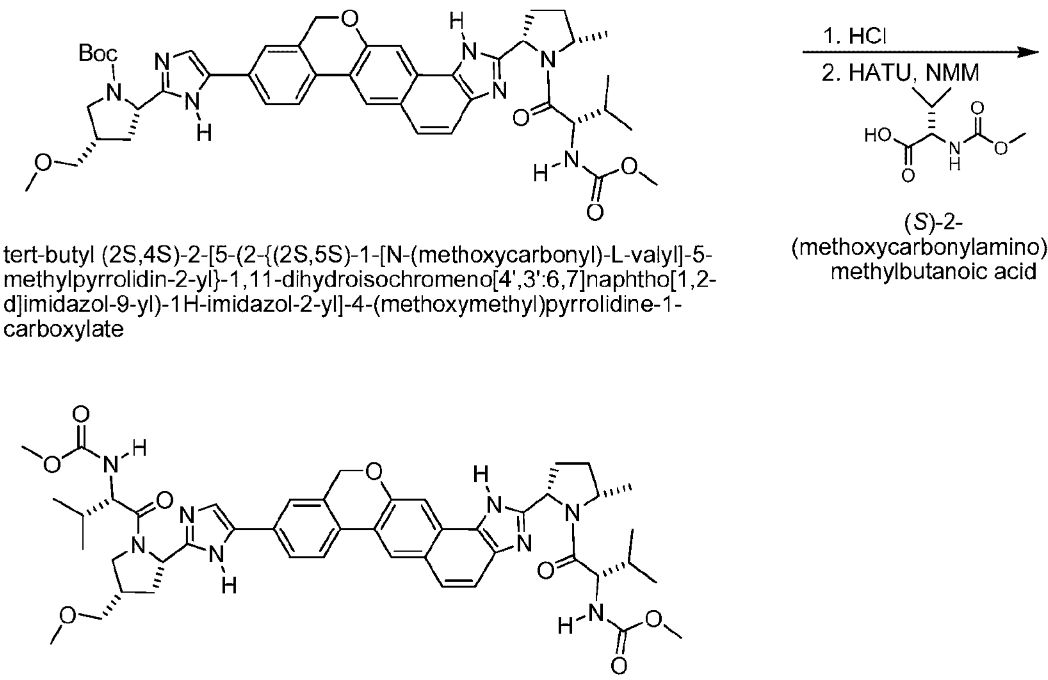


methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**Methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** A solution of tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (150 mg, 0.19 mmol) in 1.25 N HCl in EtOH (3 mL) was stirred overnight then heated to 50 °C for 3h. The reaction was concentrated and the crude material dissolved in DMF (2 mL). To this solution was added a solution of (R)-2-

(methoxycarbonylamino)-2-phenylacetic acid (52 mg, 0.25 mmol) and COMU (90 mg, 0.21 mmol). To the resulting solution was added diisopropylethylamine (0.099 mL, 0.57 mmol). After stirring for 2h at room temperature, the reaction was quenched with 1N HCl (0.200 mL) and purified purified by HPLC. After lyophilization, the TFA salt was dissolved in EtOAc and washed with saturated $NaHCO_3$. The organic phase was dried over $Na_2SO_4$ and concentrated. The free base was then dissolved in $MeCN/H_2O$ and lyophilized to afford methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (65 mg, 39%). LCMS-ESI$^+$: calculated for $C_{49}H_{54}N_8O_8$: 882.4; observed $[M+1]^+$: 884.1. Diagnostic peaks in NMR $^1H$ NMR ($CD_3OD$): 8.28 (s, 1H), 8.21 (s, 1H), 8.04 (s, 1H), 7.91-7.01 (m, 10H), 3.62 (s, 3H), 3.34 (s, 3H), 3.23 (s, 3H), 1.56 (d, 3H), 1.03 (d, 3H), 0.94 (d, 3H).

## Example CZ



tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

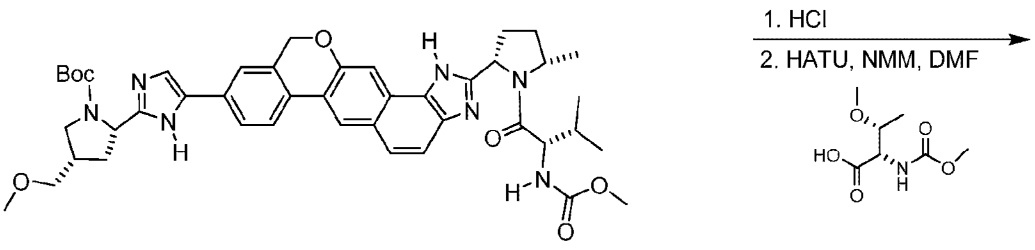
(*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid

methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**Methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-**

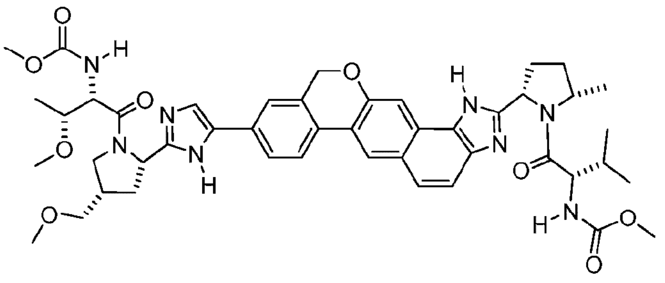
**dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** *Tert*-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (100 mg, 0.13 mmol) in 1.25 N HCl in EtOH (3 mL) was heated to 50 °C for 3h and then concentrated under reduced pressure. The crude residue was treated with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (34 mg, 0.20 mmol), HATU (54 mg, 0.14 mmol) and DMF (1.3 mL), then N-methylmorpholine (0.043 mL, 0.39 mmol) was added dropwise. After 3h, the mixture was quenched with 1N HCl (0.100 mL) and then purified by HPLC to afford methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate ( 91 mg, 82%). LCMS-ESI$^+$: calculated for $C_{46}H_{56}N_8O_8$: 848.4; observed $[M+1]^+$: 850.2.

## Example DA



tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

(2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino) butanoic acid



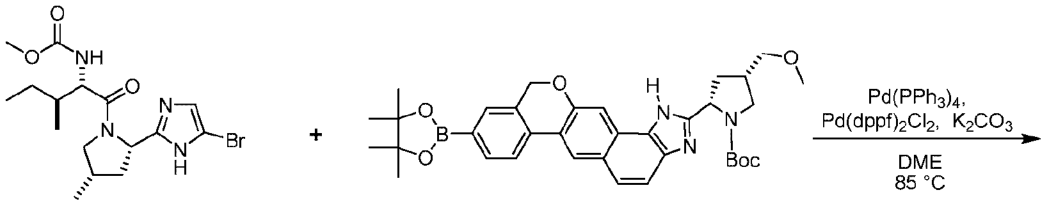
methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2S,3S)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**Methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2S,3S)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** *Tert*-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (119 mg, 0.15 mmol) in 1.25 N HCl in EtOH (3 mL) was heated to 50 °C for 3h and then concentrated under reduced pressure. The crude residue was treated with (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (43 mg, 0.23 mmol), HATU (63 mg, 0.17 mmol) and DMF (2 mL), then N-methylmorpholine (0.050 mL, 0.45 mmol) was added dropwise. After 3 hr, the mixture was quenched with 1N HCl (0.100 mL) and then purified by HPLC to afford methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2S,3S)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate ( 76 mg, 59%). LCMS-ESI$^+$: calculated for $C_{46}H_{56}N_8O_9$: 864.4; observed $[M+1]^+$: 866.1.

## Example DB

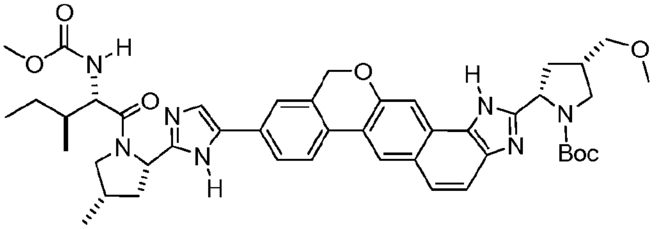
(2*S*,4*S*)-*tert*-butyl 2-(5-bromo-1*H*-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate

(2*S*,3*S*)-2-(methoxycarbonylamino)-3-methylpentanoic acid

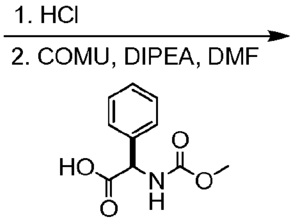


methyl (2*S*,3*S*)-1-((2*S*,4*S*)-2-(5-bromo-1*H*-imidazol-2-yl)-4-methylpyrrolidin-1-yl)-3-methyl-1-oxopentan-2-ylcarbamate

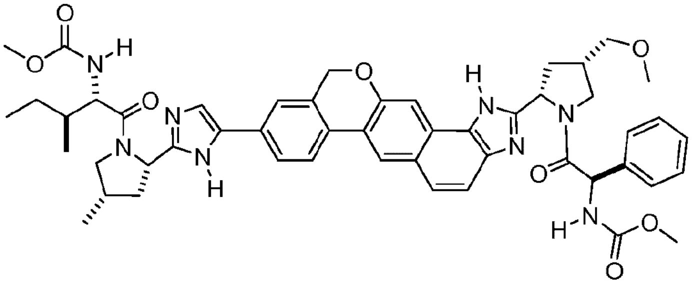
(2S,4S)-tert-butyl 4-(methoxymethyl)-2-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)- 1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate



tert-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-alloisoleucyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate



(*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid



methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S,4S)-1-{(2S,3R)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

**Methyl (2S,3S)-1-((2S,4S)-2-(5-bromo-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl)-3-methyl-1-oxopentan-2-ylcarbamate:** (2S,4S)-tert-butyl 2-(5-bromo-1H-imidazol-2-yl)-4-methylpyrrolidine-1-carboxylate (100 mg, 0.13 mmol) in 1.25 N HCl in EtOH (15 mL) was heated to 50 °C for 3h and then concentrated under reduced pressure. The crude residue was treated with (2S,3S)-2-(methoxycarbonylamino)-3-methylpentanoic acid (625 mg, 3.30 mmol), HATU (1.05 g, 2.77 mmol) and DMF (10 mL), then DIPEA (1.33 mL, 7.62 mmol) was added dropwise. After 2h, the mixture was poured into saturated aqueous $NaHCO_3$ and then extracted with EtOAc. The organic phase was washed with successively with 5% aqueous LiCl and Brine. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (30 to 90% of 10%MeOH/EtoAc to Hexanes) afforded methyl (2S,3S)-1-((2S,4S)-2-(5-bromo-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl)-3-methyl-1-oxopentan-2-ylcarbamate ( 932 mg, 81%).

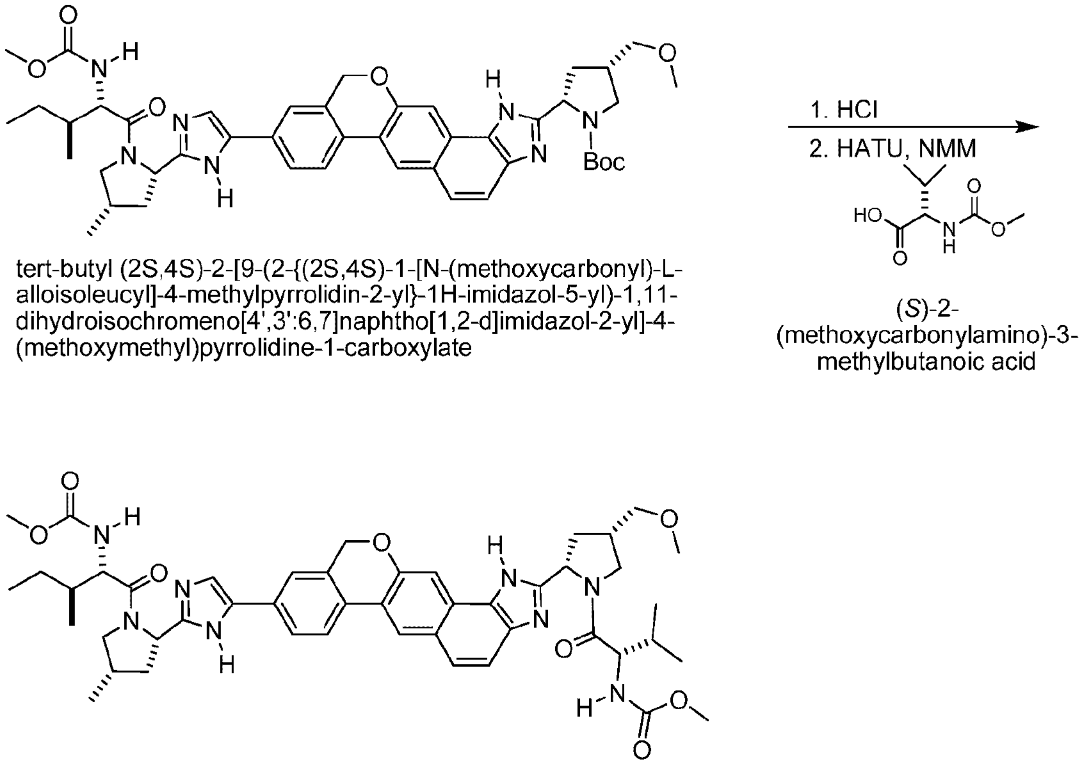
***Tert*-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-alloisoleucyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate:** (2S,4S)-*Tert*-butyl 4-(methoxymethyl)-2-(9-

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)- 1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)pyrrolidine-1-carboxylate (856 mg, 1.4 mmol), methyl (2S,3S)-1-((2S,4S)-2-(5-bromo-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl)-3-methyl-1-oxopentan-2-ylcarbamate (932 mg, 2.1 mmol), $Pd(PPh_3)_4$ (162 mg, 0.14 mmol), $PdCl_2(dppf)_2$ (102 mg, 0.14 mmol), and $K_2CO_3$ (2M in $H_2O$, 2.31 mL, 4.62 mmol) were combined in DMSO (8 mL) and dioxanes (8 mL). The mixture was degassed with bubbling Argon for 10 min the heated to 95 °C for 1h. After cooling, the reaction mixture was diluted with EtOAc, and washed successively with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (1% to 20% MeOH/EtOAc) to afford *tert*-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-alloisoleucyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (701 mg, 62%).

**Methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S,4S)-1-{(2S,3R)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate:** A solution of *tert*-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-alloisoleucyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (218 mg, 0.27 mmol) in 1.25 N HCl in EtOH (3 mL) was heated to 50 °C for 3h. The reaction was concentrated and the crude material dissolved in DMF (3 mL). To this solution was added a solution of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (73 mg, 0.35 mmol) and COMU (127 mg, 0.30 mmol). To the resulting solution was added diisopropylethylamine (0.141 mL, 0.81 mmol). After stirring for 2h at room temperature, the reaction was quenched with 1N HCl (0.200 mL) and purified purified by HPLC. After lyophilization, the TFA salt was dissolved in EtOAc and washed with saturated $NaHCO_3$. The organic phase was dried over $Na_2SO_4$ and concentrated. The free base was then dissolved in $MeCN/H_2O$ and lyophilized to afford methyl {(1R)-2-[(2S,4S)-2-(9-{2-[(2S,4S)-1-{(2S,3R)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-

yl]-2-oxo-1-phenylethyl}carbamate: (121 mg, 50%). LCMS-ESI$^+$: calculated for $C_{50}H_{56}N_8O_8$: 896.4; observed [M+1]$^+$: 897.5.

## Example DC



tert-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-alloisoleucyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

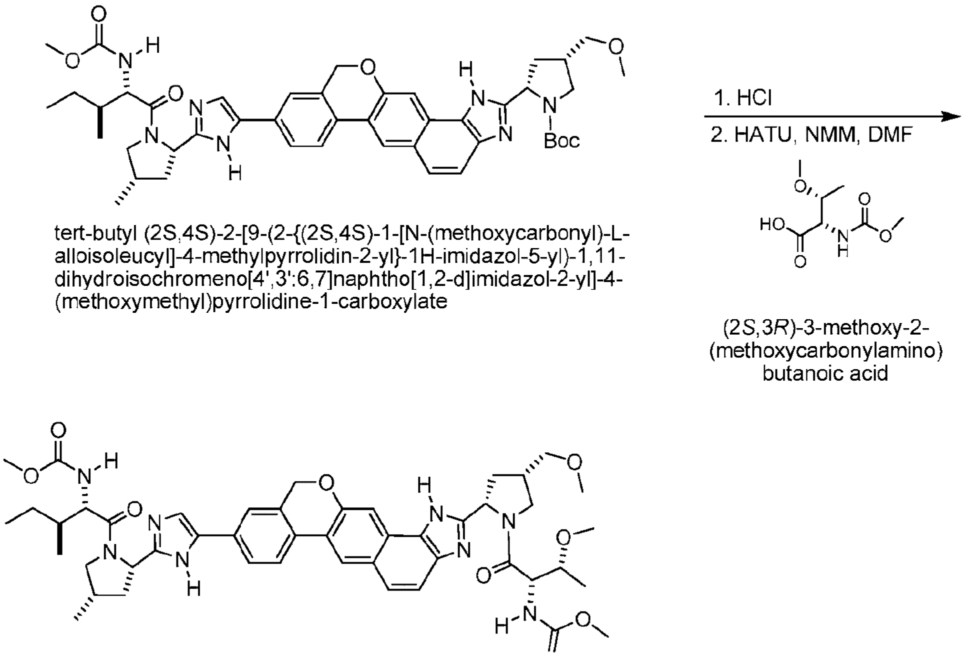
(*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid

methyl {(2S)-1-[(2S,4S)-2-(9-{2-[(2S,4S)-1-{(2S,3R)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**Methyl {(2S)-1-[(2S,4S)-2-(9-{2-[(2S,4S)-1-{(2S,3R)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** *tert*-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-alloisoleucyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (105 mg, 0.13 mmol) in 1.25 N HCl in EtOH (3 mL) was heated to 50 °C for 3h and then concentrated under reduced pressure. The crude residue was treated with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (32 mg, 0.18 mmol), HATU (59 mg, 0.16 mmol) and DMF (1.3 mL), then N-methylmorpholine (0.043 mL, 0.39 mmol) was added dropwise. After 3h, the mixture was quenched with 1N HCl

(0.100 mL) and then purified by HPLC to afford methyl {(2S)-1-[(2S,4S)-2-(9-{2-[(2S,4S)-1-{(2S,3R)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate ( 80 mg, 71%). LCMS-ESI$^+$: calculated for $C_{47}H_{58}N_8O_8$: 862.4; observed $[M+1]^+$: 864.2.

## Example DD



tert-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-alloisoleucyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

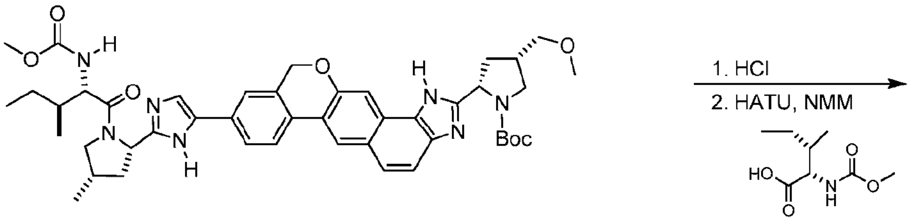
(2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid

methyl {(2S,3R)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-[N-(methoxycarbonyl)-O-methyl-L-allothreonyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate

**Methyl {(2S,3R)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-[N-(methoxycarbonyl)-O-methyl-L-allothreonyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate:** *tert*-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-alloisoleucyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (105 mg, 0.13 mmol) in 1.25 N HCl in EtOH (3 mL) was heated to 50 °C for 3h and then concentrated under reduced pressure. The crude residue was treated with (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (35 mg, 0.18 mmol), HATU (59 mg, 0.16 mmol) and DMF (1.3 mL), then N-methylmorpholine (0.043 mL, 0.39 mmol) was added dropwise. After 3 hr, the mixture was quenched with 1N

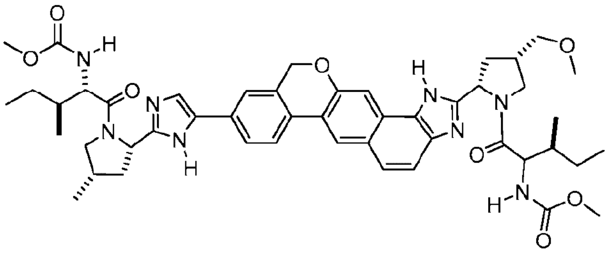
HCl (0.100 mL) and then purified by HPLC to afford methyl {(2S,3R)-1-[(2S,4S)-2-(5-{2-[(2S,4S)-1-[N-(methoxycarbonyl)-O-methyl-L-allothreonyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate ( 92 mg, 81%). LCMS-ESI$^+$: calculated for $C_{47}H_{58}N_8O_9$: 878.4; observed $[M+1]^+$: 879.3.

## Example DE



tert-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-alloisoleucyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate

(2S,3S)-2-(methoxycarbonylamino)-3-methylpentanoic acid

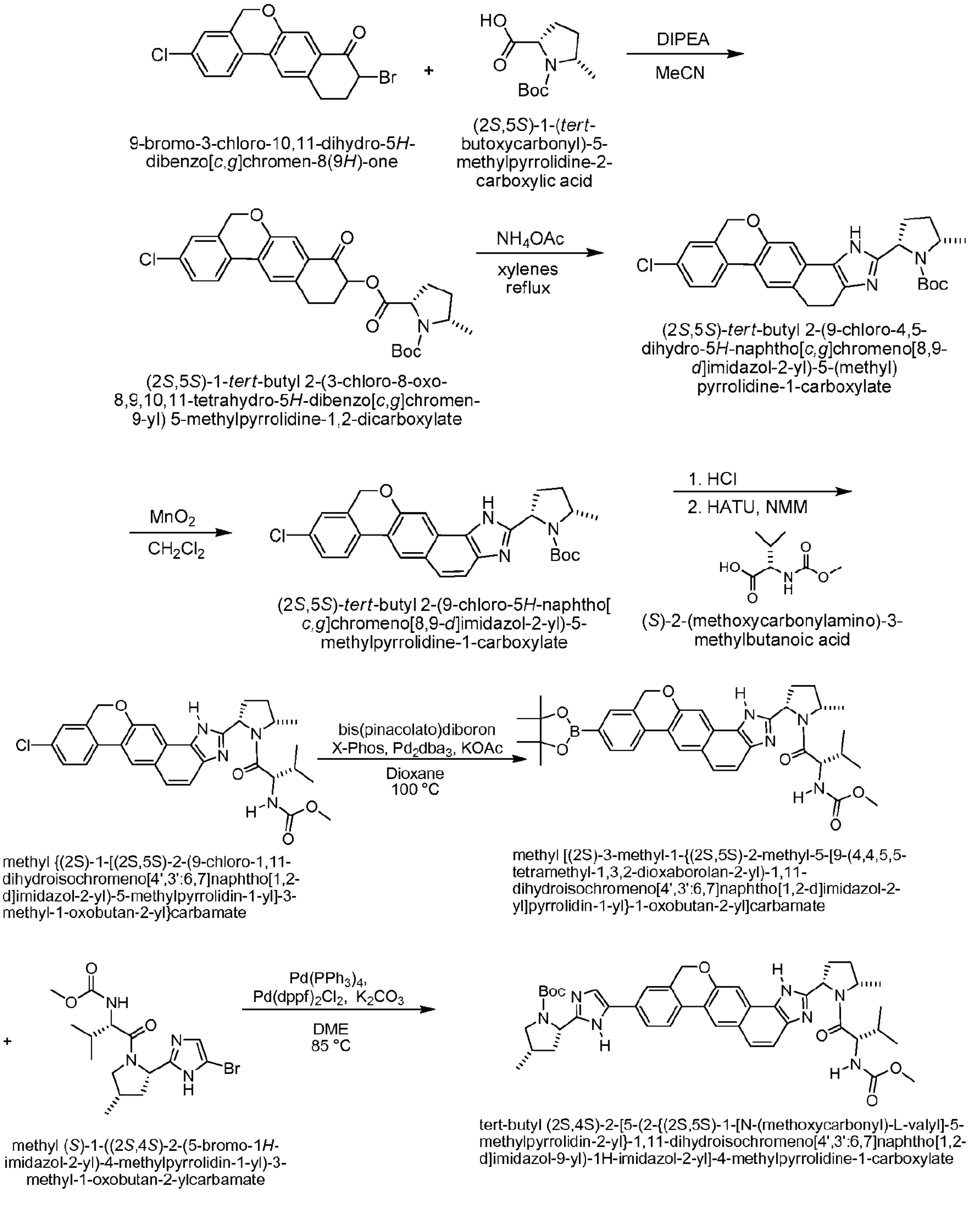


methyl {(3R)-1-[(2S,4S)-2-(9-{2-[(2S,4S)-1-{(2S,3R)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate

**Methyl {(3R)-1-[(2S,4S)-2-(9-{2-[(2S,4S)-1-{(2S,3R)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate:** *tert*-butyl (2S,4S)-2-[9-(2-{(2S,4S)-1-[N-(methoxycarbonyl)-L-alloisoleucyl]-4-methylpyrrolidin-2-yl}-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (105 mg, 0.13 mmol) in 1.25 N HCl in EtOH (3 mL) was heated to 50 °C for 3h and then concentrated under reduced pressure. The crude residue was treated with (2S,3S)-2-(methoxycarbonylamino)-3-methylpentanoic acid (34 mg, 0.18 mmol), HATU (59 mg, 0.16 mmol) and DMF (1.3 mL), then N-methylmorpholine (0.043 mL, 0.39 mmol) was added dropwise. After 3h, the mixture was quenched with 1N HCl (0.100 mL) and then purified by HPLC to afford methyl {(3R)-1-[(2S,4S)-2-(9-{2-

[(2S,4S)-1-{(2S,3R)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate ( 98 mg, 86%). LCMS-ESI$^+$: calculated for $C_{48}H_{60}N_8O_8$: 876.5; observed $[M+1]^+$: 878.2.

## Example DF



9-bromo-3-chloro-10,11-dihydro-5*H*-dibenzo[*c*,*g*]chromen-8(9*H*)-one

(2*S*,5*S*)-1-(*tert*-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid

(2*S*,5*S*)-1-*tert*-butyl 2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-5*H*-dibenzo[*c*,*g*]chromen-9-yl) 5-methylpyrrolidine-1,2-dicarboxylate

(2*S*,5*S*)-*tert*-butyl 2-(9-chloro-4,5-dihydro-5*H*-naphtho[*c*,*g*]chromeno[8,9-*d*]imidazol-2-yl)-5-(methyl) pyrrolidine-1-carboxylate

(2*S*,5*S*)-*tert*-butyl 2-(9-chloro-5*H*-naphtho[*c*,*g*]chromeno[8,9-*d*]imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate

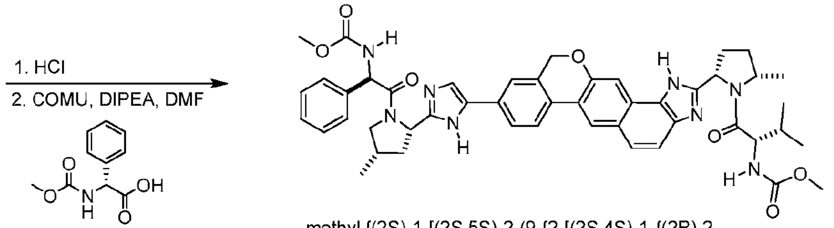
(*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid

methyl {(2S)-1-[(2S,5S)-2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

methyl [(2S)-3-methyl-1-{(2S,5S)-2-methyl-5-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate

methyl (*S*)-1-((2*S*,4*S*)-2-(5-bromo-1*H*-imidazol-2-yl)-4-methylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate



(*R*)-2-(methoxycarbonylamino)-2-phenylacetic acid

methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**(2S,5S)-1-tert-butyl 2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-9-yl) 5-methylpyrrolidine-1,2-dicarboxylate:** To a solution of 9-bromo-3-chloro-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (1.41 g, 3.88 mmol) in MeCN (17 mL) was added (2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid (980 mg, 4.27 mmol) and DIPEA (1.49 mL, 8.54 mmol). After stirring for 18 h at 50 °C, the solution was diluted with EtOAc and washed successively with 1N HCl, saturated aqueous $NaHCO_3$ and brine. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (10% to 30% EtOAc/hexanes) to afford (2S,5S)-1-tert-butyl 2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-9-yl) 5-methylpyrrolidine-1,2-dicarboxylate (1.63 g, 81%).

**(2S,5S)-tert-butyl 2-(9-chloro-4,5-dihydro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-5-(methyl)pyrrolidine-1-carboxylate:** (2S,5S)-1-*tert*-butyl 2-(3-chloro-8-oxo-8,9,10,11-tetrahydro-5H-dibenzo[c,g]chromen-9-yl) 5-methylpyrrolidine-1,2-dicarboxylate (1.63 g, 3.18 mmol) was added toluene (30 mL), 2-methoxyethanol (3 mL), and ammonium acetate (3.68 g, 77.1 mmol) and the solution was heated to reflux overnight. The following morning, the solution was cooled to rt and was diluted with EtOAc and washed successively with water, saturated aqueous $NaHCO_3$ and brine. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (40% to 80 % EtOAc/hexanes) to afford (2S,5S)-*tert*-butyl 2-(9-chloro-4,5-dihydro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (1.13 g, 72%).

**((2S,5S)-tert-butyl 2-(9-chloro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate:** To a solution of (2S,5S)-*tert*-butyl 2-(9-chloro-4,5-dihydro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-5-(methyl)pyrrolidine-1-carboxylate (1.13 g, 2.3 mmol) in $CH_2Cl_2$ (25 mL) was added $MnO_2$ (9.98 g, 115 mmol). The reaction mixture was stirred overnight then filtered over celite. The filter cake was washed with copious $CH_2Cl_2$ and MeOH, and the filtrate was concentrated under reduced pressure to afford the crude product (2S,5S)-*tert*-butyl 2-(9-chloro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (931 mg, 83%).

**Methyl {(2S)-1-[(2S,5S)-2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** (2S,5S)-*tert*-butyl 2-(9-chloro-5H-naphtho[c,g]chromeno[8,9-d]imidazol-2-yl)-5-methylpyrrolidine-1-carboxylate (931 mg, 1.9 mmol) in 1.25 N HCl in EtOH (8 mL) was heated to 50 °C for 3h and then concentrated under reduced pressure. The crude residue was treated with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (499 mg, 2.9 mmol), HATU (795 mg, 2.1 mmol) and DMF (10 mL), then N-methylmorpholine (0.627 mL, 5.7 mmol) was added dropwise. After stirring for 1 h, the reaction was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$, 5% LiCl, and brine. The organics were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica column chromatography (50% to 100% EtOAc/hexanes) to afford methyl {(2S)-1-[(2S,5S)-2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (950 mg, 91%).

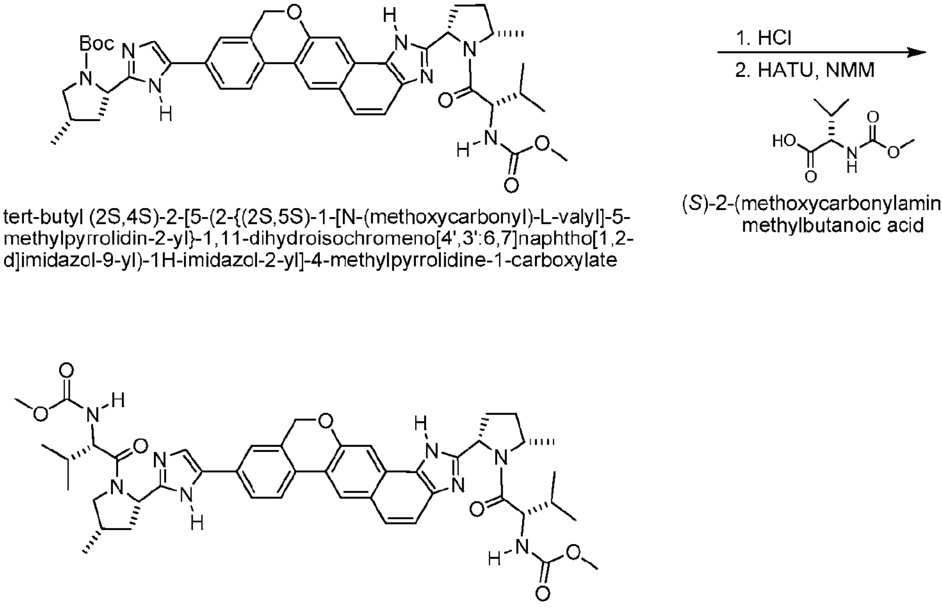
**Methyl [(2S)-3-methyl-1-{(2S,5S)-2-methyl-5-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate:** To methyl {(2S)-1-[(2S,5S)-2-(9-chloro-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (950 mg, 1.74 mmol) in dioxane (17 mL) was added bis(pinacolato)diboron (662 mg, 2.61 mmol), KOAc (512 mg, 5.22 mmol), X-Phos (25 mg, 0.05 mmol), and $Pd_2dba_3$ (80 mg, 0.08 mmol). The solution was degassed with $N_2$ for 10 min, then heated to 90 °C for 16 h. The solution was cooled to rt, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, brine, dried with $Na_2SO_4$, and concentrated. Purification by silica gel chromatography (30% to 75 % gradient using 5%MeOH/EtOAc to Hexanes) to afford methyl [(2S)-3-methyl-1-{(2S,5S)-2-methyl-5-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate (800 mg, 72%).

**tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate:** To a solution of [(2S)-3-methyl-1-{(2S,5S)-2-methyl-5-[9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,11-

dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate (269 mg, 0.42 mmol), methyl (S)-1-((2S,4S)-2-(5-bromo-1H-imidazol-2-yl)-4-methylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (206 mg, 0.54 mmol), tetrakis(triphenylphosphine) palladium(0) (49 mg, 0.042 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (31 mg, 0.042 mmol) in DMSO (3 mL) and dioxanes (3 mL) was added a solution of potassium carbonate (2M in water, 0.69 mL, 1.39 mmol). The resulting mixture was degassed and then heated to 95 °C for 2h. After cooling to room temperature, the reaction was diluted with ethyl acetate. The organics were washed with saturated sodium bicarbonate and brine, dried over $Na_2SO_4$ and concentrated. The crude residue was purified by flash chromatography (1 to 20% MeOH/EtOAc) to yield tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (202 mg, 63%).

**Methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** A solution of tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (80 mg, 0.11 mmol) in 1.25 N HCl in EtOH (2 mL) was heated to 50 °C for 3h. The reaction was concentrated and the crude material dissolved in DMF (1.5 mL). To this solution was added a solution of (R)-2-(methoxycarbonylamino)-2-phenylacetic acid (29 mg, 0.14 mmol) and COMU (52 mg, 0.12 mmol). To the resulting solution was added diisopropylethylamine (0.057 mL, 0.33 mmol). After stirring for 2h at room temperature, the reaction was quenched with 1N HCl (0.200 mL) and purified purified by HPLC. After lyophilization, the TFA salt was dissolved in EtOAc and washed with saturated $NaHCO_3$. The organic phase was dried over $Na_2SO_4$ and concentrated. The free base was then dissolved in MeCN/$H_2O$ and lyophilized to afford methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate: (42 mg, 45%). LCMS-ESI$^+$: calculated for $C_{48}H_{52}N_8O_7$: 852.4; observed $[M+1]^+$: 854.2.

## Example DG



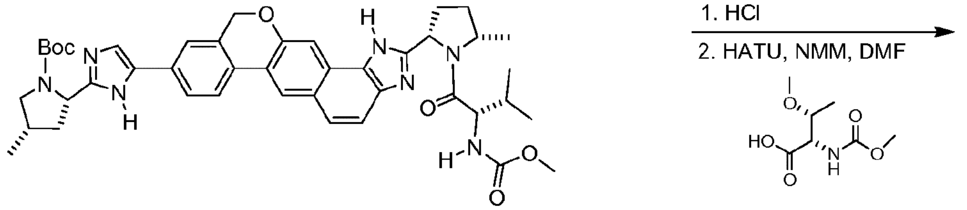
tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate

(*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid

methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

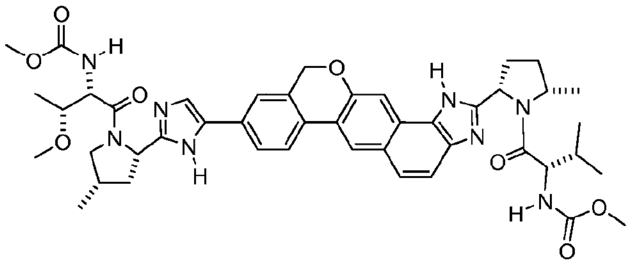
**Methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** *tert*-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (60 mg, 0.079 mmol) in 1.25 N HCl in EtOH (2 mL) was heated to 50 °C for 3h and then concentrated under reduced pressure. The crude residue was treated with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (21 mg, 0.12 mmol), HATU (36 mg, 0.095 mmol) and DMF (1.5 mL), then N-methylmorpholine (0.027 mL, 0.24 mmol) was added dropwise. After 3h, the mixture was quenched with 1N HCl (0.100 mL) and then purified by HPLC to afford methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate ( 33 mg, 51%). LCMS-ESI$^+$: calculated for $C_{45}H_{54}N_8O_7$: 818.4; observed $[M+1]^+$: 820.2.

## Example DH



tert-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate

(2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino) butanoic acid



methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2S,3S)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

**Methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate:** *tert*-butyl (2S,4S)-2-[5-(2-{(2S,5S)-1-[N-(methoxycarbonyl)-L-valyl]-5-methylpyrrolidin-2-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl]-4-methylpyrrolidine-1-carboxylate (20 mg, 0.079 mmol) in 1.25 N HCl in EtOH (2 mL) was heated to 50 °C for 3h and then concentrated under reduced pressure. The crude residue was treated with (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (8 mg, 0.04 mmol), HATU (12 mg, 0.03 mmol) and DMF (0.5 mL), then N-methylmorpholine (0.009 mL, 0.078 mmol) was added dropwise. After 3h, the mixture was quenched with 1N HCl (0.100 mL) and then purified by HPLC to afford methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylpyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate ( 7.5 mg, 35%). LCMS-ESI$^+$: calculated for $C_{45}H_{54}N_8O_8$: 834.4; observed $[M+1]^+$: 835.7.

## Examples DI-DT

Using procedures similar to those described herein, the following compounds of the invention were prepared.

| # | Compound | LCMS (observed (M+H)$^+$) |
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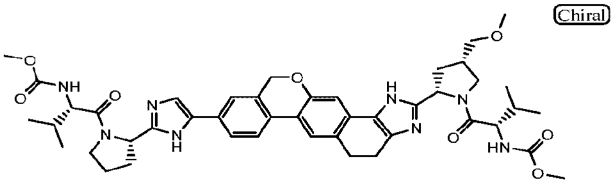
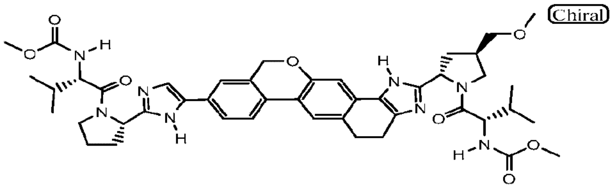
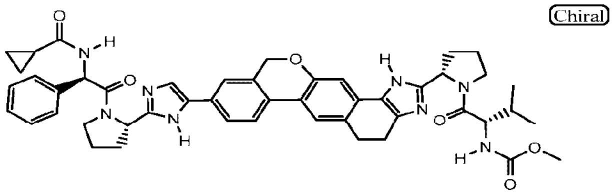
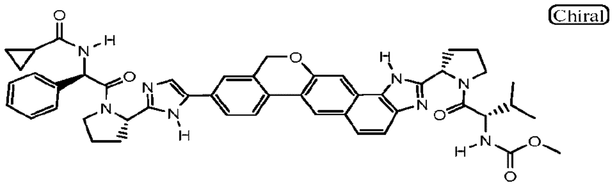
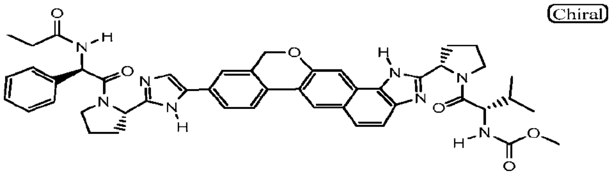
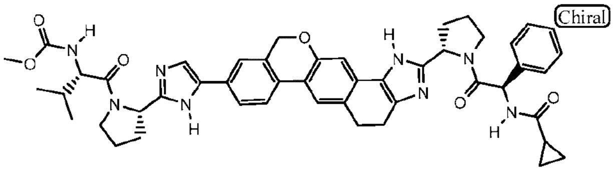
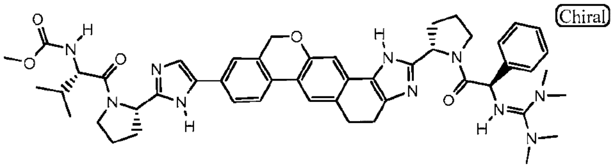
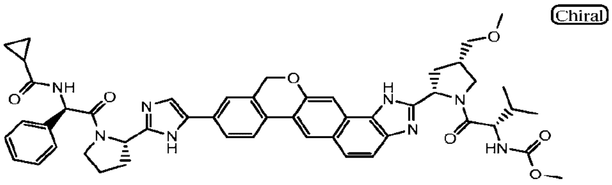
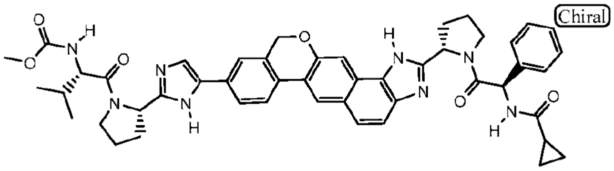
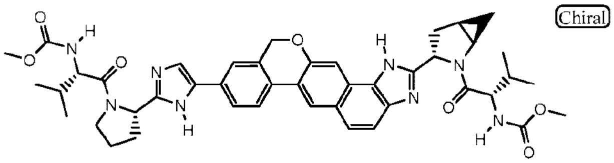
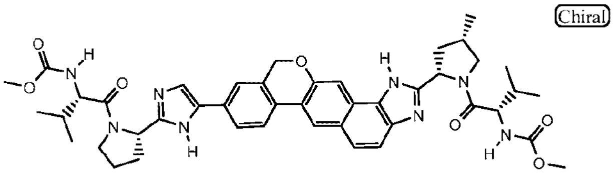
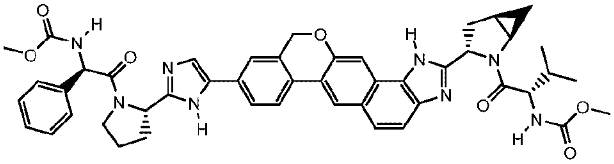
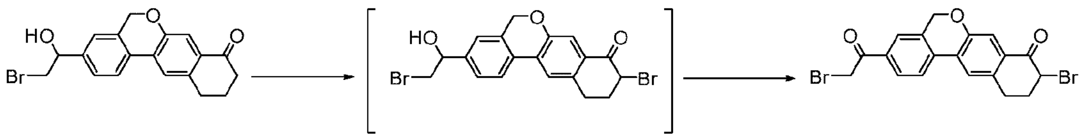
| DI |  | 879.4 |
| DJ |  | 838.2 |
| DK |  | 837.3 |
| DL |  | 835.34 |
| DM |  | 823.35 |
| DN |  | 837.35 |

| | | |
|---|---|---|
| DO |  | 865.32 |
| DP |  | 880.0 |
| DQ |  | 836.04 |
| DR |  | 803.2 |
| DS |  | 806.11 |
| DT |  | 838.29 |

## Example DU



3-(2-bromo-1-hydroxyethyl)-10,11-dihydro-5*H*-dibenzo[*c*,*g*]chromen-8(9*H*)-one

9-bromo-3-(2-bromo-1-hydroxyethyl)-10,11-dihydro-5*H*-dibenzo[*c*,*g*]chromen-8(9*H*)-one

9-bromo-3-(2-bromoacetyl)-10,11-dihydro-5*H*-dibenzo[*c*,*g*]chromen-8(9*H*)-one

**9-bromo-3-(2-bromoacetyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one:** To 3-(2-bromo-1-hydroxyethyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (20.3g, 54.4 mmol) in DCM (365 mL) was added MeOH (22 mL) and pyridinium tribromide (18.24 g, 57.0 mmol). After 2h, water was added (100mL) and after briefly agitating the layers split and the bottom organic layer was collected. The organic layer was then washed with 1M HCl (100 mL) and the bottom organic layer containing 9-bromo-3-(2-bromo-1-hydroxyethyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one was collected. 400 MHz $^1$H NMR ($CDCl_3$) 7.75 (d, J = 8.1 Hz, 1H), 7.68 (s, 1H), 7.61 (s, 1H), 7.42 (d, J = 7.5 Hz, 1H), 7.24 (s, 1H), 5.13 (s, 2H), 4.99-4.96 (m, 1H), 4.73 (dd, J = 4.1, 4.1 Hz, 1H), 3.69-3.66 (m, 1H), 3.58-3.53 (m, 1H), 3.35-3.27 (m, 1H), 2.96-2.90 (m, 1H), 2.58-2.44 (m, 2H), C-OH not observed.

To 9-bromo-3-(2-bromo-1-hydroxyethyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (approx. 54.4 mmol) in DCM (365mL) was added sodium bicarbonate (5.45 g), sodium bromide (6.14 g), TEMPO (16.55 mg) and water (60 mL). The solution was cooled between 0-5 °C and 6% bleach (91.5 mL) was added. After 1h isopropyl alcohol (20 mL) was added and the reaction mixture was warmed to room temperature. Agitation was stopped, the layers separated and the lower organic layer was collected and concentrated removing approximately 345 g of solvent. The slurry was filtered and the cake washed with 50 mL water and then 50 mL DCM (pre-cooled to 5 °C). The solids were collected and dried under vacuum to obtain 9-bromo-3-(2-bromoacetyl)-10,11-dihydro-5H-dibenzo[c,g]chromen-8(9H)-one (18.6 g, 76% yield). 400 MHz $^1$H NMR ($CDCl_3$) δ 8.03-8.01 (m, 1H), 7.85 (d, $J$ = 8.2 Hz, 1H), 7.82 (s, 1H), 7.71 (s, 1H), 7.67 (s, 1H), 5.19 (s, 2H), 4.74 (dd, $J$ = 4.1, 4.1 Hz, 1H), 4.45 (s, 2H), 3.37-3.29 (m, 1H), 2.99-2.92 (m,1H), 2.59-2.46 (m, 2H); 100 MHz $^{13}$C NMR ($CDCl_3$) δ 190.4, 189.6, 154.2, 136.6, 134.1, 133.9, 132.9, 131.8, 129.3, 127.2, 125.6, 124.2, 123.3, 117.0, 68.1, 49.9, 31.8, 30.4, 25.5.

# DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.**

**CECI EST LE TOME __1___ DE __2___**

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

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# JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.**

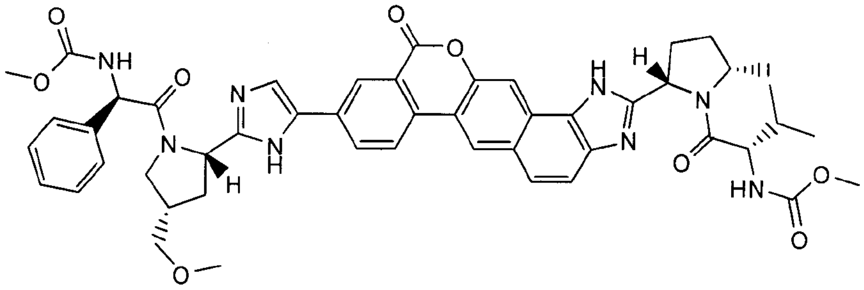
**THIS IS VOLUME __1___ OF __2___**

NOTE: For additional volumes please contact the Canadian Patent Office.

## Claims

1. A compound of formula:

97



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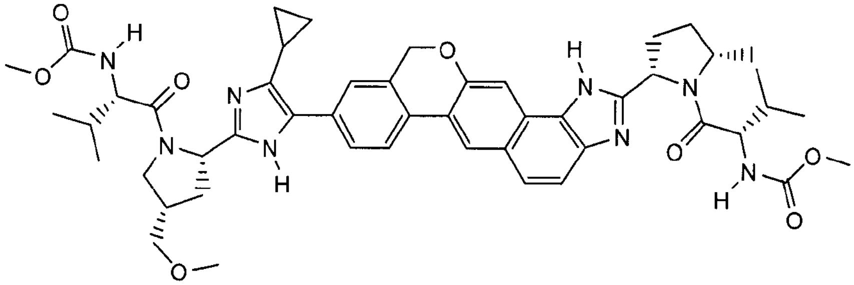

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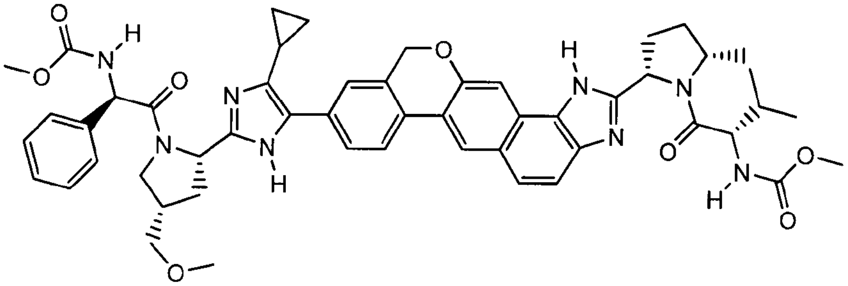

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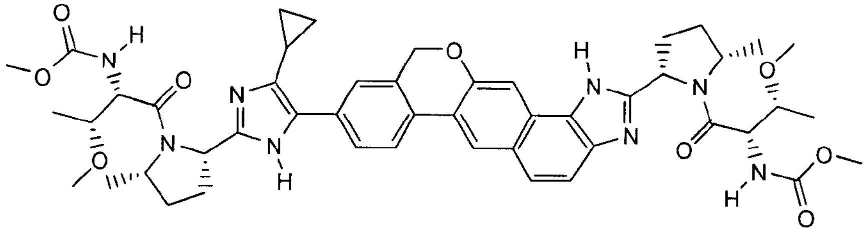

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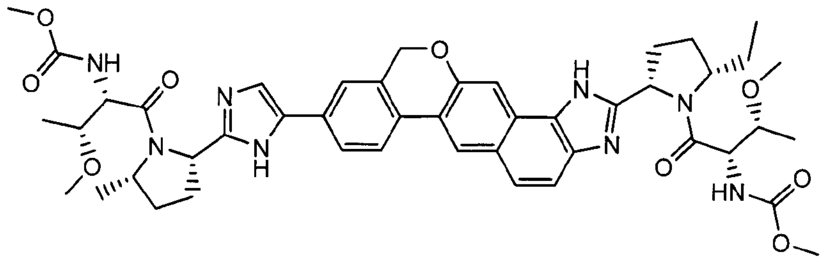

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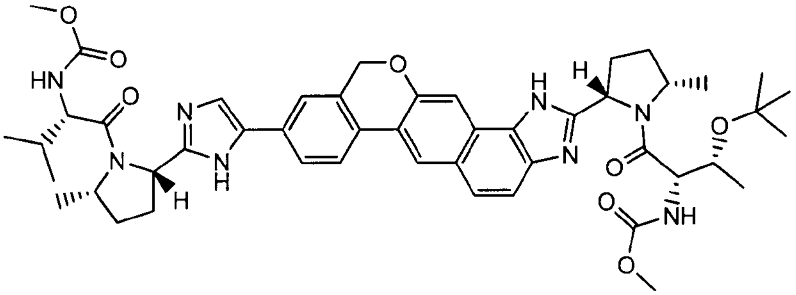

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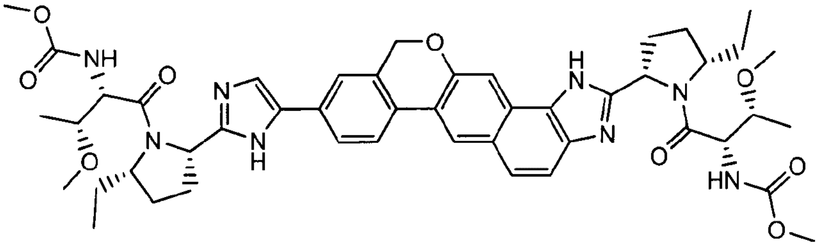

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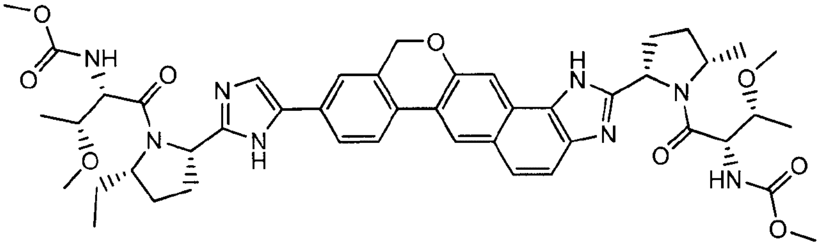

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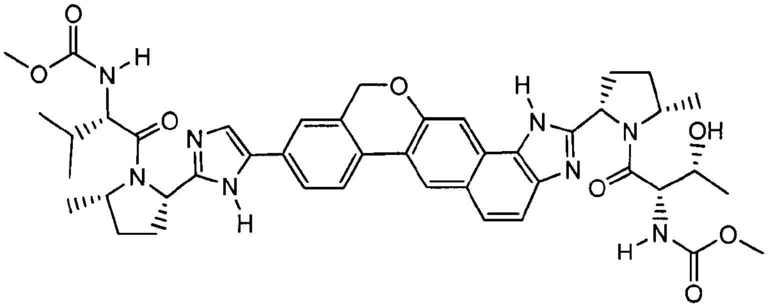

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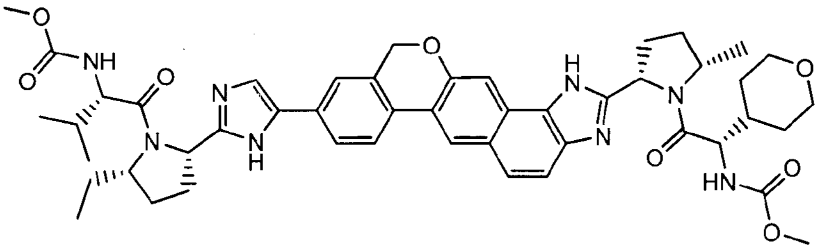

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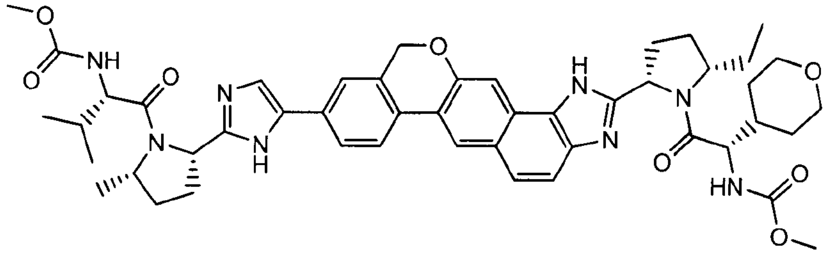

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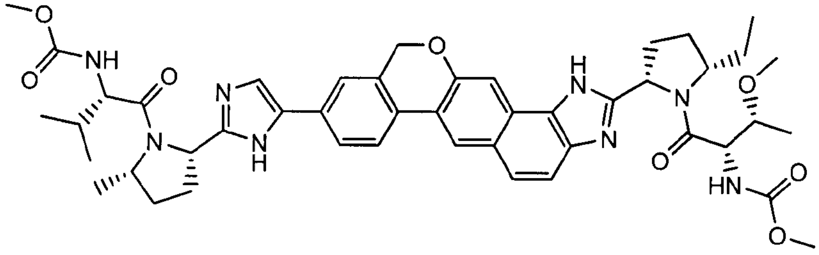

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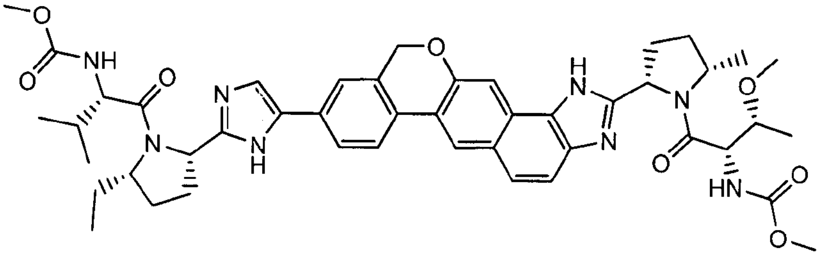

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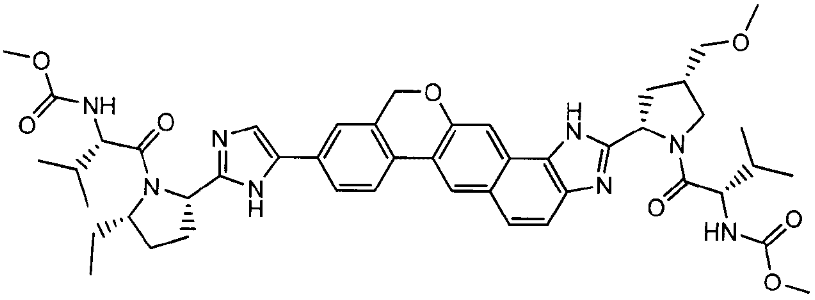

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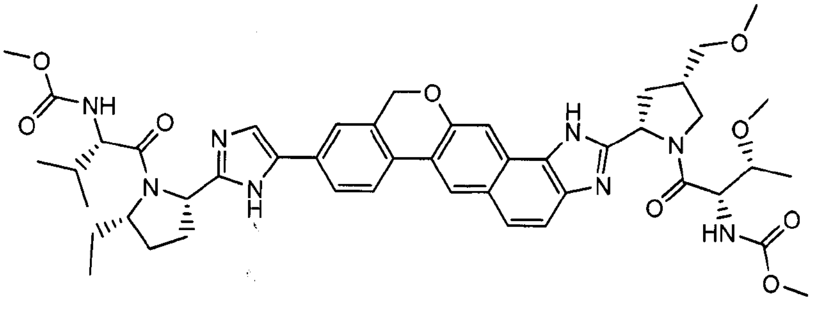

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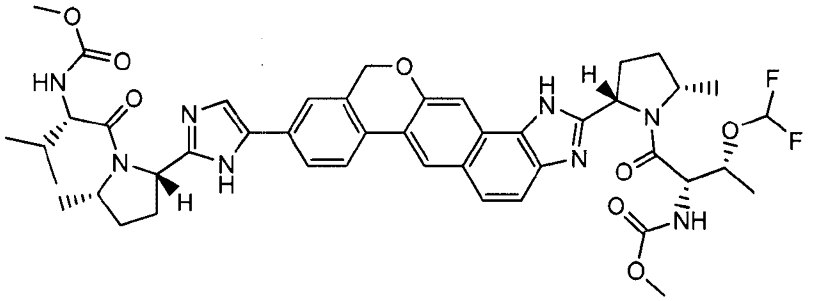

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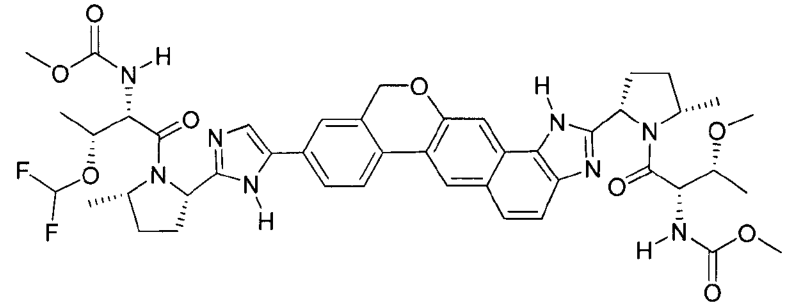

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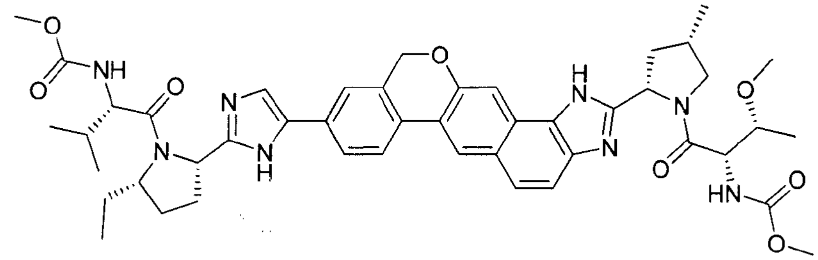

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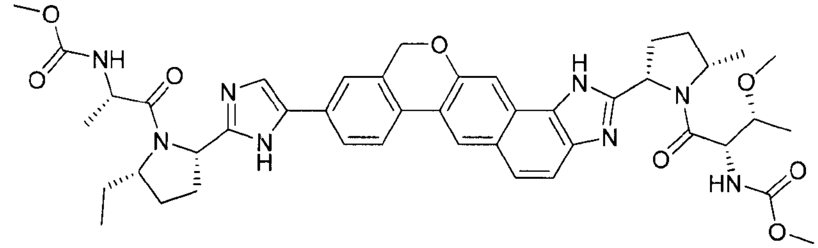

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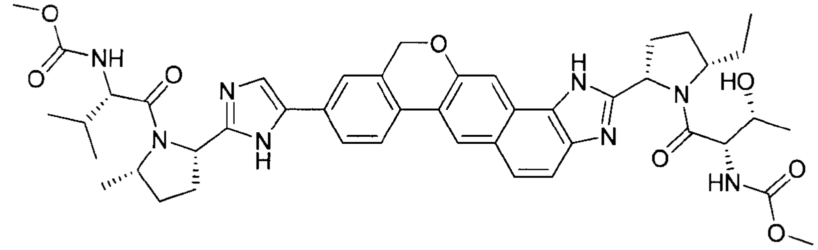

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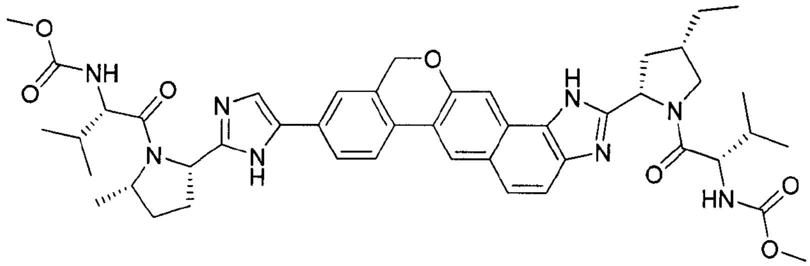

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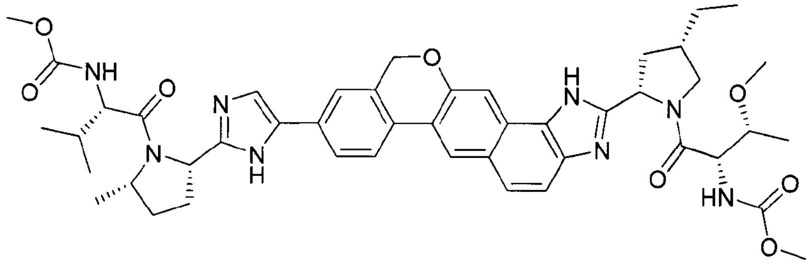

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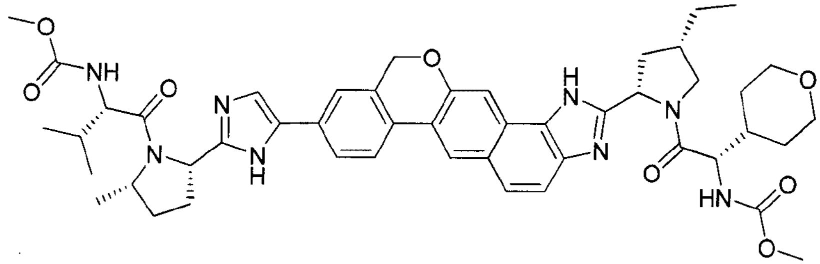

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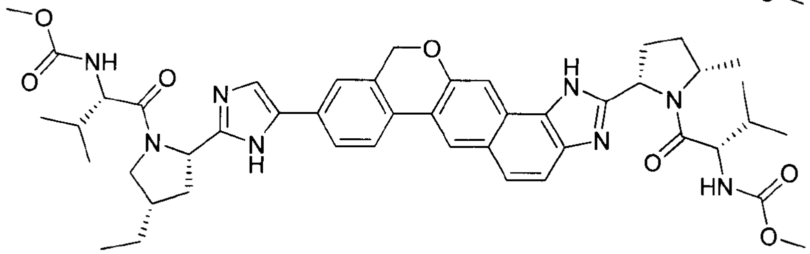

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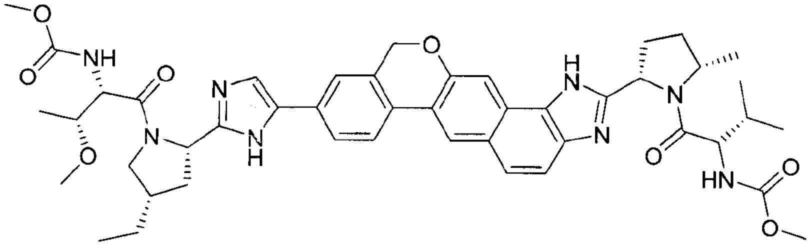

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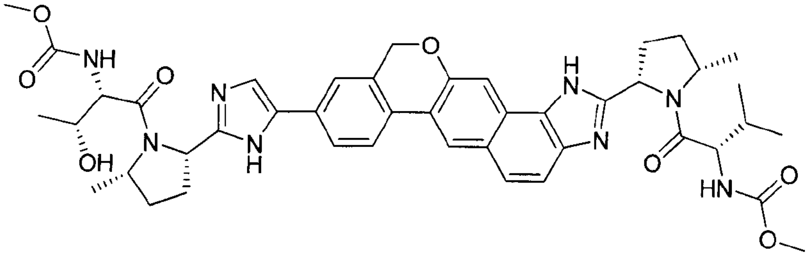

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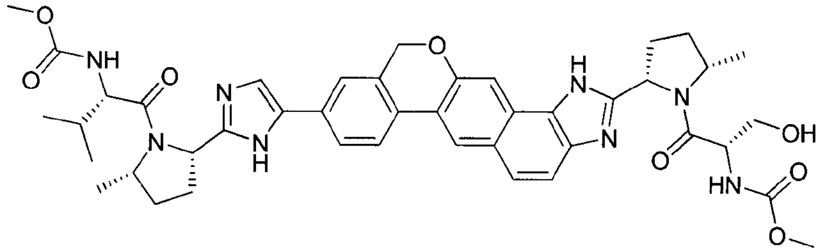

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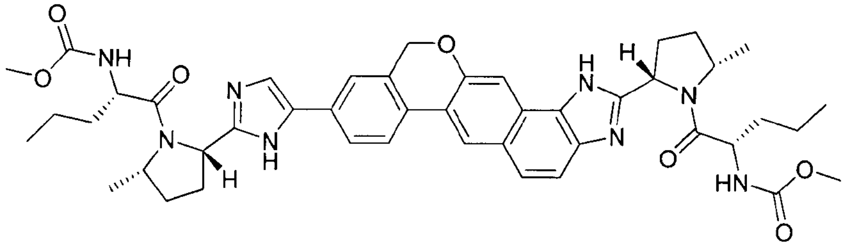

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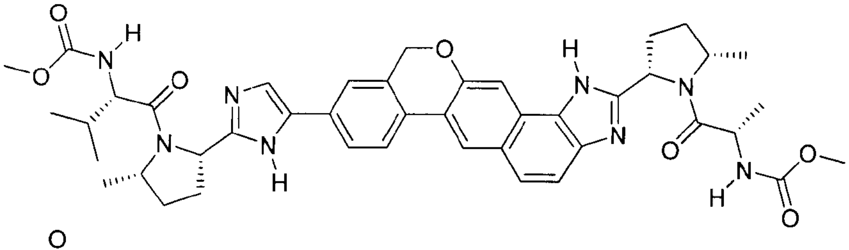

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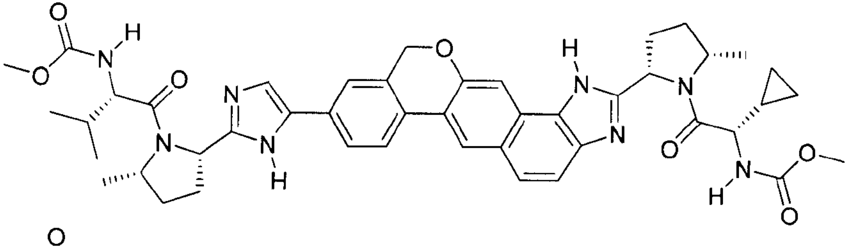

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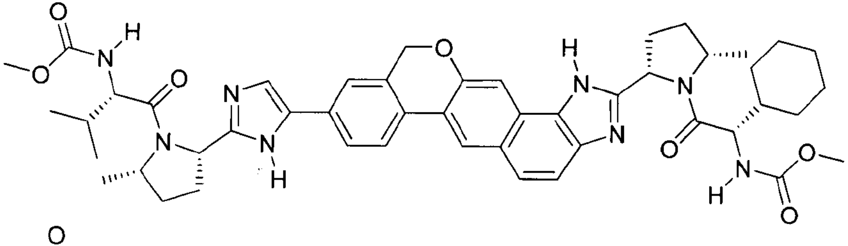

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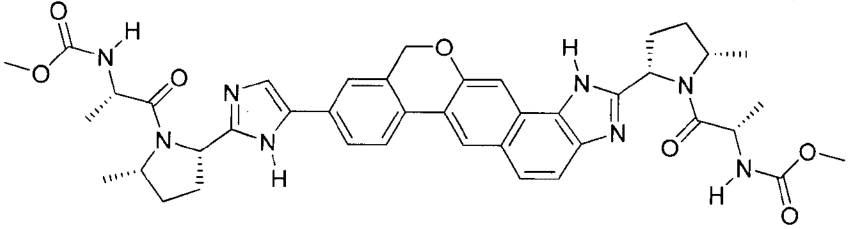

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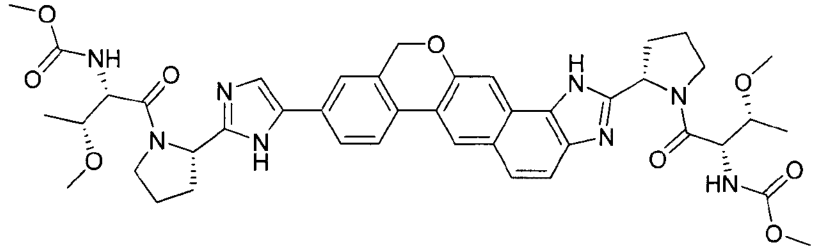

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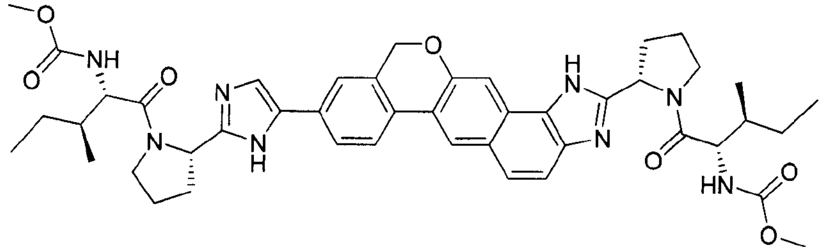

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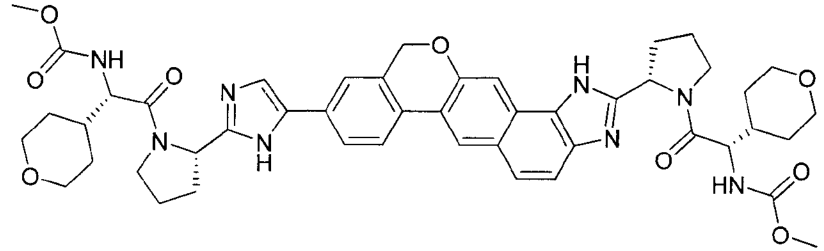

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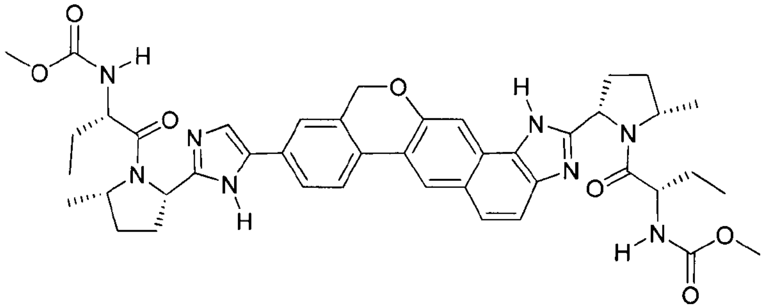

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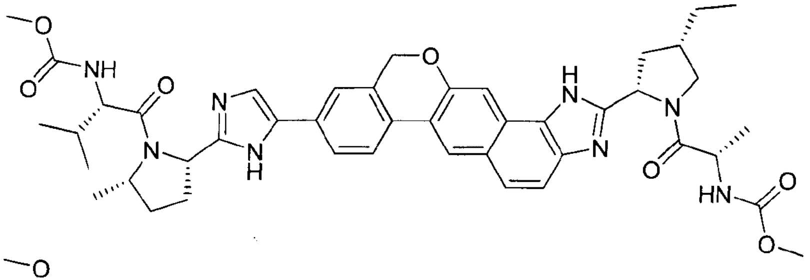

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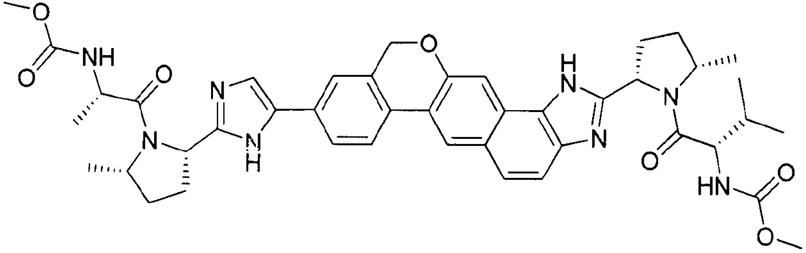

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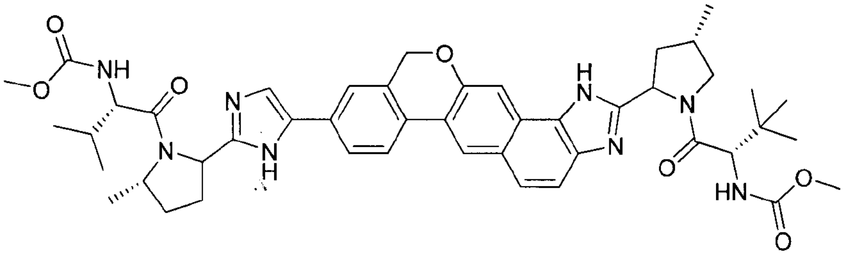

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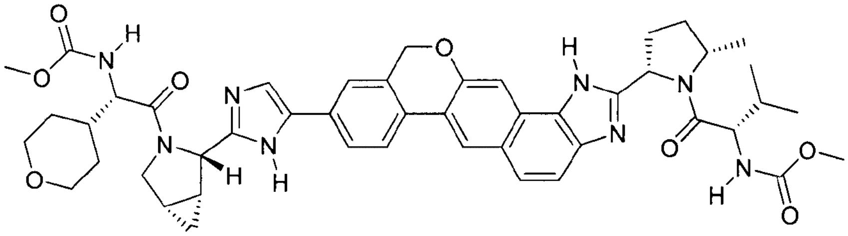

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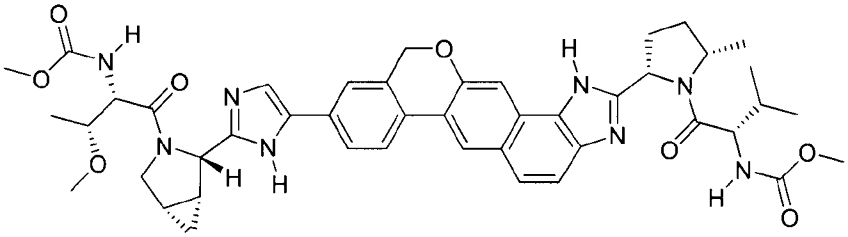

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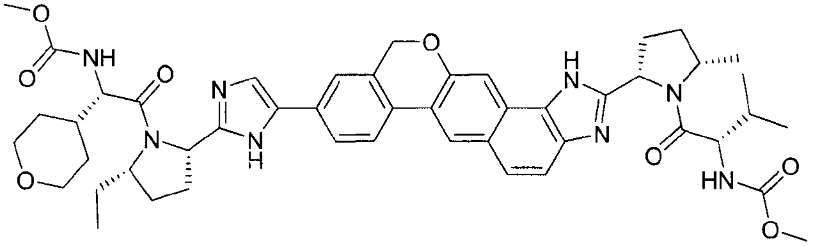

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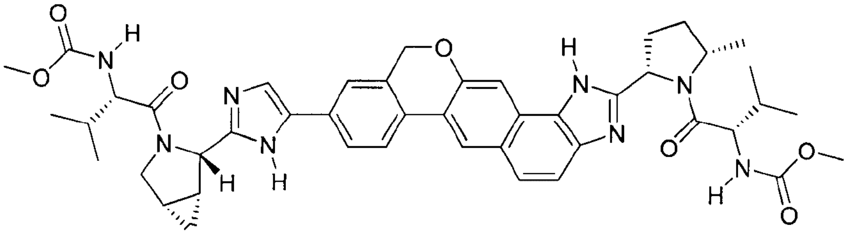

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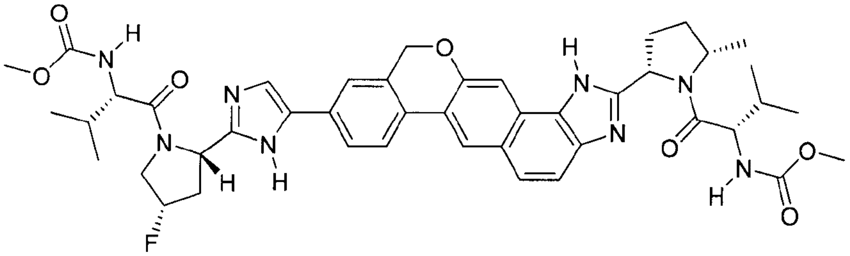

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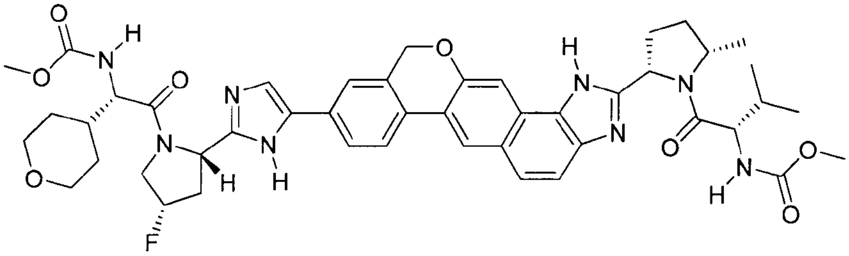

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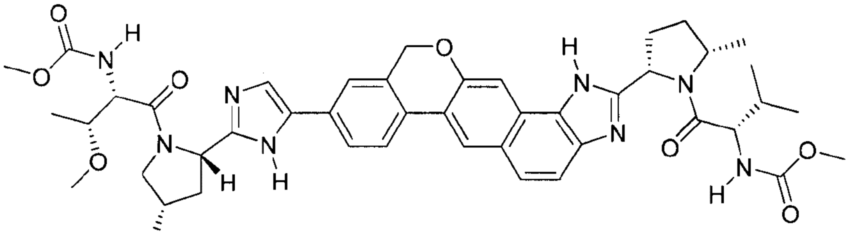

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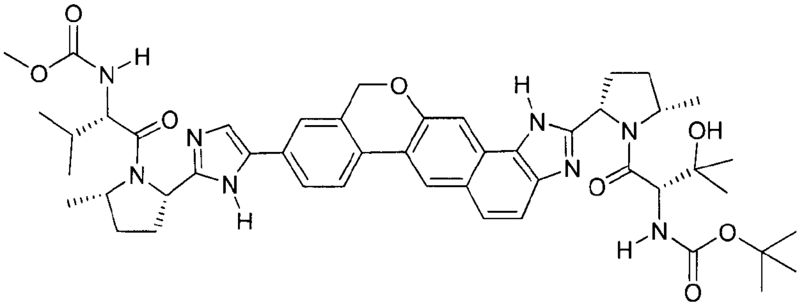

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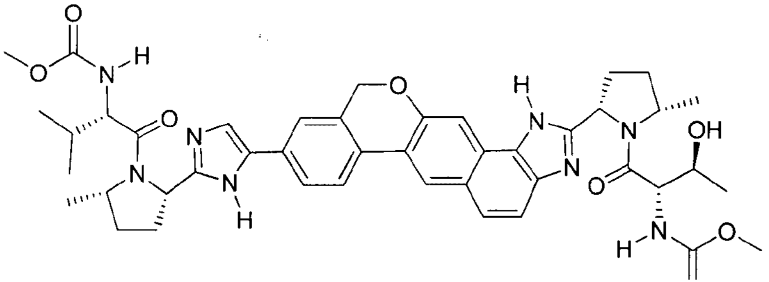

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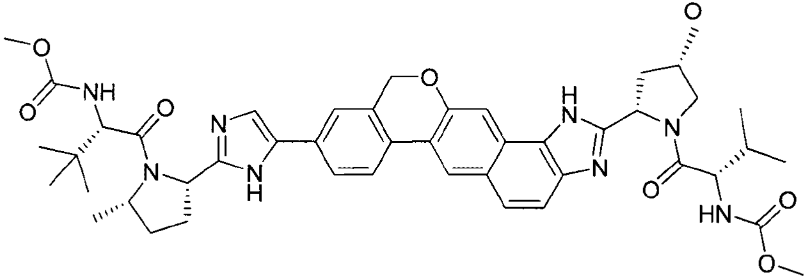

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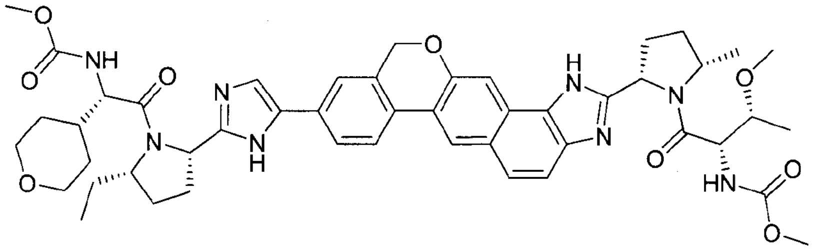

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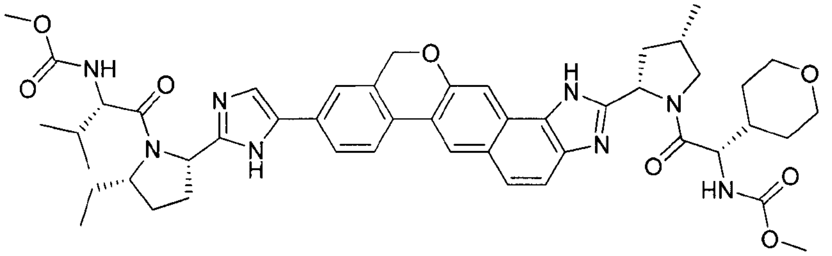

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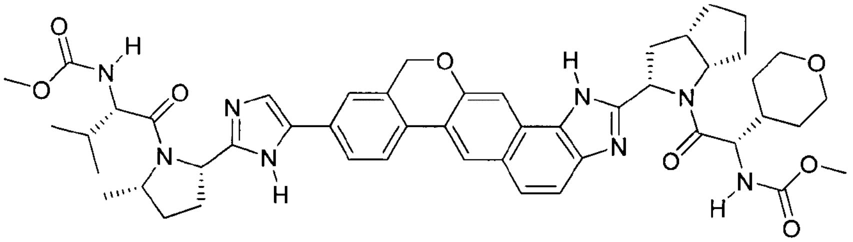

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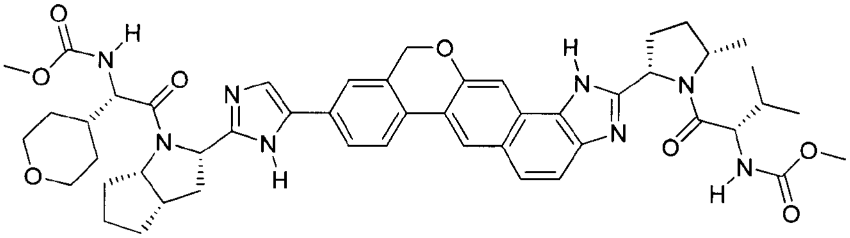

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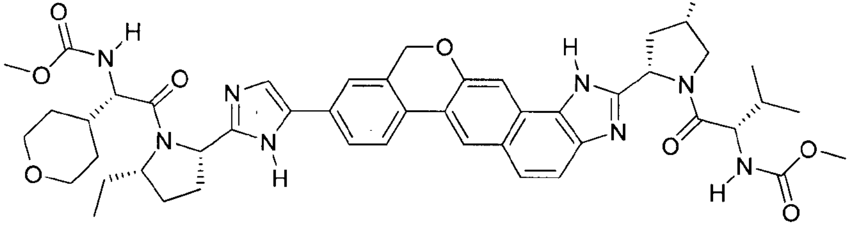

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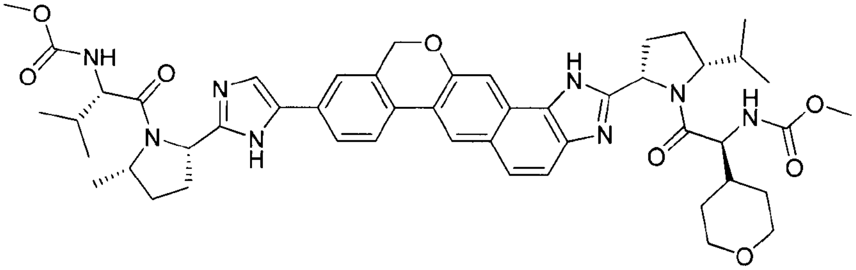

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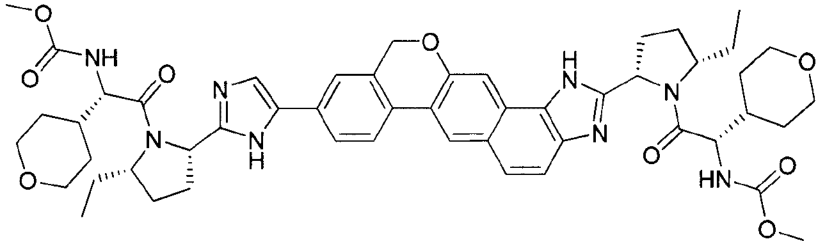

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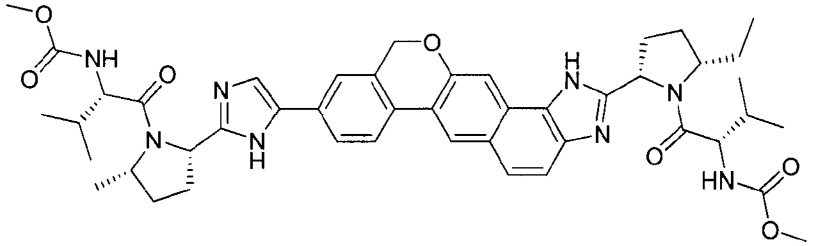

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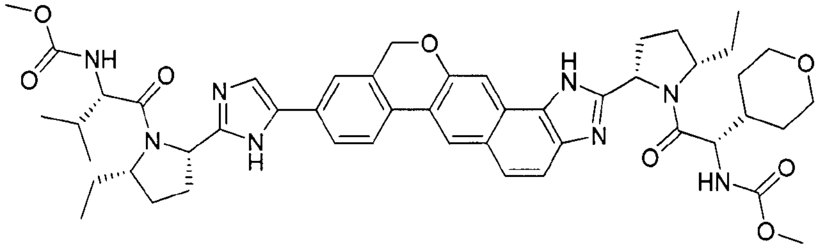

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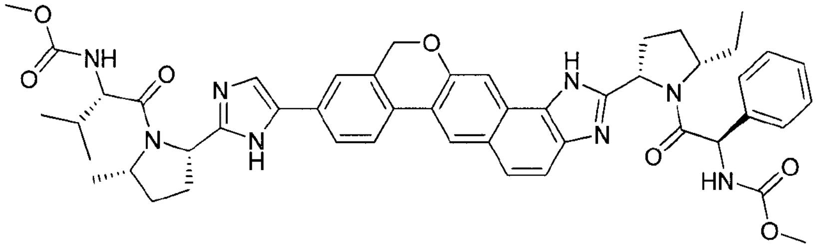

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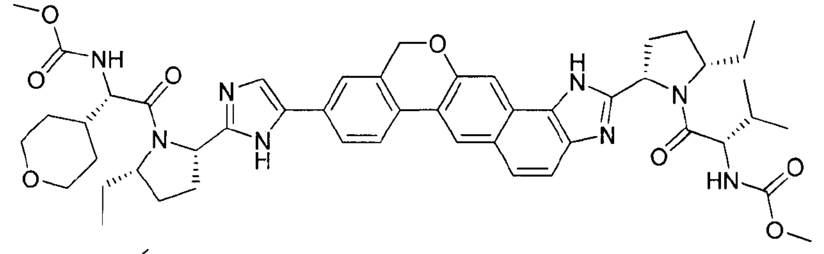

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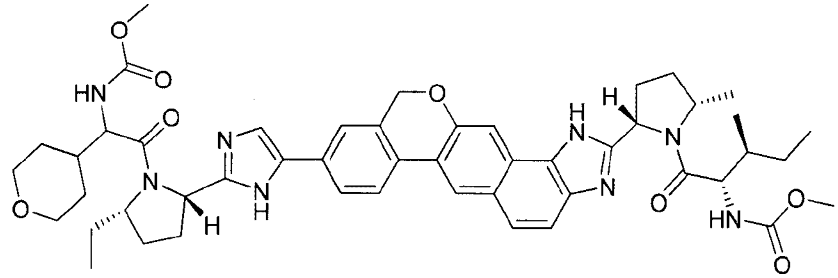

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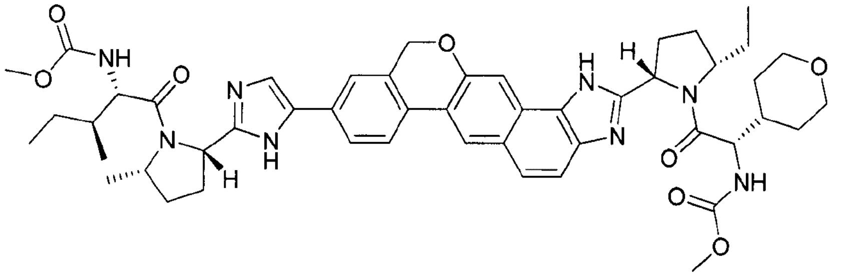

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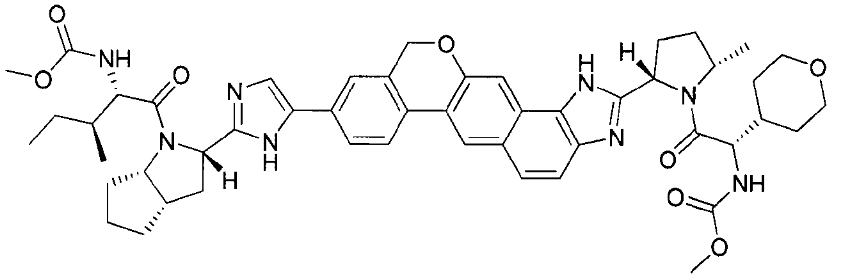

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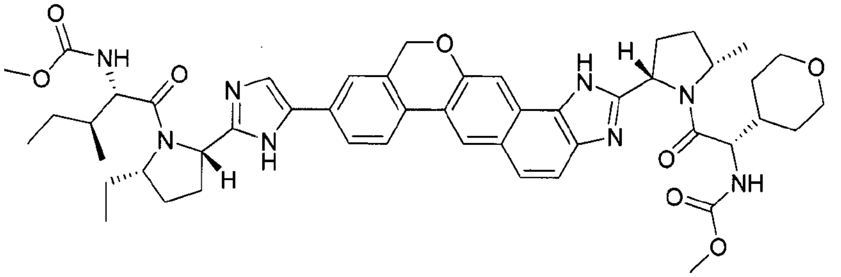

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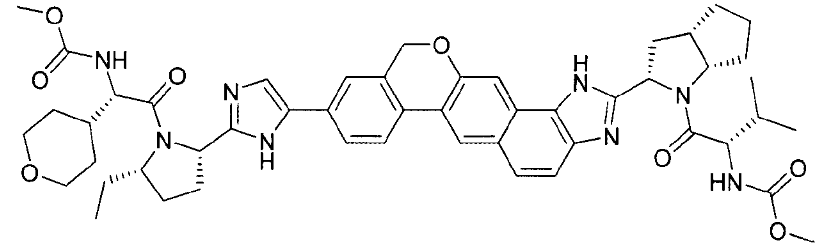

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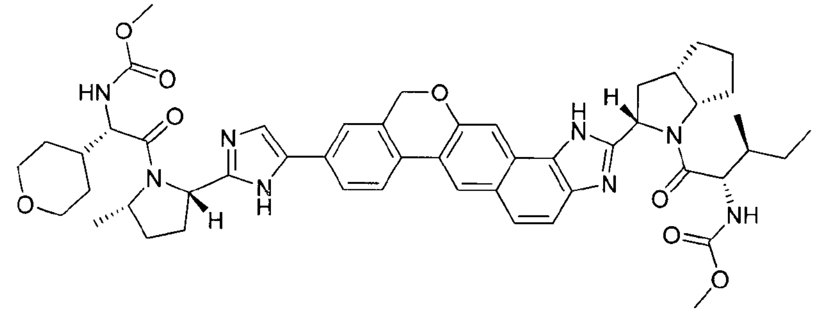

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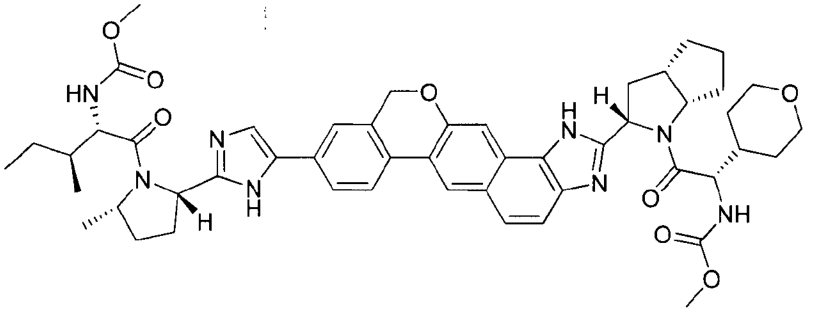

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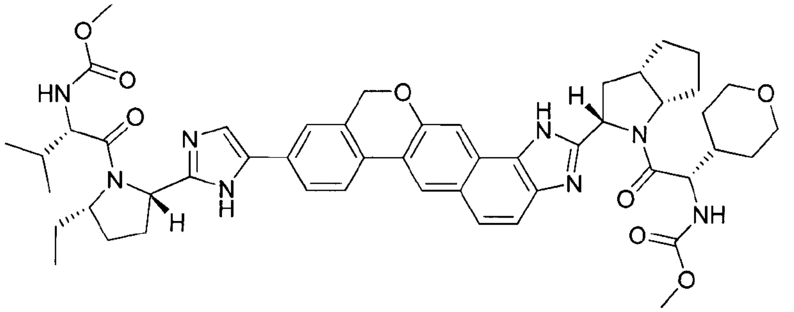

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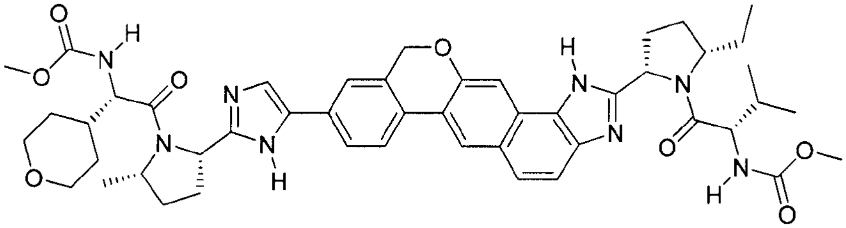

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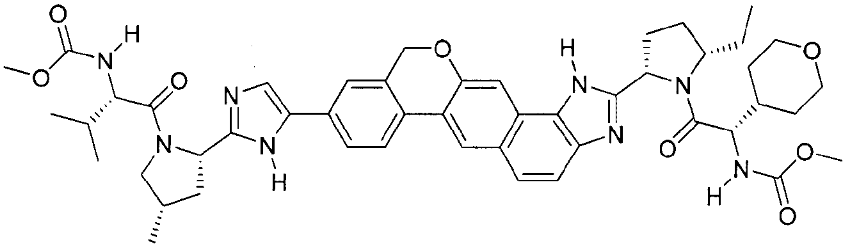

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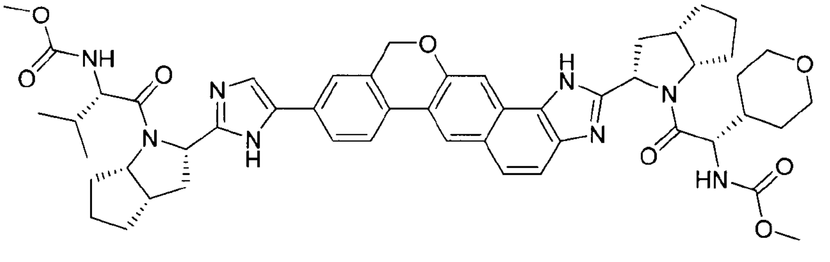

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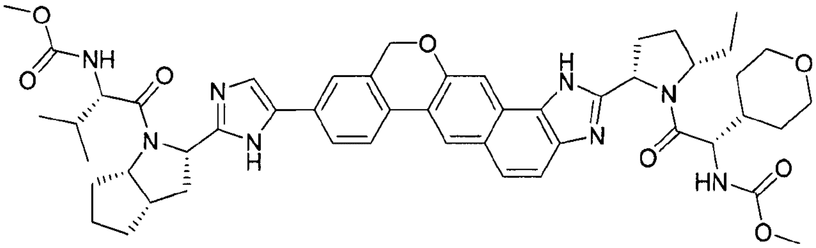

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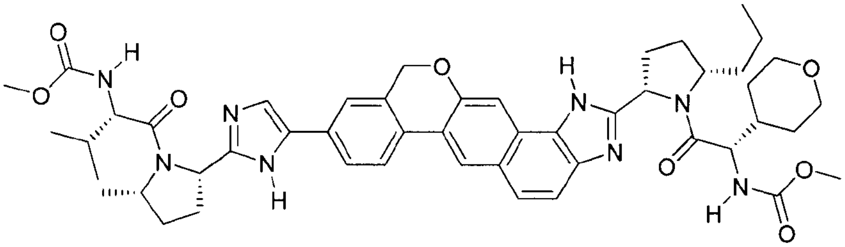

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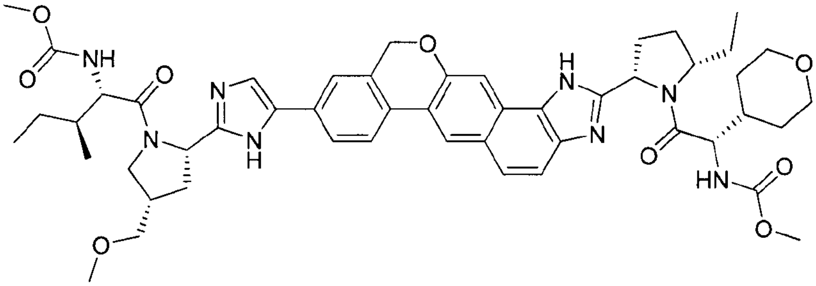

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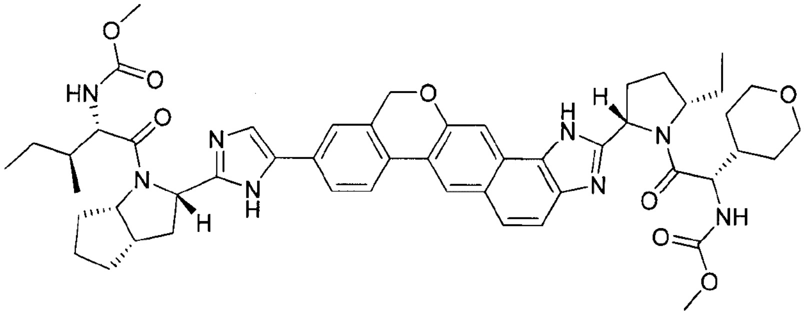

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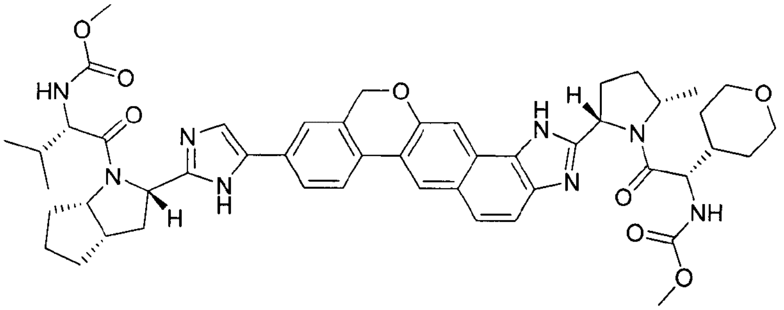

or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable diluent or carrier, or combination thereof.

3. The pharmaceutical composition of claim 2, formulated for oral administration.

4. The pharmaceutical composition of claim 2, formulated in tablet form.

5. A composition comprising the compound of claim 1 for the prophylactic or therapeutic treatment of hepatitis C.

6. Use of the compound of claim 1 in the manufacture of a medicament for the treatment of hepatitis C.

7. The pharmaceutical composition of claim 2 for use in the prophylactic or therapeutic treatment of hepatitis C.

8. A compound of formula:

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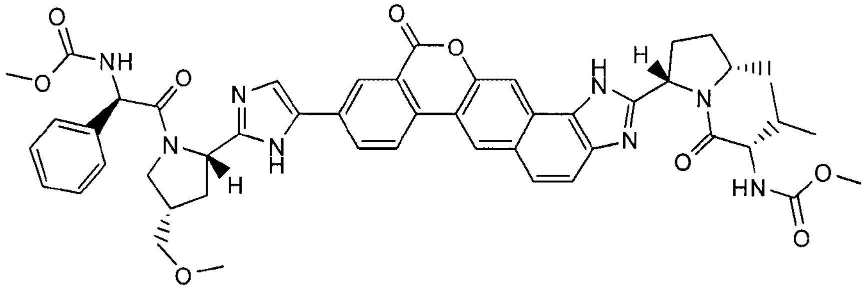

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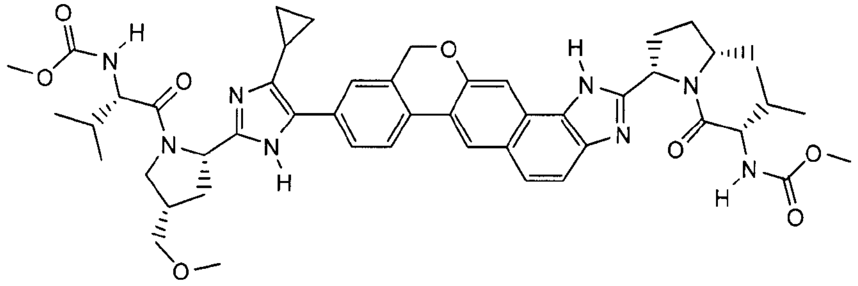

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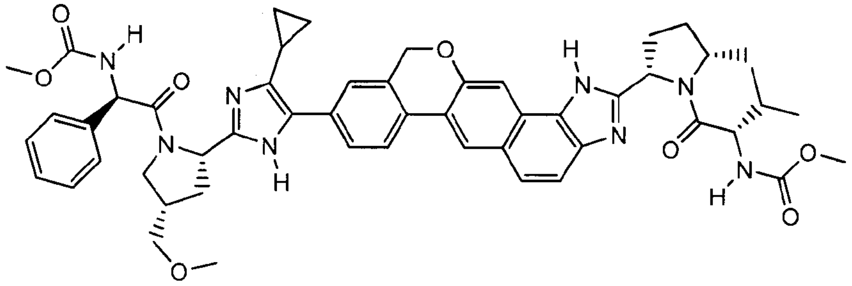

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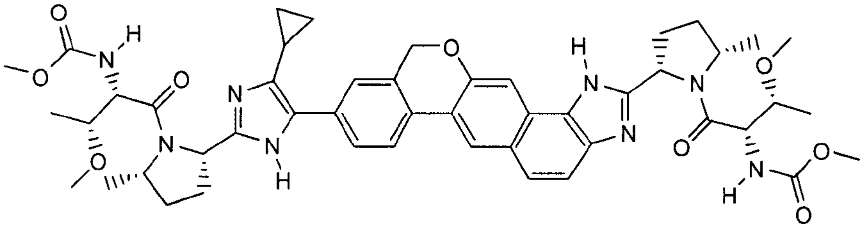

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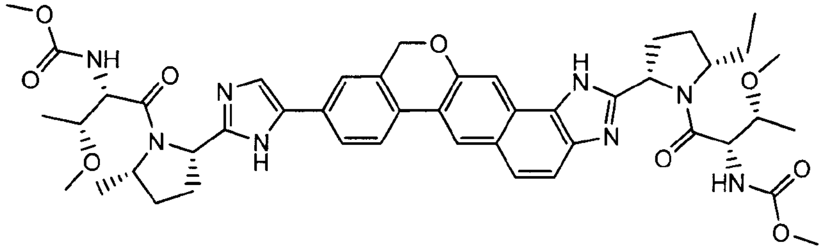

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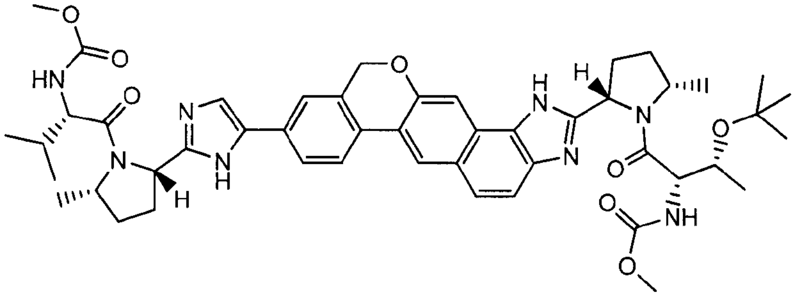

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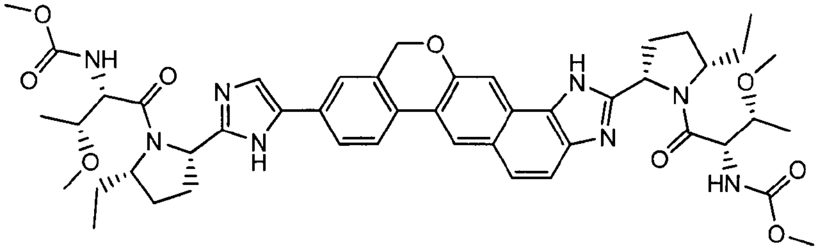

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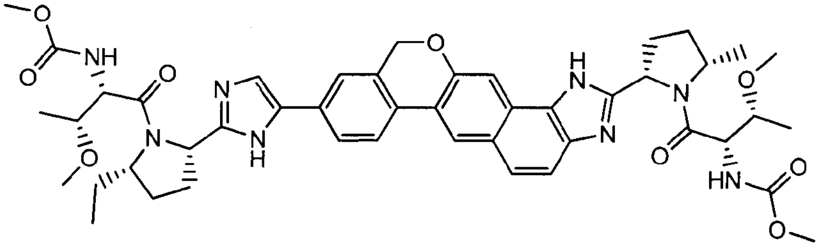

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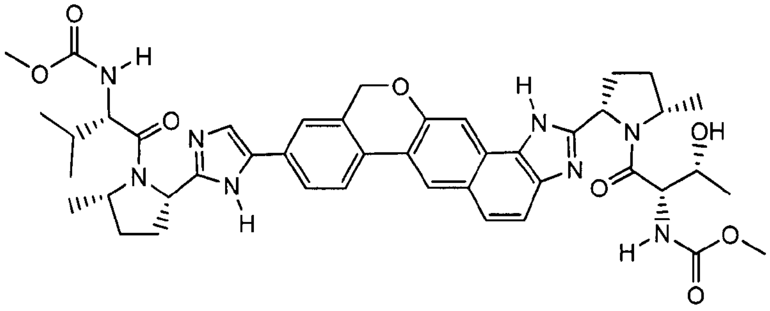

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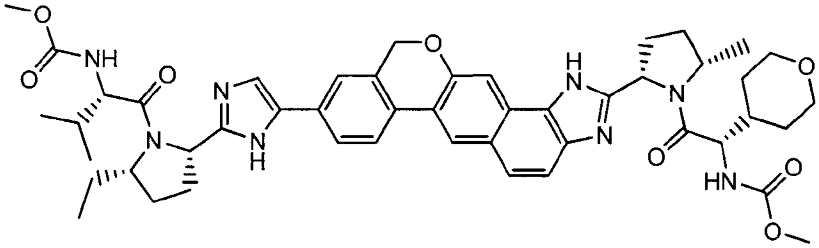

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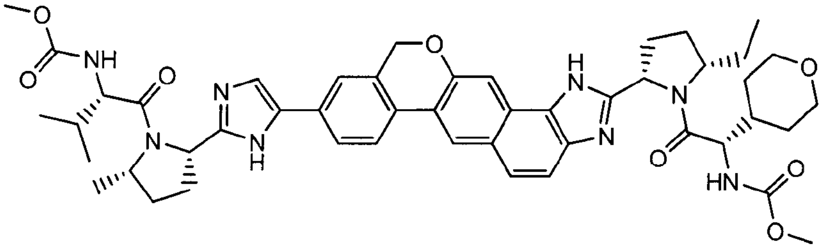

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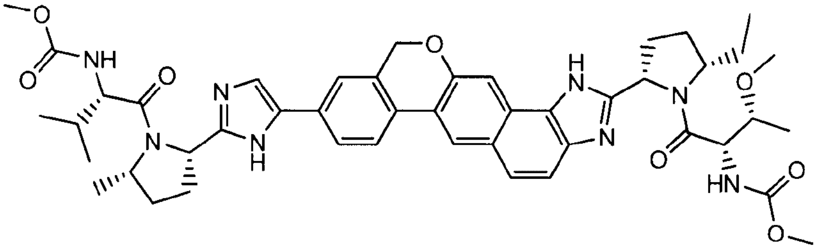

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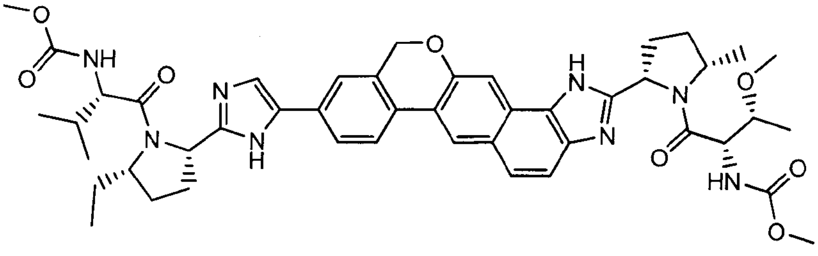

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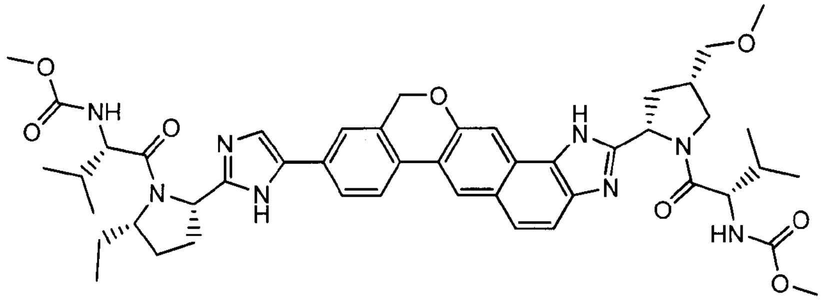

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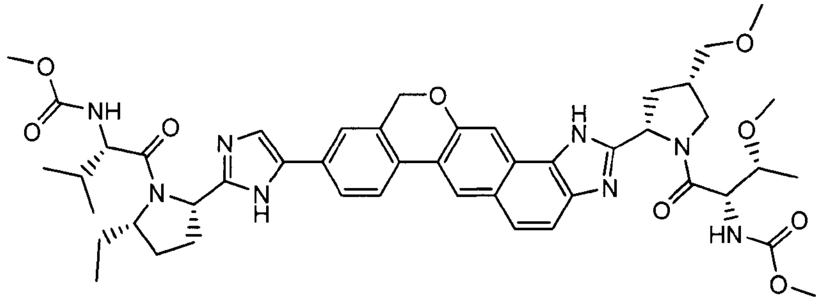

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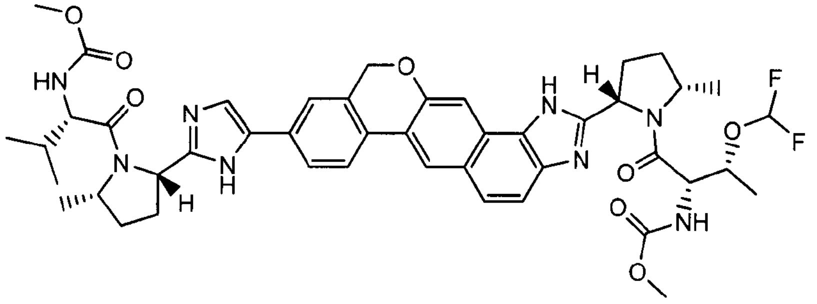

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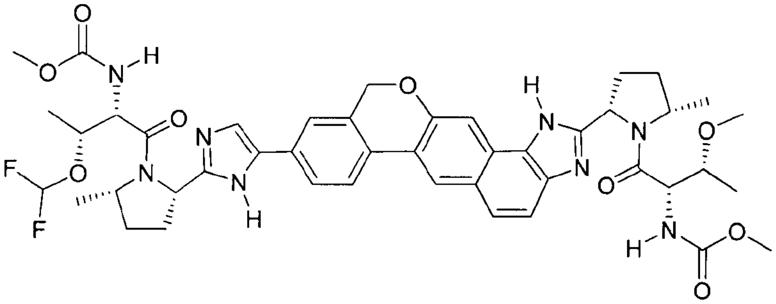

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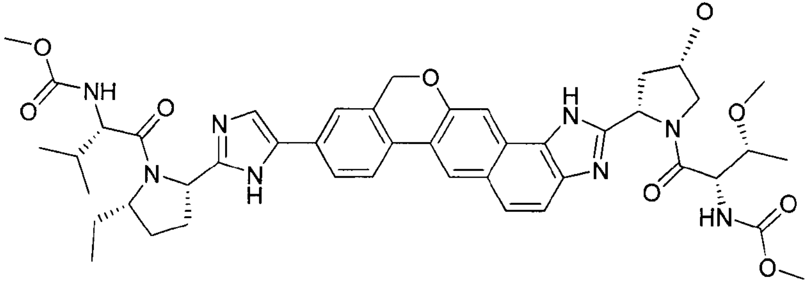

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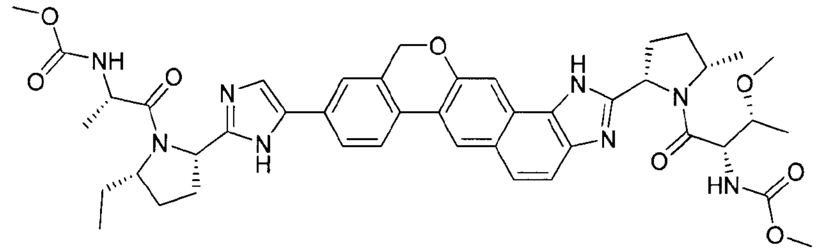

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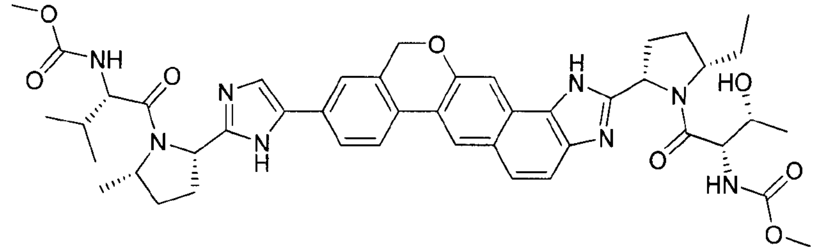

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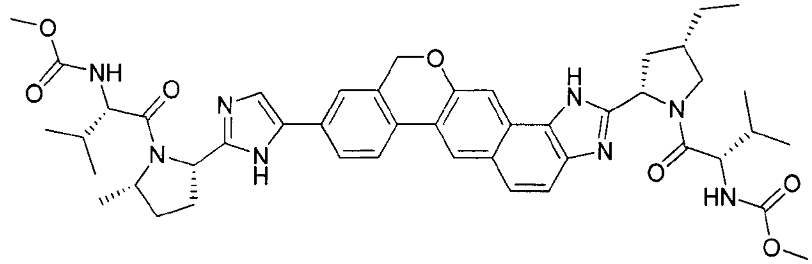

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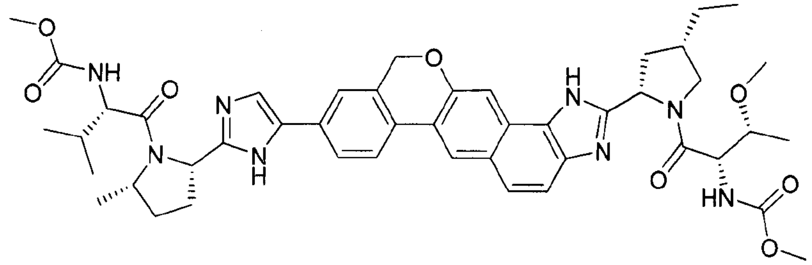

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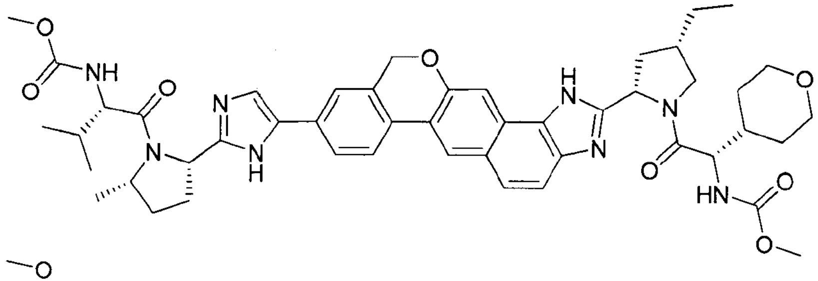

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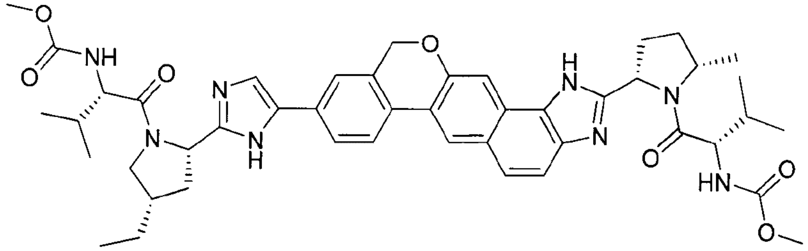

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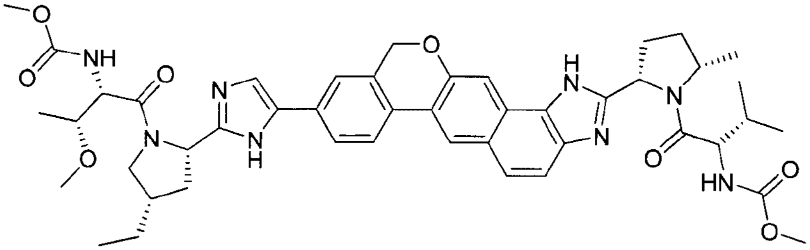

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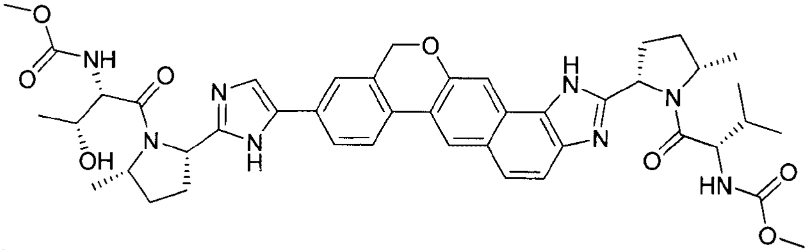

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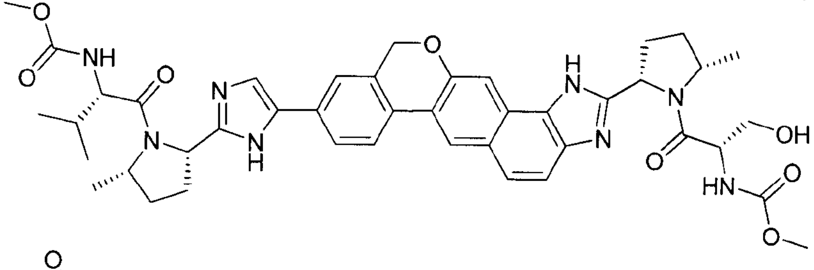

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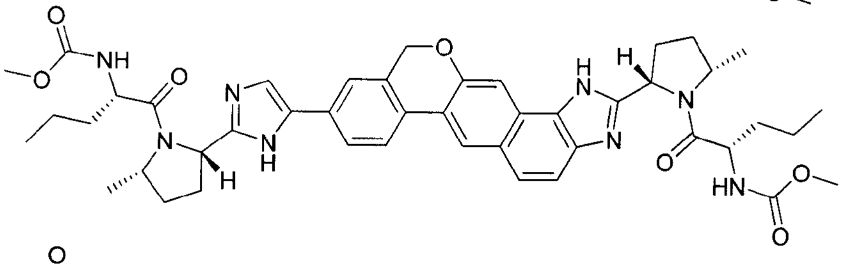

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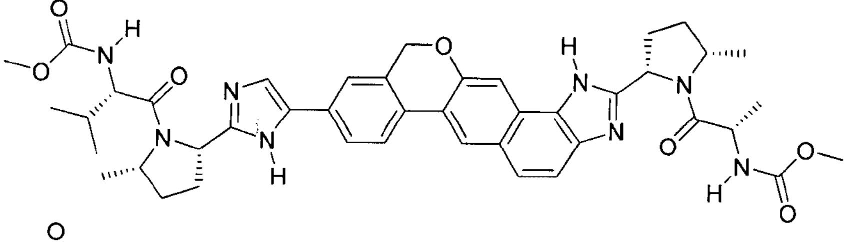

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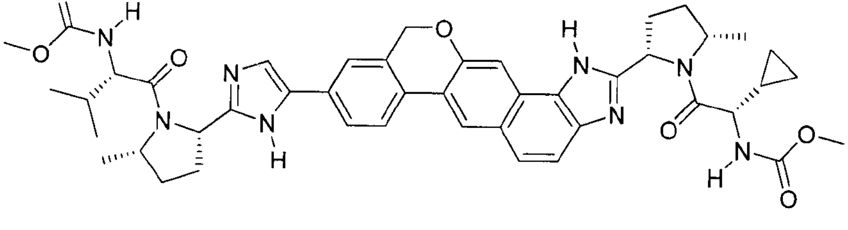

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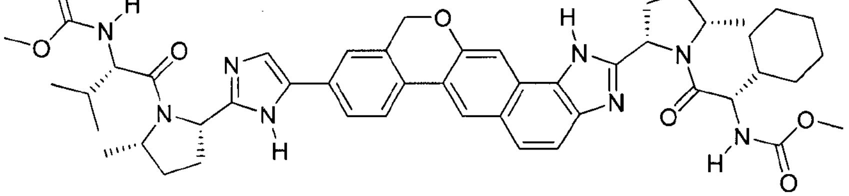

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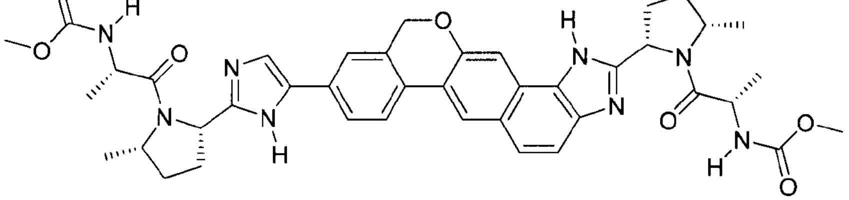

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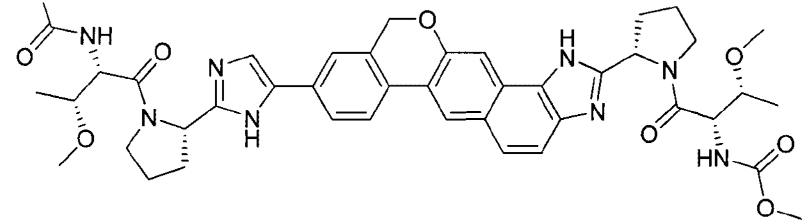

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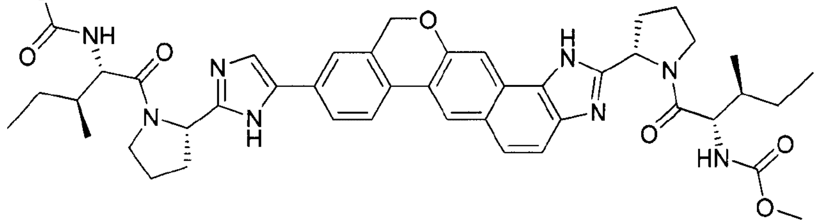

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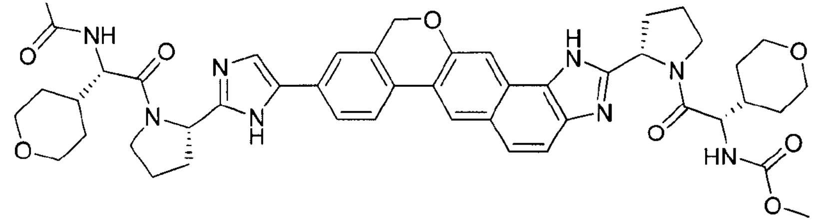

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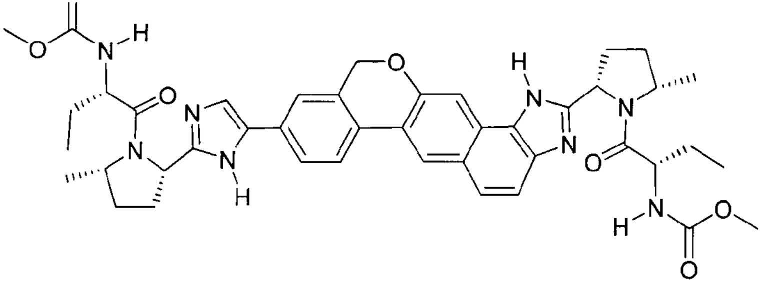

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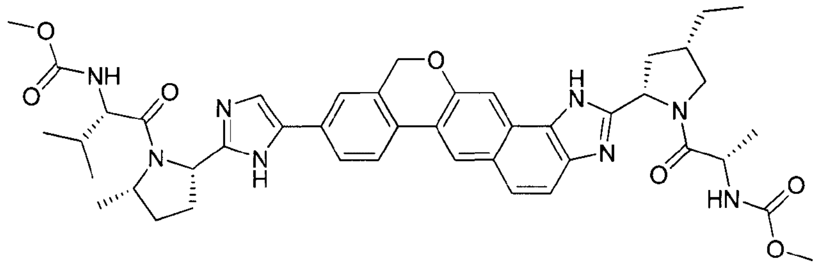

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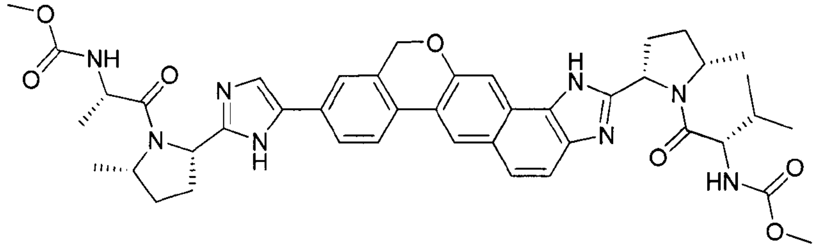

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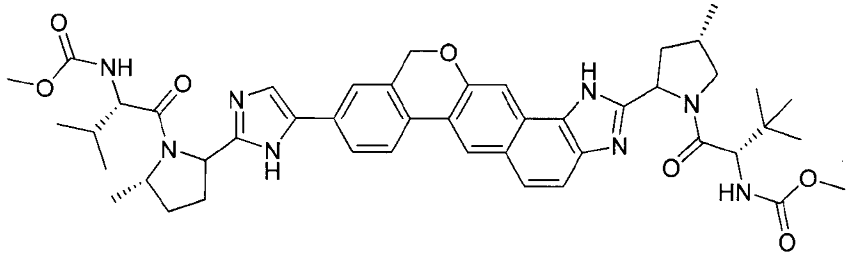

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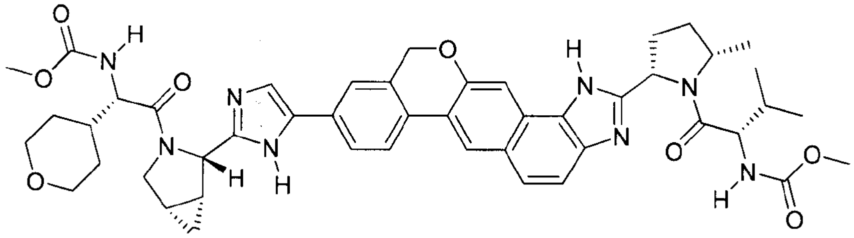

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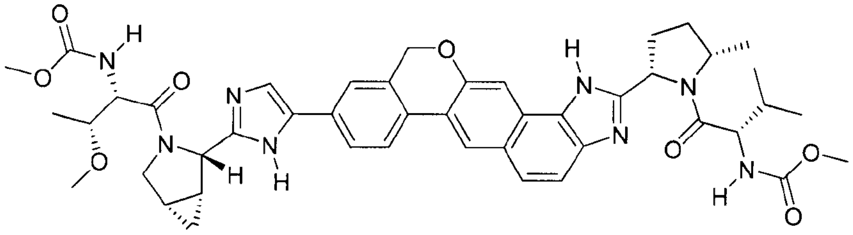

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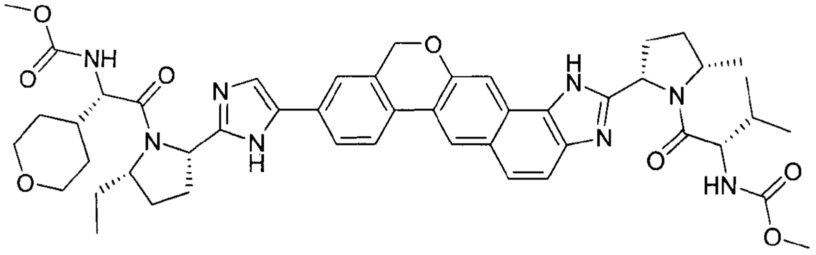

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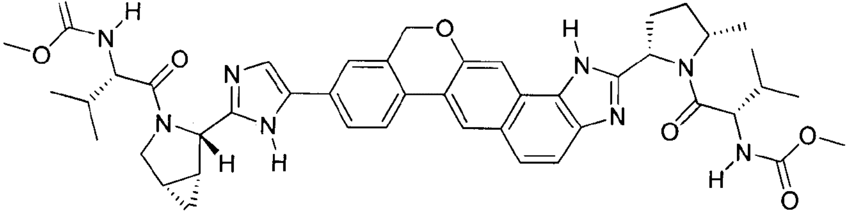

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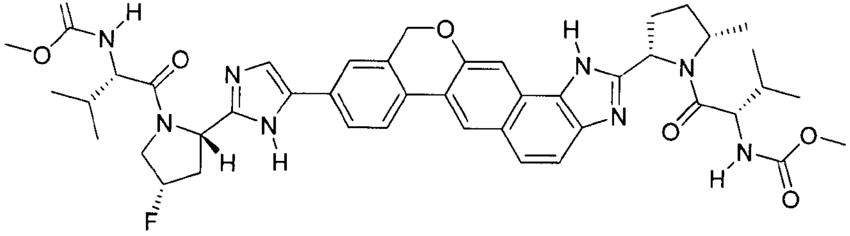

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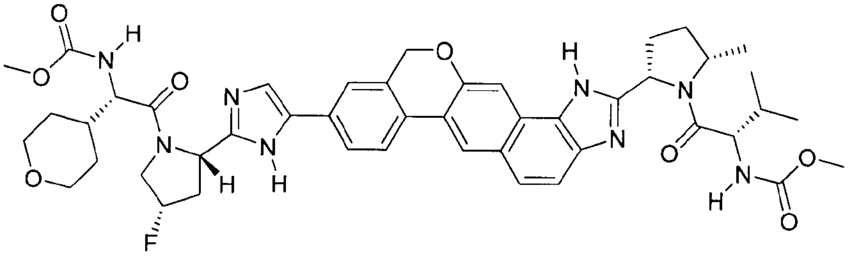

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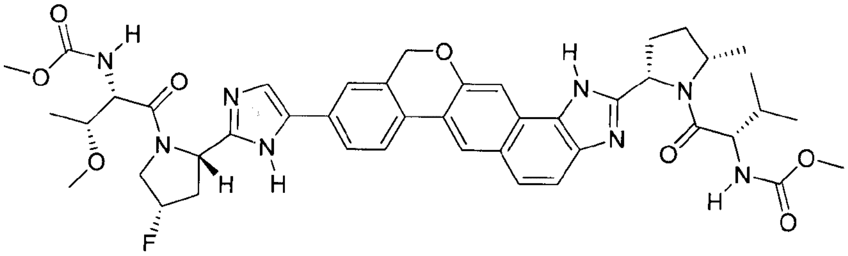

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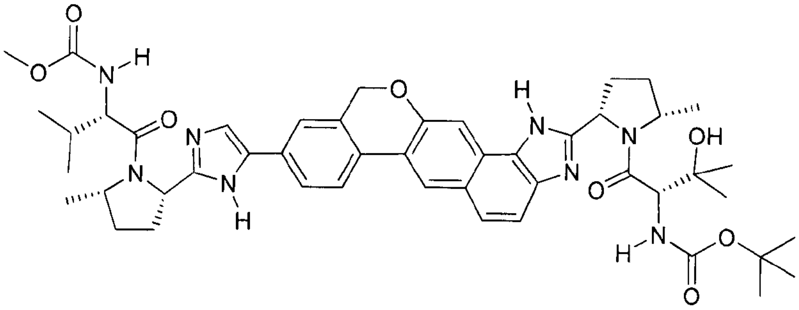

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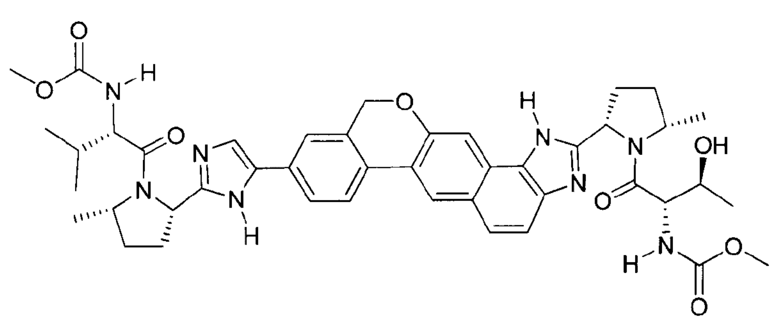

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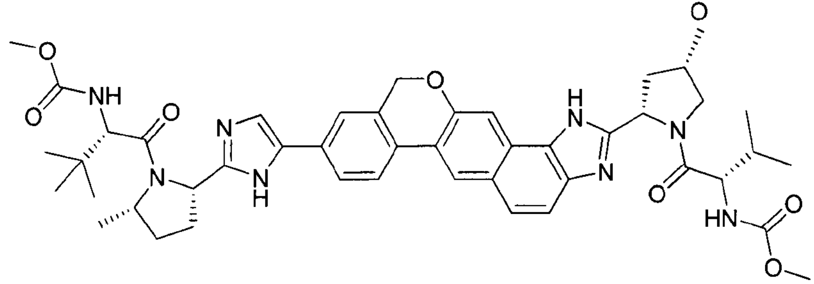

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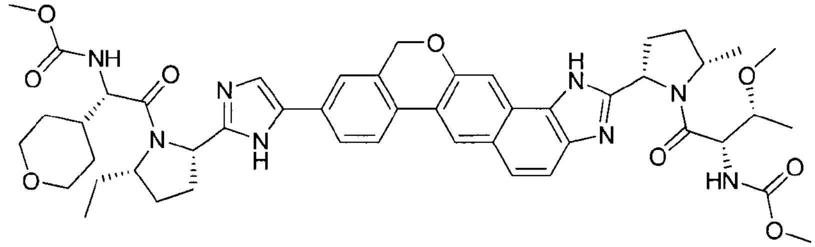

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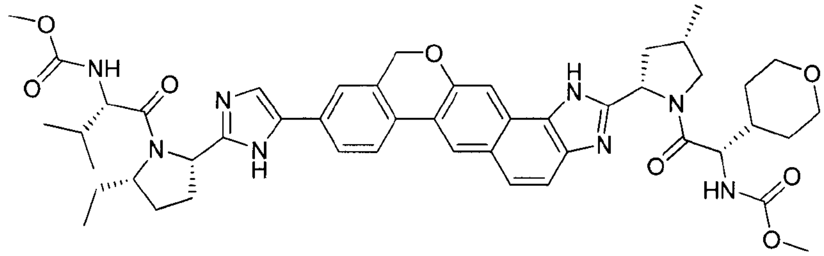

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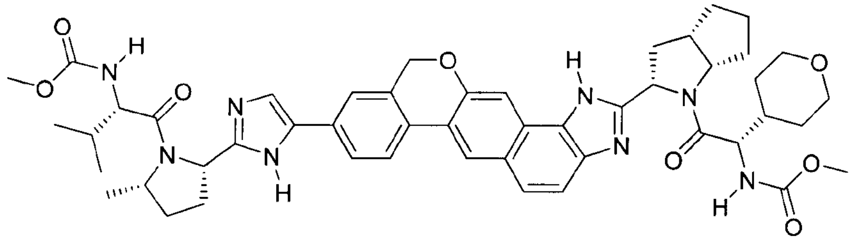

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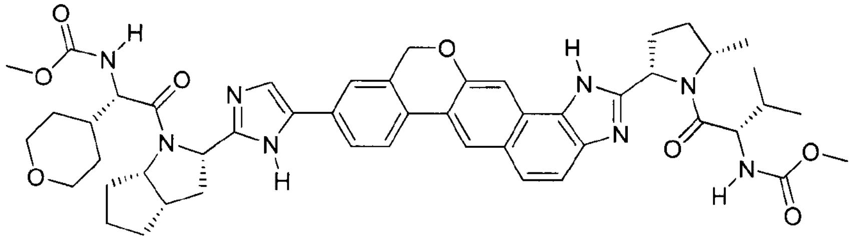

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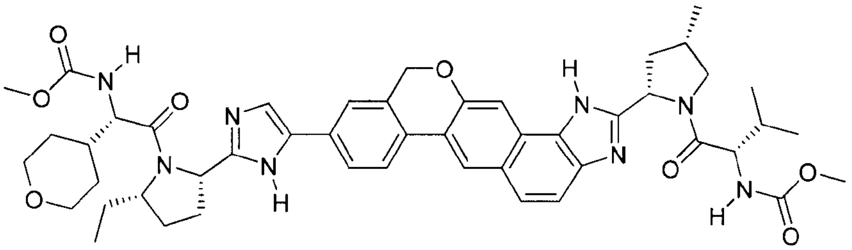

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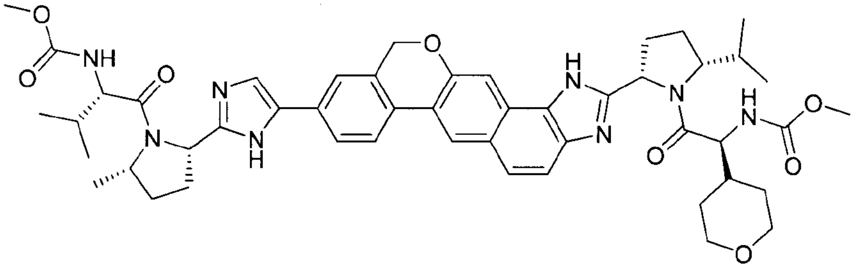

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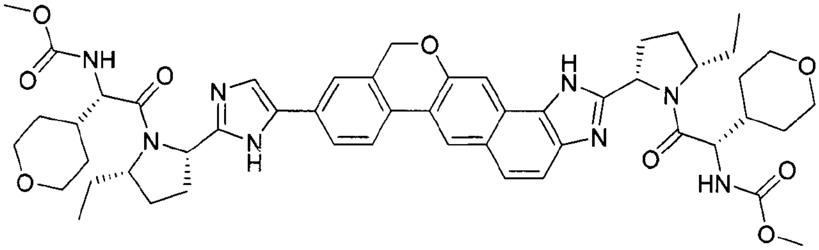

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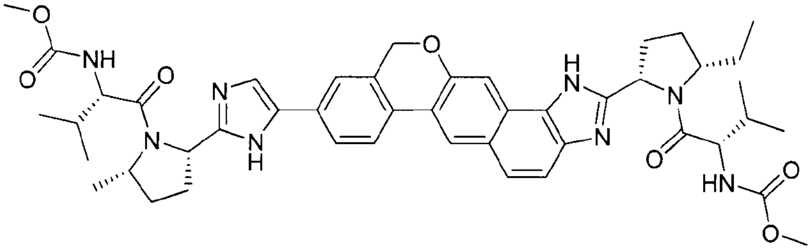

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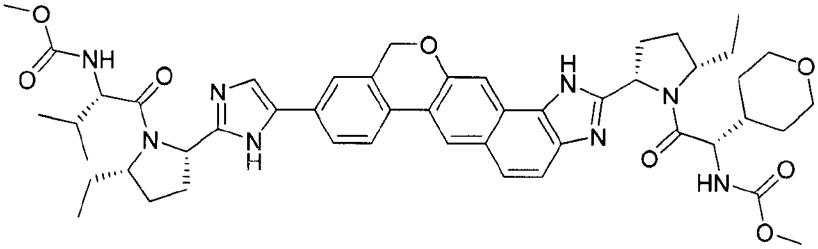

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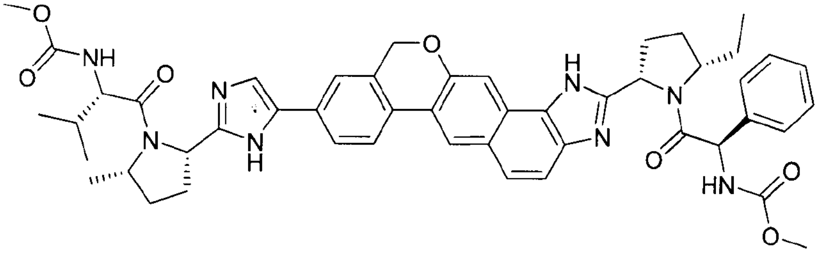

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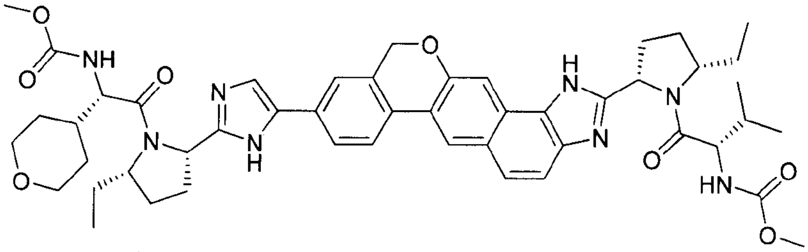

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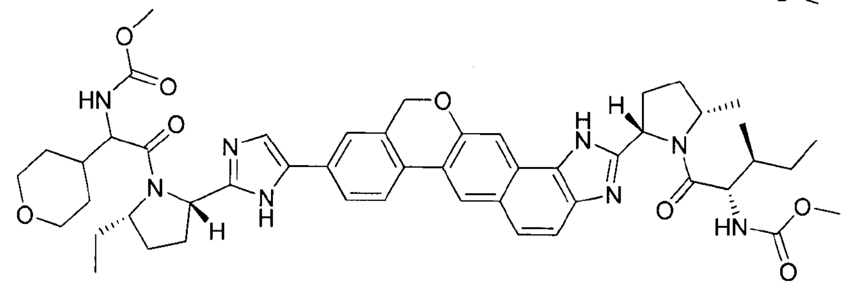

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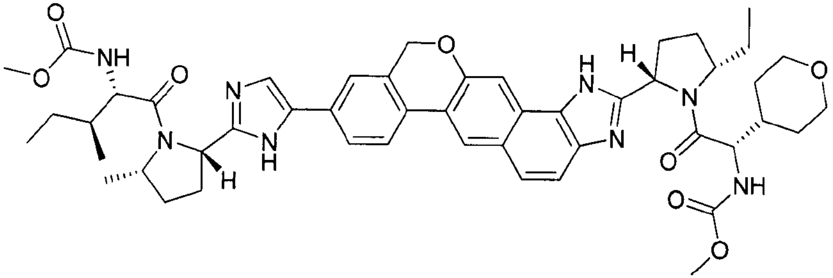

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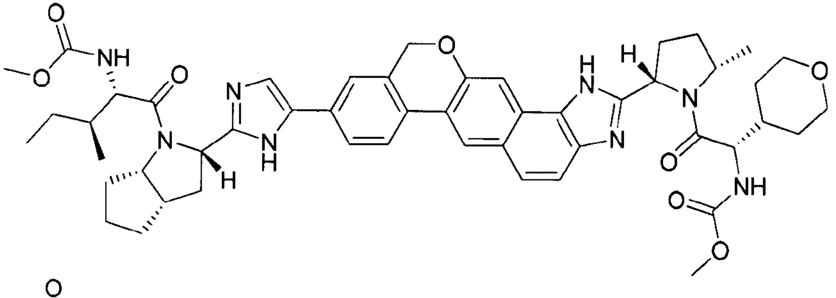

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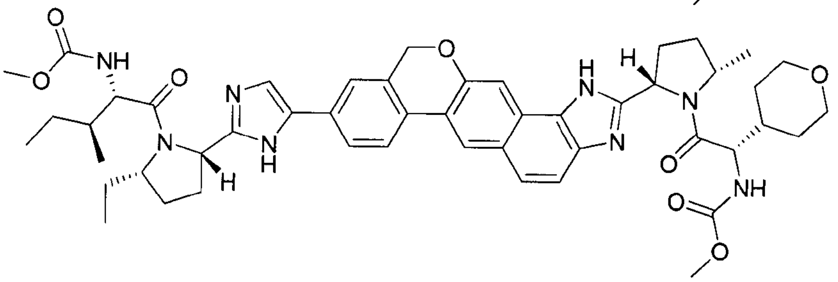

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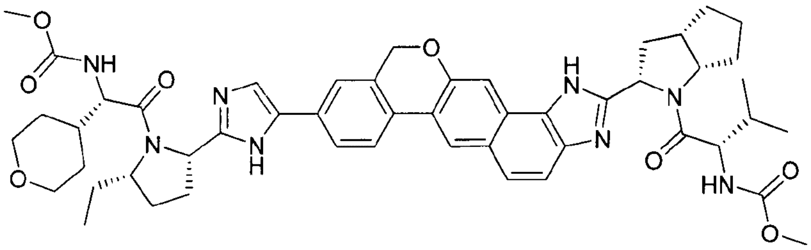

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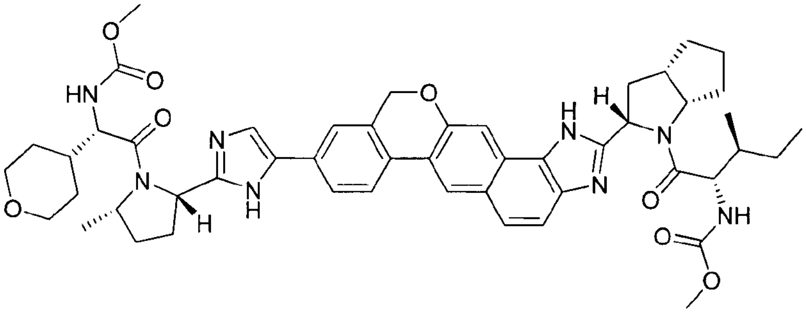

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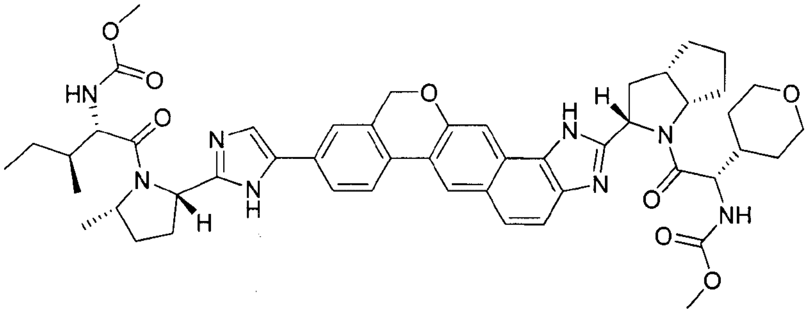

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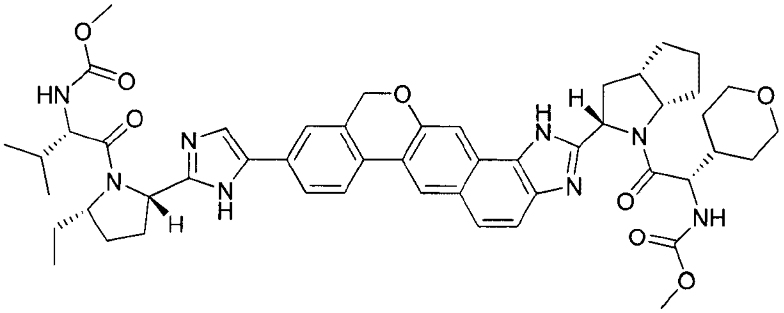

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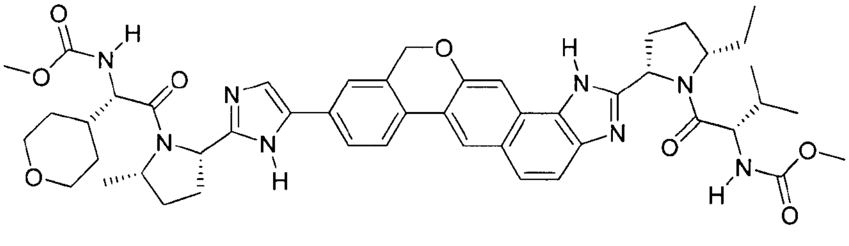

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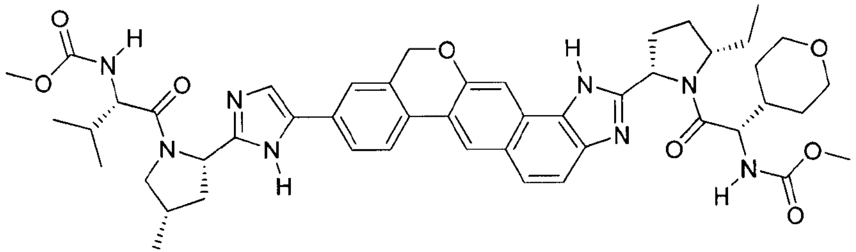

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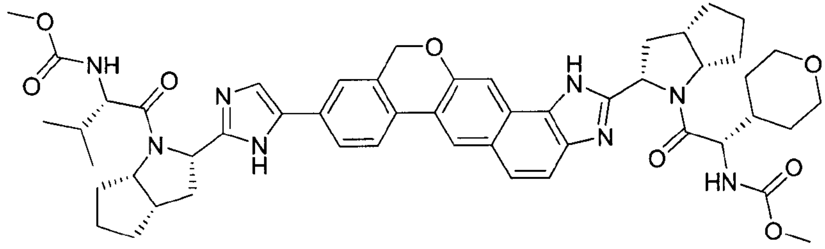

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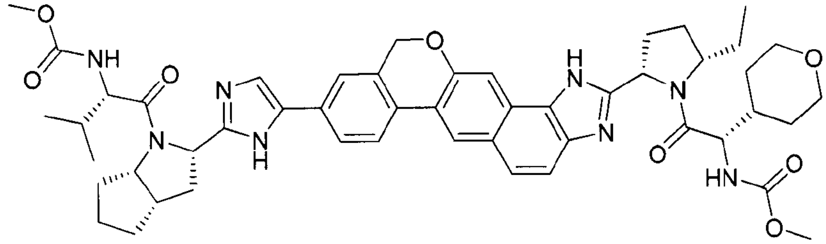

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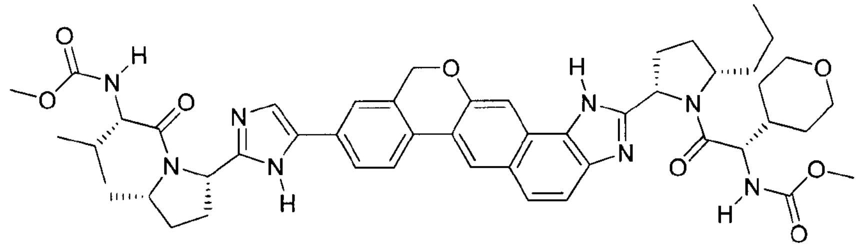

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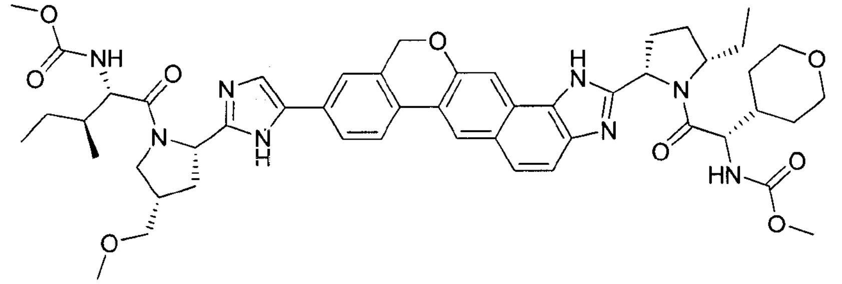

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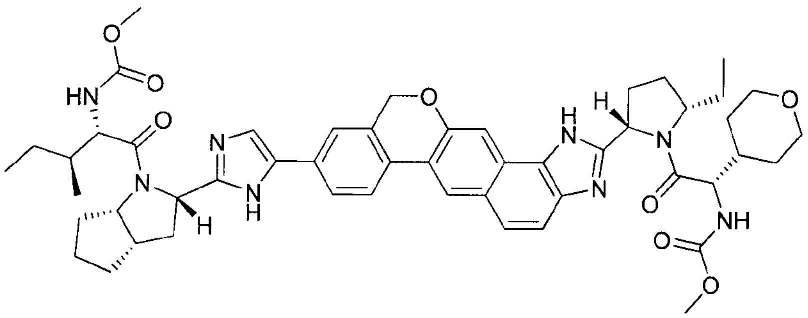

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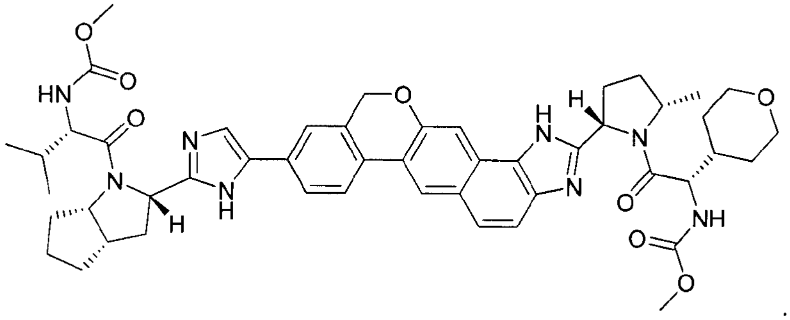


9. A pharmaceutical composition comprising the compound of claim 8 and a pharmaceutically acceptable diluent or carrier, or combination thereof.

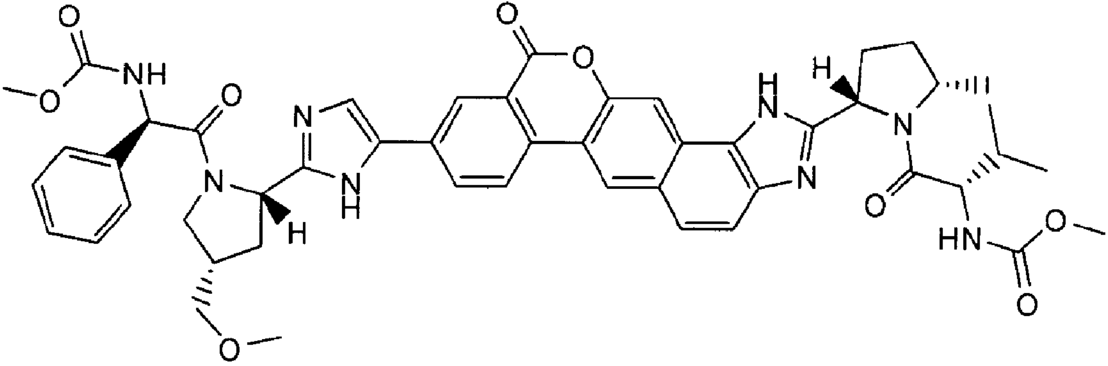
10. The pharmaceutical composition of claim 9, formulated for oral administration.

11. The pharmaceutical composition of claim 9, formulated in tablet form.

12. A composition comprising the compound of claim 8 for the prophylactic or therapeutic treatment of hepatitis C.

13. Use of the compound of claim 8 in the manufacture of a medicament for the treatment of hepatitis C.

14. The pharmaceutical composition of claim 9 for use in the prophylactic or therapeutic treatment of hepatitis C.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