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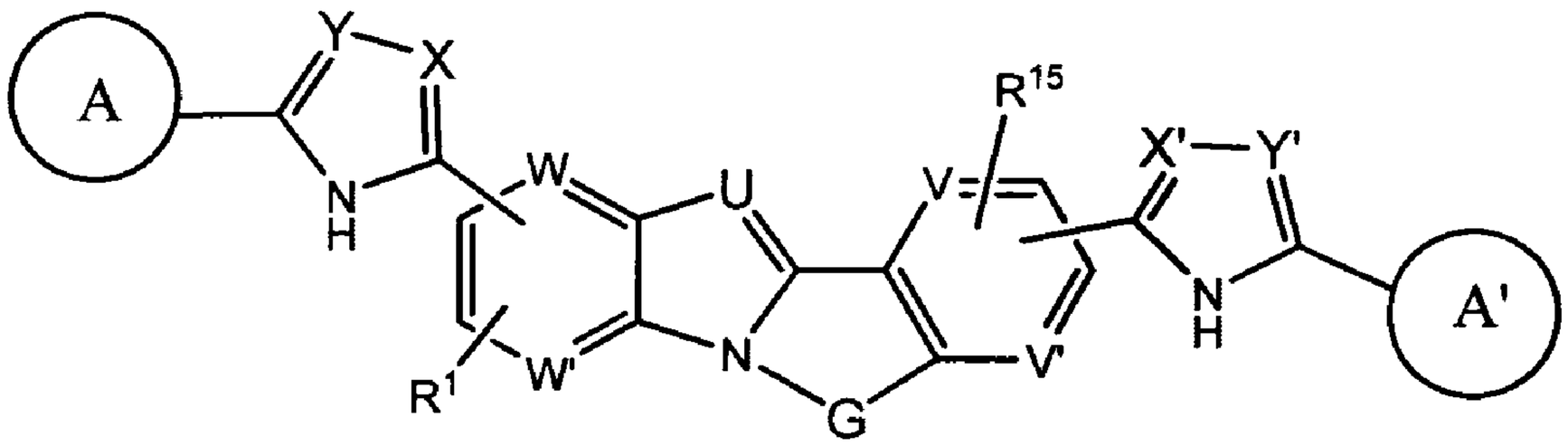
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(54) Titre : DERIVES D'INDOLES TETRACYCLIQUES POUR LE TRAITEMENT D'UNE INFECTION PAR LE VIRUS DE L'HEPATITE C

(54) Title: TETRACYCLIC INDOLE DERIVATIVES FOR TREATING HEPATITIS C VIRUS INFECTION



(I)

(57) Abrégé/Abstract:
Tetracyclic indole derivatives of formula (I), pharmaceutically acceptable salts and the pharmaceutical compositions thereof are provided, wherein A, A', G, R^1, R^{15}, U, V, V, W, W, X, X', Y, Y' are as defined in the invention. Use of these derivatives for treating hepatitis C virus (HCV) infection is also provided.

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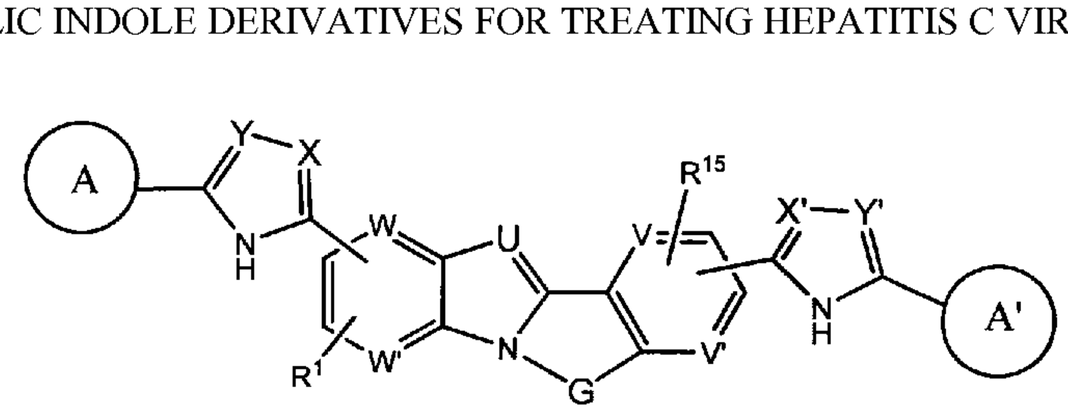
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[Continued on next page]

(54) Title: TETRACYCLIC INDOLE DERIVATIVES FOR TREATING HEPATITIS C VIRUS INFECTION



(I)

(57) Abstract: Tetracyclic indole derivatives of formula (I), pharmaceutically acceptable salts and the pharmaceutical compositions thereof are provided, wherein A, A', G, R^1, R^{15}, U, V, V, W, W, X, X', Y, Y' are as defined in the invention. Use of these derivatives for treating hepatitis C virus (HCV) infection is also provided.

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TETRACYCLIC INDOLE DERIVATIVES FOR TREATING HEPATITIS C VIRUS INFECTION

FIELD OF THE INVENTION

The present invention relates to novel Tetracyclic Indole Derivatives, compositions comprising at least one Tetracyclic Indole Derivative, and methods of using the Tetracyclic Indole Derivatives for treating or preventing HCV infection in a patient.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) is a major human pathogen. A substantial fraction of these HCV-infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma, which are often fatal. HCV is a (+)-sense single-stranded enveloped RNA virus that has been implicated as the major causative agent in non-A, non-B hepatitis (NANBH), particularly in blood-associated NANBH (BB-NANBH) (see, International Publication No. WO 89/04669 and European Patent Publication No. EP 381 216). NANBH is to be distinguished from other types of viral-induced liver disease, such as hepatitis A virus (HAV), hepatitis B virus (HBV), delta hepatitis virus (HDV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV), as well as from other forms of liver disease such as alcoholism and primary biliar cirrhosis.

It is well-established that persistent infection of HCV is related to chronic hepatitis, and as such, inhibition of HCV replication is a viable strategy for the prevention of hepatocellular carcinoma. Current therapies for HCV infection include α-interferon monotherapy and combination therapy comprising α-interferon and ribavirin. These therapies have been shown to be effective in some patients with chronic HCV infection, but suffer from poor efficacy and unfavorable side-effects and there are currently efforts directed to the discovery of HCV replication inhibitors that are useful for the treatment and prevention of HCV related disorders.

Current research efforts directed toward the treatment of HCV includes the use of antisense oligonucleotides, free bile acids (such as ursodeoxycholic acid and chenodeoxycholic acid) and conjugated bile acids (such as tauroursodeoxycholic

acid). Phosphonoformic acid esters have also been proposed as potentially useful for the treatment of various viral infections, including HCV. Vaccine development, however, has been hampered by the high degree of viral strain heterogeneity and immune evasion and the lack of protection against reinfection, even with the same inoculum.

In light of these treatment hurdles, the development of small-molecule inhibitors directed against specific viral targets has become a major focus of anti-HCV research. The determination of crystal structures for NS3 protease, NS3 RNA helicase, NS5A, and NS5B polymerase, with and without bound ligands, has provided important structural insights useful for the rational design of specific inhibitors.

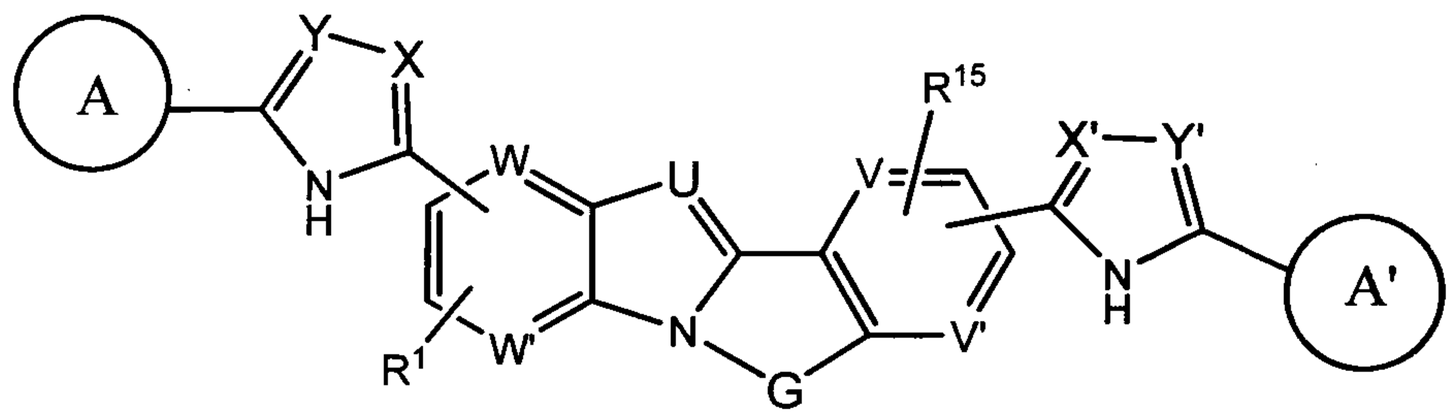
Recent attention has been focused toward the identification of inhibitors of HCV NS5A. HCV NS5A is a 447 amino acid phosphoprotein which lacks a defined enzymatic function. It runs as 56kd and 58kd bands on gels depending on phosphorylation state (Tanji, *et al. J. Virol.* 69:3980-3986 (1995)). HCV NS5A resides in replication complex and may be responsible for the switch from replication of RNA to production of infectious virus (Huang, Y, *et al., Virology* 364:1-9 (2007)).

Multicyclic HCV NS5A inhibitors have been reported. See U.S. Patent Publication Nos. US20080311075, US20080044379, US20080050336, US20080044380, US20090202483 and US2009020478. HCV NS5A inhibitors having fused tricyclic moieties are disclosed in International Patent Publication Nos. WO 10/065681, WO 10/065668, and WO 10/065674.

Other HCV NS5A inhibitors and their use for reducing viral load in HCV infected humans have been described in U.S. Patent Publication No. US20060276511.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides Compounds of Formula



(I)

or a pharmaceutically acceptable salt thereof, wherein:

A and A' are each independently a 5 or 6-membered monocyclic heterocycloalkyl, wherein said 5 or 6-membered monocyclic heterocycloalkyl group can be optionally fused to an aryl group; and wherein said 5 or 6-membered monocyclic heterocycloalkyl group can be optionally and independently substituted on one or more ring carbon atoms with R^{13}, such that any two R^{13} groups on the same ring, together with the carbon atoms to which they are attached, can join to form a fused, bridged or spirocyclic 3 to 6-membered cycloalkyl group or a fused, bridged or spirocyclic 4 to 6-membered heterocycloalkyl group, wherein said 5 or 6-membered monocyclic heterocycloalkyl contains from 1 to 2 ring heteroatoms, each independently selected from $N(R^4)$, S, O and $Si(R^{16})_2$;

G is selected from $-C(R^3)_2$-O-, $-C(R^3)_2$-$N(R^5)$-, -C(O)-O-, -C(O)-$N(R^5)$-, -C(O)-$C(R^3)_2$-, -$C(R^3)_2$-C(O)-, -$C(=NR^5)$-$N(R^5)$-, $-C(R^3)_2$-SO_2-, -SO_2-$C(R^3)_2$-, -$SO_2N(R^5)$-, $-C(R^3)_2-C(R^3)_2$-, $-C(R^{14})=C(R^{14})$- and $-C(R^{14})=N$-;

U is selected from N and $C(R^2)$;

V and V' are each independently selected from N and $C(R^{15})$;

W and W' are each independently selected from N and $C(R^1)$;

X and X' are each independently selected from N and $C(R^{10})$;

Y and Y' are each independently selected from N and $C(R^{10})$;

R^1 is selected from H, C_1-C_6 alkyl, 3 to 6-membered cycloalkyl, halo, -OH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl and –O-(C_1-C_6 haloalkyl);

each occurrence of R^2 is independently selected from H, C_1-C_6 alkyl, 3 to 6 membered cycloalkyl, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl –O-(C_1-C_6 haloalkyl); halo, -OH, aryl, and heteroaryl;

each occurrence of R^3 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-(3 to 6 membered cycloalkyl), 3 to 6-membered cycloalkyl, 4 to 6-membered

heterocycloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl, 9 or 10-membered bicyclic heteroaryl and benzyl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group, said 9 or 10-membered bicyclic heteroaryl group or the phenyl moiety of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), -O(C_1-C_6 haloalkyl), halo, –(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl) and –CN and wherein two R^3 groups attached to the same carbon atom, together with the common carbon atom to which they are attached, can join to form a carbonyl group, a 3 to 6-membered spirocyclic cycloalkyl group or a 3 to 6-membered spirocyclic heterocycloalkyl group;

each occurrence of R^4 is independently selected from -$[C(R^7)_2]_qN(R^6)_2$, -$C(O)R^{11}$, -C(O)-$[C(R^7)_2]_qN(R^6)_2$, -C(O)-$[C(R^7)_2]_q$-R^{11}, -C(O)-$[C(R^7)_2]_qN(R^6)C(O)$-R^{11}, -C(O)$[C(R^7)_2]_qN(R^6)SO_2$-R^{11}, -C(O)-$[C(R^7)_2]_qN(R^6)C(O)O$-R^{11}, -C(O)-$[C(R^7)_2]_qC(O)O$-R^{11} and -alkylene-$N(R^6)$-$[C(R^7)_2]_q$-$N(R^6)$-$C(O)O$-R^{11};

each occurrence of R^5 is independently selected from H, C_1-C_6 alkyl, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl and benzyl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group or the phenyl moiety of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), halo, –(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl) and –CN;

each occurrence of R^6 is independently selected from H, C_1-C_6 alkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl and 5 or 6-membered monocyclic heteroaryl, wherein said 3 to 6-membered cycloalkyl group, said 4 to 6-membered heterocycloalkyl group, said aryl group and said 5 or 6-membered monocyclic heteroaryl group can be optionally and independently substituted with up to two R^8 groups, and wherein two R^6 groups that are attached to the same nitrogen atom, together with the common nitrogen atom to which they are attached, can join to form a 4 to 6-membered heterocycloalkyl group;

each occurrence of R^7 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -alkylene-O-(C_1-C_6 alkyl), 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl and 5 or 6-membered monocyclic heteroaryl, wherein said 3 to 6-membered cycloalkyl group, said 4 to 6-membered

heterocycloalkyl group, said aryl group and said 5 or 6-membered monocyclic heteroaryl group can be optionally substituted with up to three R^8 groups;

each occurrence of R^8 is independently selected from H, C_1-C_6 alkyl, halo, -C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -OH, -C(O)NH-(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -O-(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$ and -NHC(O)-(C_1-C_6 alkyl);

each occurrence of R^9 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl and 5 or 6-membered monocyclic heteroaryl;

each occurrence of R^{10} is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, -OH, -O-(C_1-C_6 alkyl) and –CN;

each occurrence of R^{11} is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, 3 to 6-membered cycloalkyl and 4 to 6-membered heterocycloalkyl;

each occurrence of R^{12} is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl and 5 or 6-membered monocyclic heteroaryl;

each occurrence of R^{13} is independently selected from H, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, -CN, -OR^9, -N(R^9)$_2$, -C(O)R^{12}, -C(O)OR^9, -C(O)N(R^9)$_2$, -NHC(O)R^{12}, -NHC(O)NHR^9, -NHC(O)OR^9, -OC(O)R^{12}, -SR^9 and –S(O)$_2$$R^{12}$, wherein two R^{12} groups together with the carbon atom(s) to which they are attached, can optionally join to form a 3 to 6-membered cycloalkyl group or 4 to 6-membered heterocycloalkyl group;

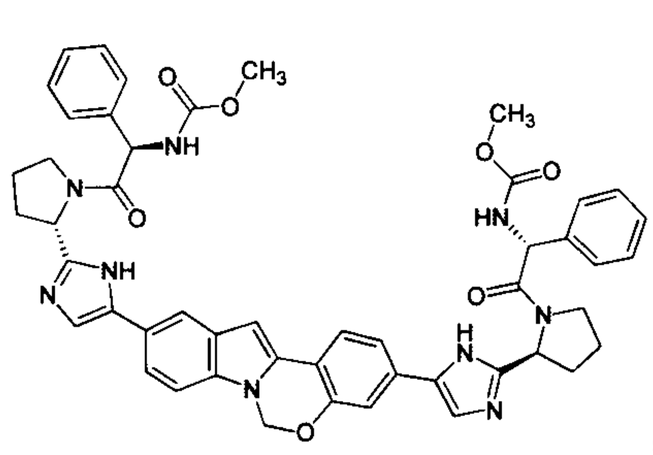
each occurrence of R^{14} is independently selected from H, halo, C_1-C_6 alkyl, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), 3 to 6-membered cycloalkyl, C_1-C_6 haloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl and benzyl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group or the phenyl moiety of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), –(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl) and -O-(C_1-C_6 haloalkyl);

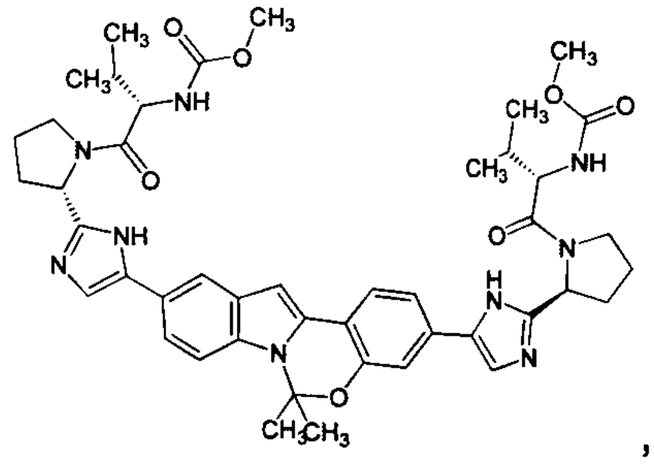
each occurrence of R^{15} is independently selected from H, C_1-C_6 alkyl, 3 to 6-membered cycloalkyl, halo, -OH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl and –O-(C_1-C_6 haloalkyl);

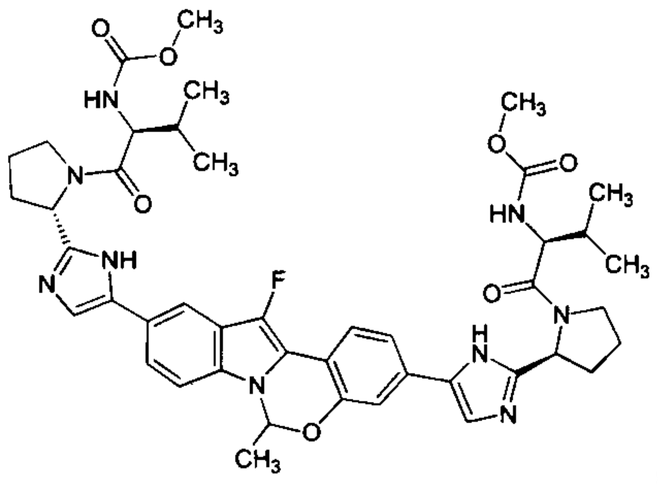
each occurrence of R^{16} is independently selected from H, halo, C_1-C_6 alkyl and 3 to 6-membered cycloalkyl, wherein two R^{16} groups that are attached to a common silicon atom can join to form a $-(CH_2)_4$- or a $-(CH_2)_5$- group; and

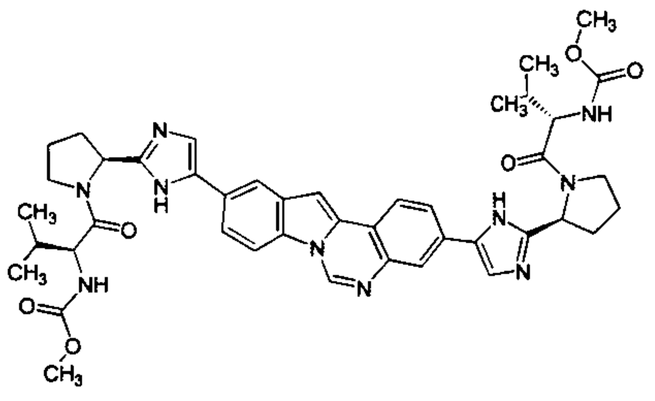
each occurrence of q is independently an integer ranging from 0 to 4,

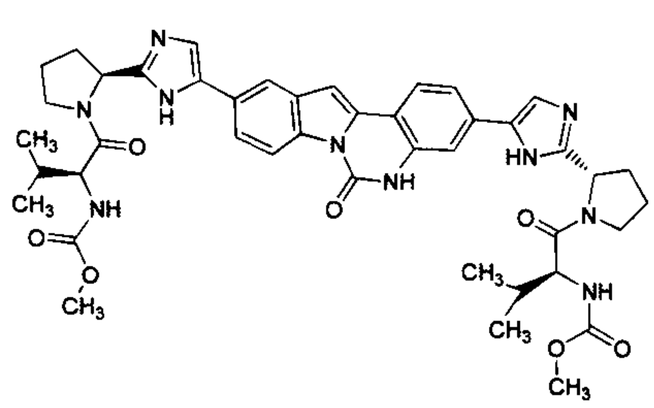
provided that the compound of formula (I) is other than:

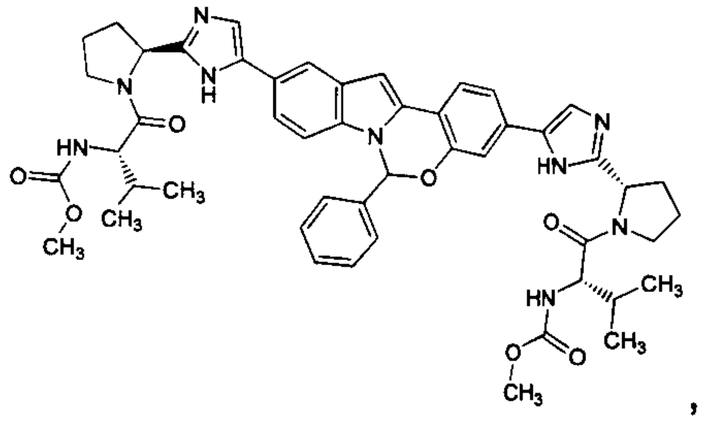

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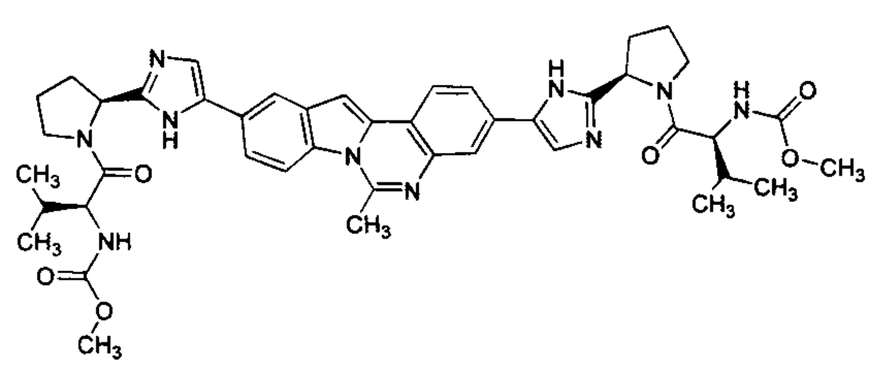

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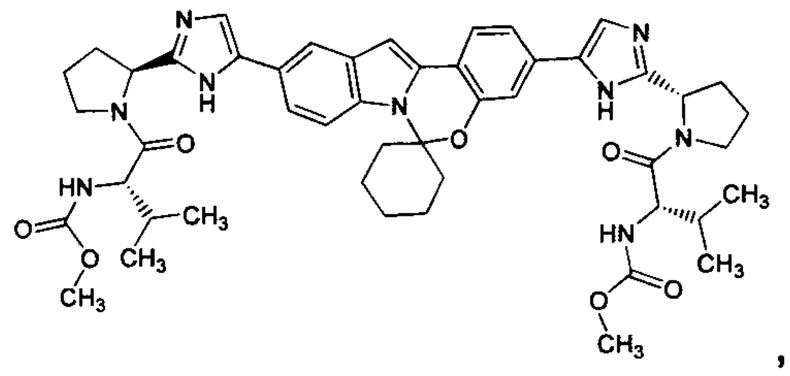

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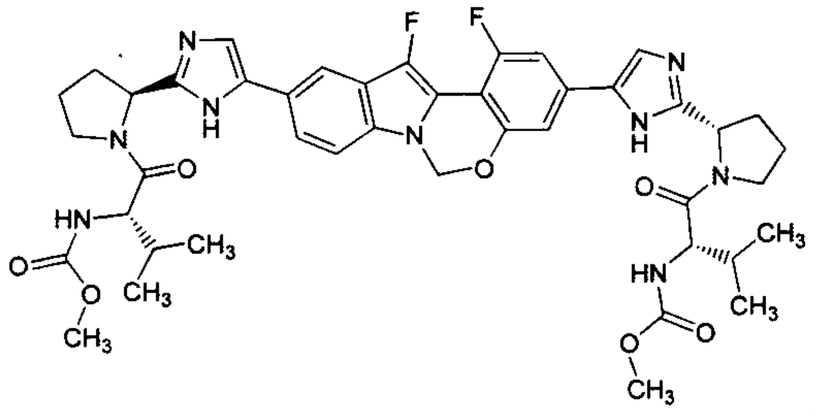

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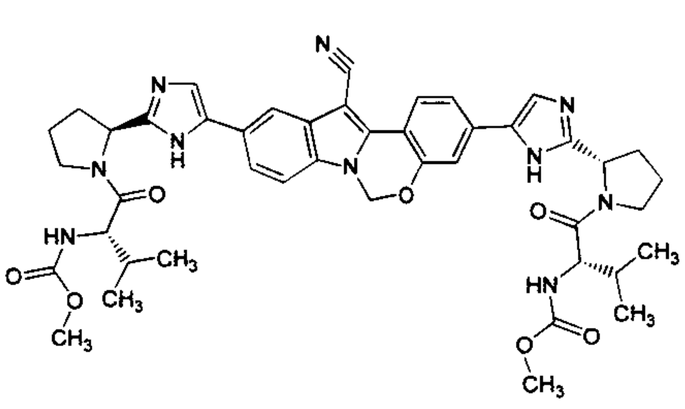

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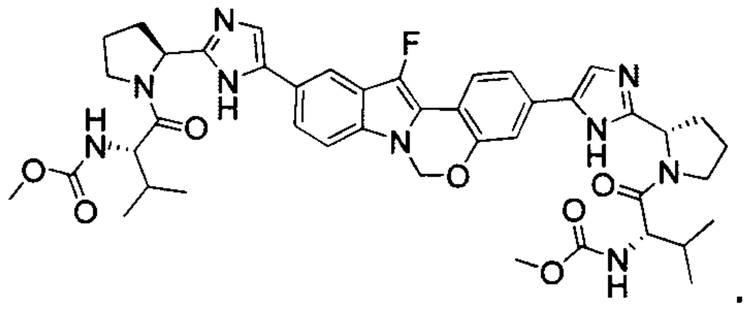

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or  .

The Compounds of Formula (I) (also referred to herein as the "Tetracyclic Indole Derivatives") and pharmaceutically acceptable salts thereof can be useful, for example, for inhibiting HCV viral replication or replicon activity, and for treating or preventing HCV infection in a patient. Without being bound by any specific theory, it is believed that the Tetracyclic Indole Derivatives inhibit HCV viral replication by inhibiting HCV NS5A.

Accordingly, the present invention provides methods for treating or preventing HCV infection in a patient, comprising administering to the patient an effective amount of at least one Tetracyclic Indole Derivative.

The details of the invention are set forth in the accompanying detailed description below.

Although any methods and materials similar to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel Tetracyclic Indole Derivatives, compositions comprising at least one Tetracyclic Indole Derivative, and methods of using the Tetracyclic Indole Derivatives for treating or preventing HCV infection in a patient.

Definitions and Abbreviations

The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures

may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name and an ambiguity exists between the structure and the name, the structure predominates. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl," "haloalkyl," "-O-alkyl," etc...

As used herein, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

A “patient” is a human or non-human mammal. In one embodiment, a patient is a human. In another embodiment, a patient is a chimpanzee.

The term "effective amount" as used herein, refers to an amount of Tetracyclic Indole Derivative and/or an additional therapeutic agent, or a composition thereof that is effective in producing the desired therapeutic, ameliorative, inhibitory or preventative effect when administered to a patient suffering from a viral infection or virus-related disorder. In the combination therapies of the present invention, an effective amount can refer to each individual agent or to the combination as a whole, wherein the amounts of all agents administered are together effective, but wherein the component agent of the combination may not be present individually in an effective amount.

The term “preventing,” as used herein with respect to an HCV viral infection or HCV-virus related disorder, refers to reducing the likelihood of HCV infection.

The term "alkyl,” as used herein, refers to an aliphatic hydrocarbon group having one of its hydrogen atoms replaced with a bond. An alkyl group may be straight or branched and contain from about 1 to about 20 carbon atoms. In one embodiment, an alkyl group contains from about 1 to about 12 carbon atoms. In different embodiments, an alkyl group contains from 1 to 6 carbon atoms (C_1-C_6 alkyl) or from about 1 to about 4 carbon atoms (C_1-C_4 alkyl). Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopentyl, n-hexyl, isohexyl and neohexyl. An alkyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH(cycloalkyl),

-O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and –C(O)O-alkyl. In one embodiment, an alkyl group is linear. In another embodiment, an alkyl group is branched. Unless otherwise indicated, an alkyl group is unsubstituted.

The term "alkenyl," as used herein, refers to an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and having one of its hydrogen atoms replaced with a bond. An alkenyl group may be straight or branched and contain from about 2 to about 15 carbon atoms. In one embodiment, an alkenyl group contains from about 2 to about 12 carbon atoms. In another embodiment, an alkenyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl. An alkenyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and –C(O)O-alkyl. The term "C_2-C_6 alkenyl" refers to an alkenyl group having from 2 to 6 carbon atoms. Unless otherwise indicated, an alkenyl group is unsubstituted.

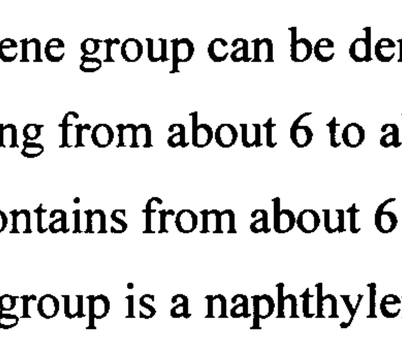
The term "alkynyl," as used herein, refers to an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and having one of its hydrogen atoms replaced with a bond. An alkynyl group may be straight or branched and contain from about 2 to about 15 carbon atoms. In one embodiment, an alkynyl group contains from about 2 to about 12 carbon atoms. In another embodiment, an alkynyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. An alkynyl group may be unsubstituted or substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, aryl, cycloalkyl, cyano, hydroxy, -O-alkyl, -O-aryl, -alkylene-O-alkyl, alkylthio, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH(cycloalkyl), -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, -C(O)OH and –C(O)O-alkyl. The term "C_2-C_6 alkynyl" refers to an alkynyl group having from 2 to 6 carbon atoms. Unless otherwise indicated, an alkynyl group is unsubstituted.

The term "alkylene," as used herein, refers to an alkyl group, as defined above, wherein one of the alkyl group's hydrogen atoms has been replaced

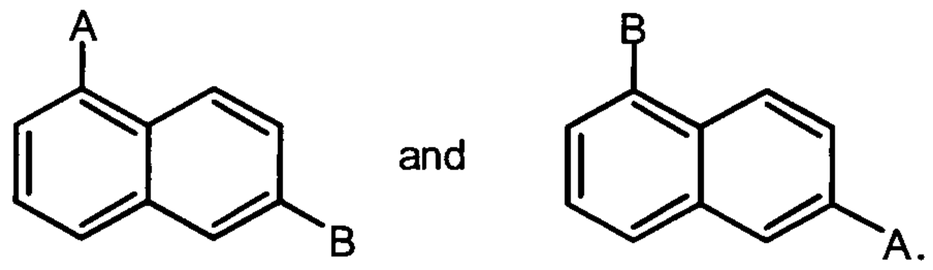
with a bond. Non-limiting examples of alkylene groups include –CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -$CH(CH_3)CH_2CH_2$-, -$CH(CH_3)$- and -$CH_2CH(CH_3)CH_2$-. In one embodiment, an alkylene group has from 1 to about 6 carbon atoms. In another embodiment, an alkylene group is branched. In another embodiment, an alkylene group is linear. In one embodiment, an alkylene group is -CH_2-. The term "C_1-C_6 alkylene" refers to an alkylene group having from 1 to 6 carbon atoms.

The term "aryl," as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising from about 6 to about 14 carbon atoms. In one embodiment, an aryl group contains from about 6 to about 10 carbon atoms. An aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. In one embodiment, an aryl group can be optionally fused to a cycloalkyl or cycloalkanoyl group. Non-limiting examples of aryl groups include phenyl and naphthyl. In one embodiment, an aryl group is phenyl. Unless otherwise indicated, an aryl group is unsubstituted.

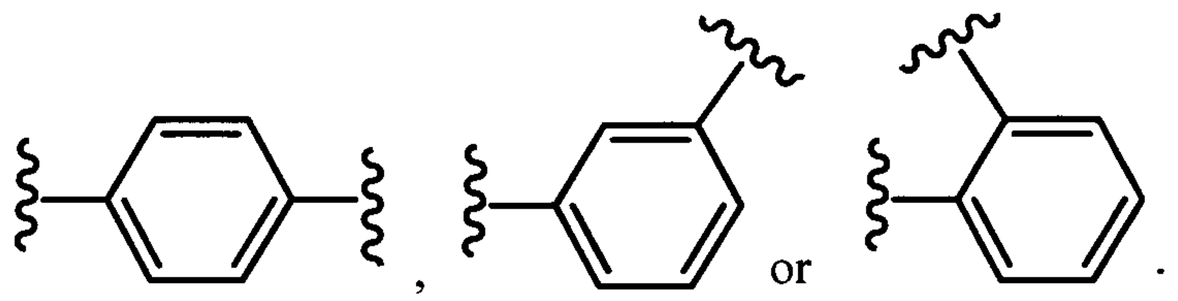
The term "arylene," as used herein, refers to a bivalent group derived from an aryl group, as defined above, by removal of a hydrogen atom from a ring carbon of an aryl group. An arylene group can be derived from a monocyclic or multicyclic ring system comprising from about 6 to about 14 carbon atoms. In one embodiment, an arylene group contains from about 6 to about 10 carbon atoms. In another embodiment, an arylene group is a naphthylene group. In another embodiment, an arylene group is a phenylene group. An arylene group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. An arylene group is divalent and either available bond on an arylene group can connect to either group flanking the arylene group. For example, the group "A-arylene-B," wherein the arylene group is:



is understood to represent both:

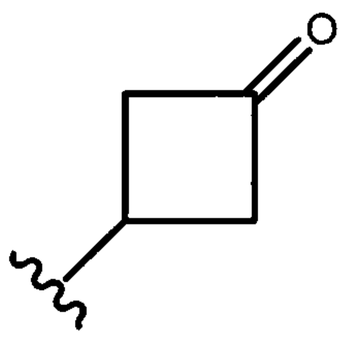


In one embodiment, an arylene group can be optionally fused to a cycloalkyl or cycloalkanoyl group. Non-limiting examples of arylene groups include phenylene and naphthalene. In one embodiment, an arylene group is unsubstituted. In another embodiment, an arylene group is:



Unless otherwise indicated, an arylene group is unsubstituted.

The term "cycloalkyl," as used herein, refers to a non-aromatic mono- or multicyclic ring system comprising from about 3 to about 10 ring carbon atoms. In one embodiment, a cycloalkyl contains from about 5 to about 10 ring carbon atoms. In another embodiment, a cycloalkyl contains from about 3 to about 7 ring atoms. In another embodiment, a cycloalkyl contains from about 5 to about 6 ring atoms. The term "cycloalkyl" also encompasses a cycloalkyl group, as defined above, which is fused to an aryl (*e.g.*, benzene) or heteroaryl ring. Non-limiting examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Non-limiting examples of multicyclic cycloalkyls include 1-decalinyl, norbornyl and adamantyl. A cycloalkyl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. In one embodiment, a cycloalkyl group is unsubstituted. The term "3 to 6-membered cycloalkyl" refers to a cycloalkyl group having from 3 to 6 ring carbon atoms. Unless otherwise indicated, a cycloalkyl group is unsubstituted. A ring carbon atom of a cycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a cycloalkyl group (also referred to herein as a "cycloalkanoyl" group) includes, but is not limited to, cyclobutanoyl:



The term "cycloalkenyl," as used herein, refers to a non-aromatic mono- or multicyclic ring system comprising from about 4 to about 10 ring carbon atoms and containing at least one endocyclic double bond. In one embodiment, a cycloalkenyl contains from about 4 to about 7 ring carbon atoms. In another embodiment, a cycloalkenyl contains 5 or 6 ring atoms. Non-limiting examples of monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. A cycloalkenyl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. A ring carbon atom of a cycloalkyl group may be functionalized as a carbonyl group. In one embodiment, a cycloalkenyl group is cyclopentenyl. In another embodiment, a cycloalkenyl group is cyclohexenyl. The term "4 to 6-membered cycloalkenyl" refers to a cycloalkenyl group having from 4 to 6 ring carbon atoms. Unless otherwise indicated, a cycloalkenyl group is unsubstituted.

The term "halo," as used herein, means –F, -Cl, -Br or -I.

The term "haloalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with a halogen. In one embodiment, a haloalkyl group has from 1 to 6 carbon atoms. In another embodiment, a haloalkyl group is substituted with from 1 to 3 F atoms. Non-limiting examples of haloalkyl groups include $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$ and $-CCl_3$. The term "C_1-C_6 haloalkyl" refers to a haloalkyl group having from 1 to 6 carbon atoms.

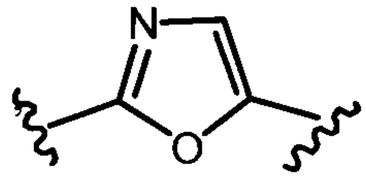
The term "hydroxyalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with an –OH group. In one embodiment, a hydroxyalkyl group has from 1 to 6 carbon atoms. Non-limiting examples of hydroxyalkyl groups include $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ and $-CH_2CH(OH)CH_3$. The term "C_1-C_6 hydroxyalkyl" refers to a hydroxyalkyl group having from 1 to 6 carbon atoms.

The term "heteroaryl," as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, wherein from 1 to 4 of the ring atoms is independently O, N or S and the remaining ring atoms are carbon atoms. In one embodiment, a heteroaryl group has 5 to 10 ring atoms. In another embodiment, a heteroaryl group is monocyclic and has 5 or 6 ring atoms. In another embodiment, a heteroaryl group is bicyclic and had 9 or 10 ring atoms. A heteroaryl group can be optionally substituted by one or more "ring system

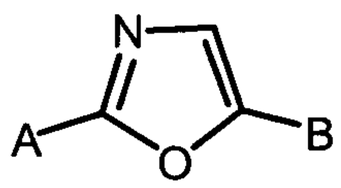
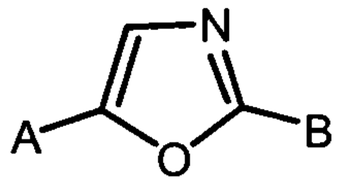
substituents" which may be the same or different, and are as defined herein below. A heteroaryl group is joined via a ring carbon atom, and any nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. The term "heteroaryl" also encompasses a heteroaryl group, as defined above, which is fused to a benzene ring. Non-limiting examples of heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, benzimidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like, and all isomeric forms thereof. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like. In one embodiment, a heteroaryl group is a 5 or 6-membered monocyclic heteroaryl. In another embodiment, a heteroaryl group is a 6-membered monocyclic heteroaryl. In another embodiment, a heteroaryl group is a 5-membered monocyclic heteroaryl. In one embodiment, a heteroaryl group is a 9 or 10-membered monocyclic heteroaryl. In another embodiment, a heteroaryl group is a 9-membered monocyclic heteroaryl. Unless otherwise indicated, a heteroaryl group is unsubstituted.

The term "heteroarylene," as used herein, refers to a bivalent group derived from an heteroaryl group, as defined above, by removal of a hydrogen atom from a ring carbon or ring heteroatom of a heteroaryl group. A heteroarylene group can be derived from a monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, wherein from 1 to 4 of the ring atoms are each independently O, N or S and the remaining ring atoms are carbon atoms. A heteroarylene group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. A heteroarylene group is joined via a ring carbon atom or by a nitrogen atom with an open valence, and any nitrogen atom of a heteroarylene can be optionally oxidized to the corresponding N-oxide. The term "heteroarylene" also encompasses a heteroarylene group, as defined above, which is fused to a benzene ring. Non-limiting examples of heteroarylenes include pyridylene, pyrazinylene, furanylene, thienylene, pyrimidinylene, pyridonylene (including those derived from N-substituted pyridonyls), isoxazolylene,

isothiazolylene, oxazolylene, oxadiazolylene, thiazolylene, pyrazolylene, thiophenylene, furazanylene, pyrrolylene, triazolylene, 1,2,4-thiadiazolylene, pyrazinylene, pyridazinylene, quinoxalinylene, phthalazinylene, oxindolylene, imidazo[1,2-a]pyridinylene, imidazo[2,1-b]thiazolylene, benzofurazanylene, indolylene, azaindolylene, benzimidazolylene, benzothienylene, quinolinylene, imidazolylene, benzimidazolylene, thienopyridylene, quinazolinylene, thienopyrimidylene, pyrrolopyridylene, imidazopyridylene, isoquinolinylene, benzoazaindolylene, 1,2,4-triazinylene, benzothiazolylene and the like, and all isomeric forms thereof. The term "heteroarylene" also refers to partially saturated heteroarylene moieties such as, for example, tetrahydroisoquinolylene, tetrahydroquinolylene, and the like. A heteroarylene group is divalent and either available bond on a heteroarylene ring can connect to either group flanking the heteroarylene group. For example, the group "A-heteroarylene-B," wherein the heteroarylene group is:

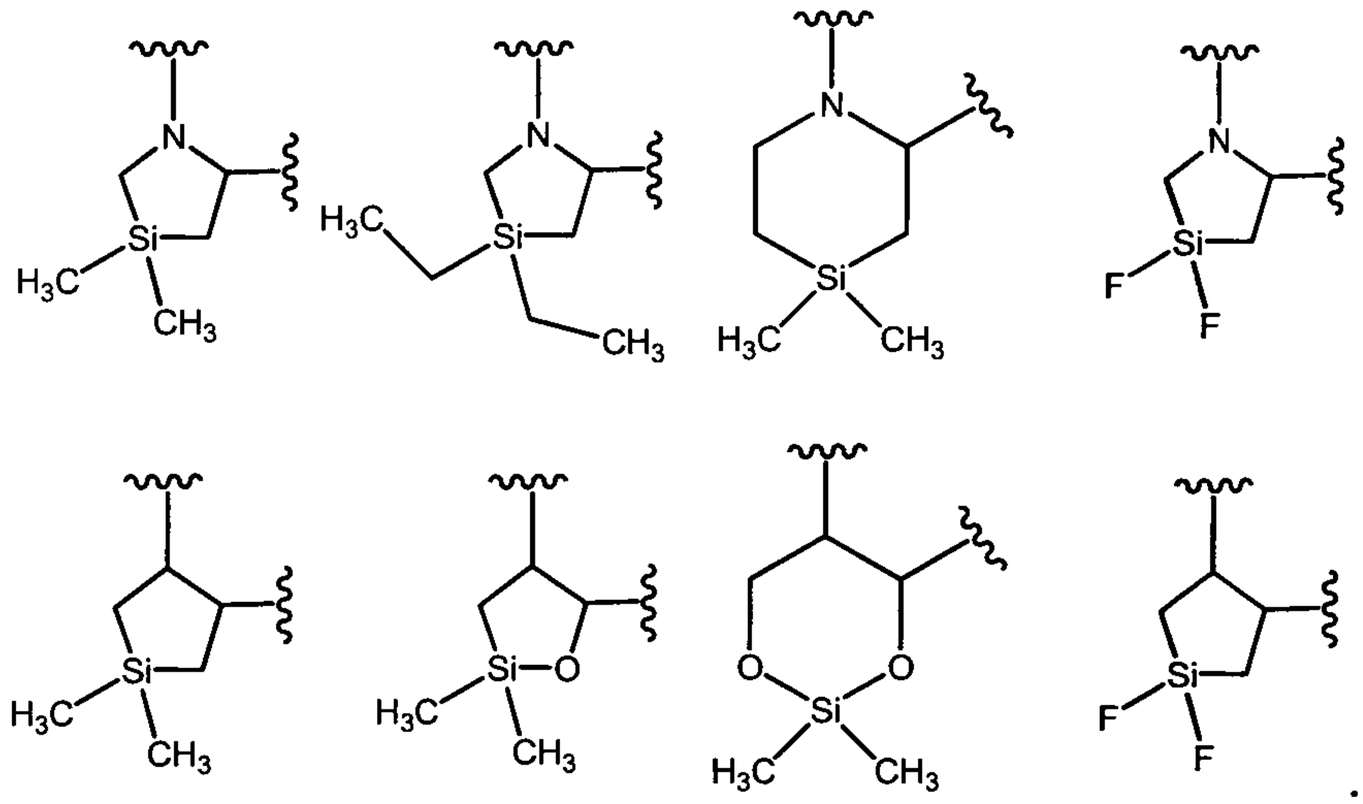


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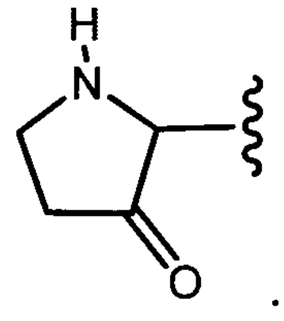
 and .

In one embodiment, a heteroarylene group is a monocyclic heteroarylene group or a bicyclic heteroarylene group. In another embodiment, a heteroarylene group is a monocyclic heteroarylene group. In another embodiment, a heteroarylene group is a bicyclic heteroarylene group. In still another embodiment, a heteroarylene group has from about 5 to about 10 ring atoms. In another embodiment, a heteroarylene group is monocyclic and has 5 or 6 ring atoms. In another embodiment, a heteroarylene group is bicyclic and has 9 or 10 ring atoms. In another embodiment, a heteroarylene group is a 5-membered monocyclic heteroarylene. In another embodiment, a heteroarylene group is a 6-membered monocyclic heteroarylene. In another embodiment, a bicyclic heteroarylene group comprises a 5 or 6-membered monocyclic heteroarylene group fused to a benzene ring. Unless otherwise indicated, a heteroarylene group is unsubstituted.

The term "heterocycloalkyl," as used herein, refers to a non-aromatic saturated monocyclic or multicyclic ring system comprising 3 to about 11 ring atoms, wherein from 1 to 4 of the ring atoms are independently O, S, N or Si, and the remainder of the ring atoms are carbon atoms. A heterocycloalkyl group can be joined via a ring carbon, ring silicon atom or ring nitrogen atom. In one embodiment, a heterocycloalkyl group is monocyclic and has from about 3 to about 7 ring atoms. In another embodiment, a heterocycloalkyl group is monocyclic has from about 4 to about 7 ring atoms. In another embodiment, a heterocycloalkyl group is bicyclic and has from about 7 to about 11 ring atoms. In still another embodiment, a heterocycloalkyl group is monocyclic and has 5 or 6 ring atoms. In one embodiment, a heterocycloalkyl group is monocyclic. In another embodiment, a heterocycloalkyl group is bicyclic. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Any –NH group in a heterocycloalkyl ring may exist protected such as, for example, as an -N(BOC), -N(Cbz), -N(Tos) group and the like; such protected heterocycloalkyl groups are considered part of this invention. The term "heterocycloalkyl" also encompasses a heterocycloalkyl group, as defined above, which is fused to an aryl (*e.g.*, benzene) or heteroaryl ring. A heterocycloalkyl group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. The nitrogen or sulfur atom of the heterocycloalkyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of monocyclic heterocycloalkyl rings include oxetanyl, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, delta-lactam, delta-lactone, silacyclopentane, silapyrrolidine and the like, and all isomers thereof. Non-limiting illustrative examples of a silyl-containing heterocycloalkyl group include:



A ring carbon atom of a heterocycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a heterocycloalkyl group is:



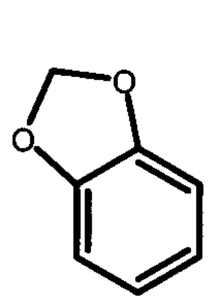
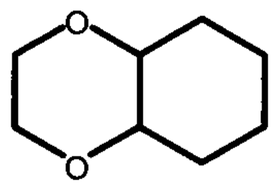
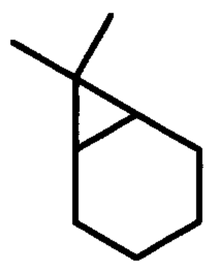
In one embodiment, a heterocycloalkyl group is a 5-membered monocyclic heterocycloalkyl. In another embodiment, a heterocycloalkyl group is a 6-membered monocyclic heterocycloalkyl. The term "3 to 6-membered monocyclic cycloalkyl" refers to a monocyclic heterocycloalkyl group having from 3 to 6 ring atoms. The term "4 to 6-membered monocyclic cycloalkyl" refers to a monocyclic heterocycloalkyl group having from 4 to 6 ring atoms. The term "7 to 11-membered bicyclic heterocycloalkyl" refers to a bicyclic heterocycloalkyl group having from 7 to 11 ring atoms. Unless otherwise indicated, an heterocycloalkyl group is unsubstituted.

The term "heterocycloalkenyl," as used herein, refers to a heterocycloalkyl group, as defined above, wherein the heterocycloalkyl group contains from 4 to 10 ring atoms, and at least one endocyclic carbon-carbon or carbon-nitrogen double bond. A heterocycloalkenyl group can be joined via a ring carbon or ring nitrogen atom. In one embodiment, a heterocycloalkenyl group has from 4 to 6 ring atoms. In another embodiment, a heterocycloalkenyl group is monocyclic and has 5 or 6 ring atoms. In another embodiment, a heterocycloalkenyl group is bicyclic. A heterocycloalkenyl group can optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above.

The nitrogen or sulfur atom of the heterocycloalkenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of heterocycloalkenyl groups include 1,2,3,4- tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluoro-substituted dihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranyl, and the like and the like. A ring carbon atom of a heterocycloalkenyl group may be functionalized as a carbonyl group. In one embodiment, a heterocycloalkenyl group is a 5-membered heterocycloalkenyl. In another embodiment, a heterocycloalkenyl group is a 6-membered heterocycloalkenyl. The term "4 to 6-membered heterocycloalkenyl" refers to a heterocycloalkenyl group having from 4 to 6 ring atoms. Unless otherwise indicated, a heterocycloalkenyl group is unsubstituted.

The term "ring system substituent," as used herein, refers to a substituent group attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, -alkylene-aryl, -arylene-alkyl, -alkylene-heteroaryl, -alkenylene-heteroaryl, -alkynylene-heteroaryl, -OH, hydroxyalkyl, haloalkyl, -O-alkyl, -O-haloalkyl, -alkylene-O-alkyl, -O-aryl, -O-alkylene-aryl, acyl, -C(O)-aryl, halo, $-NO_2$, -CN, $-SF_5$, -C(O)OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-alkylene-aryl, -S(O)-alkyl, $-S(O)_2$-alkyl, -S(O)-aryl, $-S(O)_2$-aryl, -S(O)-heteroaryl, $-S(O)_2$-heteroaryl, -S-alkyl, -S-aryl, -S-heteroaryl, -S-alkylene-aryl, -S-alkylene-heteroaryl, $-S(O)_2$-alkylene-aryl, $-S(O)_2$-alkylene-heteroaryl, $-Si(alkyl)_2$, $-Si(aryl)_2$, $-Si(heteroaryl)_2$, -Si(alkyl)(aryl), -Si(alkyl)(cycloalkyl), -Si(alkyl)(heteroaryl), cycloalkyl, heterocycloalkyl, -O-C(O)-alkyl, -O-C(O)-aryl, -O-C(O)-cycloalkyl, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, -C(=NH)-NH(alkyl), $-N(Y_1)(Y_2)$, -alkylene-$N(Y_1)(Y_2)$, $-C(O)N(Y_1)(Y_2)$ and $-S(O)_2N(Y_1)(Y_2)$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and –alkylene-aryl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of

such moiety are methylenedioxy, ethylenedioxy, $-C(CH_3)_2-$ and the like which form moieties such as, for example:


, 
and 
.

The term "silylalkyl," as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with a $-Si(R^x)_3$ group, wherein each occurrence of R^x is independently C_1-C_6 alkyl, phenyl or a 3 to 6-membered cycloalkyl group. In one embodiment, a silylalkyl group has from 1 to 6 carbon atoms. In another embodiment, a silyl alkyl group contains a $-Si(CH_3)_3$ moiety. Non-limiting examples of silylalkyl groups include $-CH_2$-$Si(CH_3)_3$ and $-CH_2CH_2$-$Si(CH_3)_3$.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "in substantially purified form," as used herein, refers to the physical state of a compound after the compound is isolated from a synthetic process (*e.g.*, from a reaction mixture), a natural source, or a combination thereof. The term "in substantially purified form," also refers to the physical state of a compound after the compound is obtained from a purification process or processes described herein or well-known to the skilled artisan (*e.g.*, chromatography, recrystallization and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well-known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the

protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in Organic Synthesis* (1991), Wiley, New York.

When any substituent or variable (*e.g.*, alkyl, R^6, R^a, etc.) occurs more than one time in any constituent or in Formula (I), its definition on each occurrence is independent of its definition at every other occurrence, unless otherwise indicated.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (*e.g.*, a drug precursor) that is transformed *in vivo* to provide a Tetracyclic Indole Derivative or a pharmaceutically acceptable salt or solvate of the compound. The transformation may occur by various mechanisms (*e.g.*, by metabolic or chemical processes), such as, for example, through hydrolysis in blood.

For example, if a Tetracyclic Indole Derivative or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, $(C_1–C_8)$alkyl, $(C_2\text{-}C_{12})$alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 6 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-$(C_1\text{-}C_2)$alkylamino$(C_2\text{-}C_3)$alkyl (such as β-dimethylaminoethyl), carbamoyl-$(C_1\text{-}C_2)$alkyl, N,N-di $(C_1$-

C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a Tetracyclic Indole Derivative contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkyl, α-amino(C_1-C_4)alkylene-aryl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, -P(O)$(OH)_2$, -P(O)(O(C_1-C_6)alkyl)$_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a Tetracyclic Indole Derivative incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl-, RO-carbonyl-, NRR'-carbonyl- wherein R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, a natural α-aminoacyl, -C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, -C(OY^2)Y^3 wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl; carboxy (C_1-C_6)alkyl; amino(C_1-C_4)alkyl or mono-N- or di-N,N-(C_1-C_6)alkylaminoalkyl; -C(Y^4)Y^5 wherein Y^4 is H or methyl and Y^5 is mono-N- or di-N,N-(C_1-C_6)alkylamino morpholino; piperidin-1-yl or pyrrolidin-1-yl, and the like.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy group of a hydroxyl compound, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (*e.g.,* methyl, ethyl, n-propyl, isopropyl, t-butyl, sec-butyl or n-butyl), alkoxyalkyl (*e.g.,* methoxymethyl), aralkyl (*e.g.,* benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (*e.g.,* phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, -O-(C_{1-4}alkyl) or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (*e.g.,* L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of solvates include ethanolates, methanolates, and the like. A "hydrate" is a solvate wherein the solvent molecule is water.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTechours.* , 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than room temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example IR spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

The Tetracyclic Indole Derivatives can form salts which are also within the scope of this invention. Reference to a Tetracyclic Indole Derivative herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a Tetracyclic Indole Derivative contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. In one embodiment, the salt is a pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salt. In another embodiment, the salt is other than a pharmaceutically acceptable salt. Salts of

the Compounds of Formula (I) may be formed, for example, by reacting a Tetracyclic Indole Derivative with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamine, t-butyl amine, choline, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, and dibutyl sulfates), long chain halides (*e.g.*, decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well-known to those skilled in the art, such as, for example, by chromatography and/or

fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Sterochemically pure compounds may also be prepared by using chiral starting materials or by employing salt resolution techniques. Also, some of the Tetracyclic Indole Derivatives may be atropisomers (*e.g.*, substituted biaryls) and are considered as part of this invention. Enantiomers can also be directly separated using chiral chromatographic techniques.

It is also possible that the Tetracyclic Indole Derivatives may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. For example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, hydrates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. If a Tetracyclic Indole Derivative incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to apply equally to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

In the Compounds of Formula (I), the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass

number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched Compounds of Formula (I) can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates. In one embodiment, a Compound of Formula (I) has one or more of its hydrogen atoms replaced with deuterium.

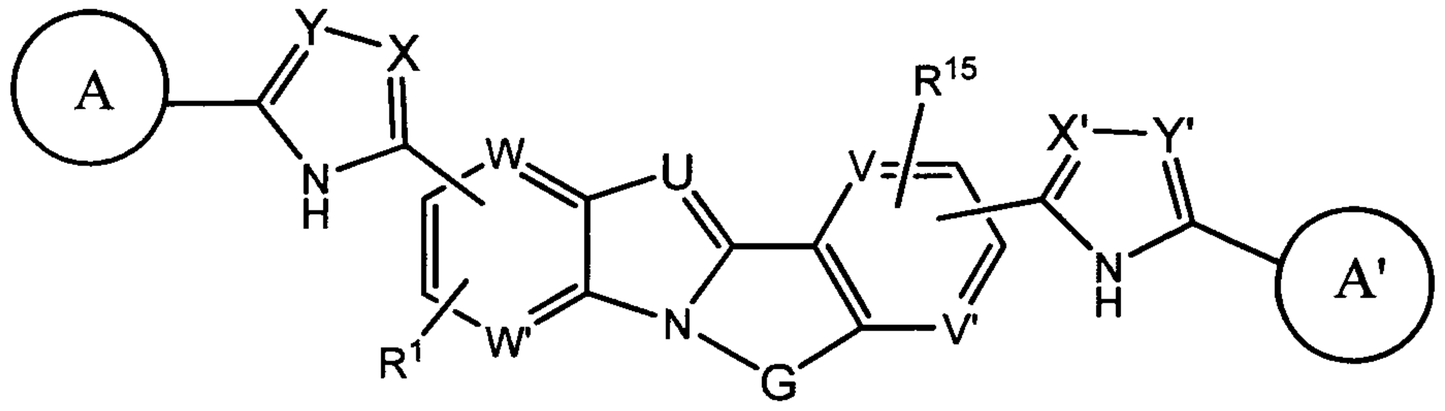
Polymorphic forms of the Tetracyclic Indole Derivatives, and of the salts, solvates, hydrates, esters and prodrugs of the Tetracyclic Indole Derivatives, are intended to be included in the present invention.

The following abbreviations are used below and have the following meanings: Ac is acyl; AcCl is acetyl chloride; AcOH or HOAc is acetic acid; Amphos is (4-(*N*,*N*)-dimethylaminophenyl)-di-tertbutylphosphine; Aq is aqueous; BF_3•OEt_2 is boron trifluoride etherate; BOC or Boc is *tert*-butyloxycarbonyl; Boc_2O is Boc anhydride; Boc-Pro-OH is Boc protected proline; L-Boc-Val-OH is Boc protected L-valine; BOP is Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate; n-BuLi is n-butyllithium; CBZ or Cbz is carbobenzoxy; DCM is dichloromethane; DDQ is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; Dess-Martin reagent is ,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one; DIPEA is diisopropylethylamine; DME is dimethoxyethane; DMF is *N*,*N*-dimethylformamide; dppf is diphenylphosphinoferrocene; DMSO is dimethylsulfoxide; EtMgBr is ethylmagnesium bromide; EtOAc is ethyl acetate; Et_2O is diethyl ether; Et_3N or NEt_3 is triethylamine; HATU is O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; HPLC is high performance liquid chromatography; HRMS is high resolution mass spectrometry; KOAc is potassium acetate; LCMS is liquid chromatography/mass spectrometry; LiHMDS is lithium hexamethyldisilazide; LRMS is low resolution mass spectrometry; MeI is iodomethane; MeOH is methanol; NBS is N-bromosuccinimide; NH_4OAc is ammonium acetate; NMM is N-

methylmorpholine; Pd/C is palladium on carbon; $Pd(PPh_3)_4$ is tetrakis (triphenylphosphine)palladium(0); $PdCl_2(dppf)_2$ is [1,1 -Bis(diphenylphosphino) ferrocene]dichloro palladium(II); $PdCl_2(dppf)_2 \cdot CH_2Cl_2$ is [1,1 - Bis(diphenylphosphino)ferrocene] dichloro palladium(II) complex with dichloromethane; $pinacol_2B_2$ is bis(pinacolato)diboron; PPTS is pyridinium p-toluene sulfonate; RPLC is reverse-phase liquid chromatography; Select-F is 1-Chloromethyl-4-Fluoro-1, 4-Diazoniabicyclo[2.2.2]Octane Bis-(Tetrafluoroborate); SEM-Cl is 2-(trimethylsilyl)ethoxymethyl chloride; TBAF is tetrabutylammonium fluoride; TBDMSCl is *tert*-butyldimethylsilyl chloride; TFA is trifluoroacetic acid; Tf_2O is triflic anhydride; THF is tetrahydrofuran; TLC is thin-layer chromatography; and TosCl is p-toluenesulfonyl chloride.

The Compounds of Formula (I)

The present invention provides Tetracyclic Indole Derivatives of Formula (I):



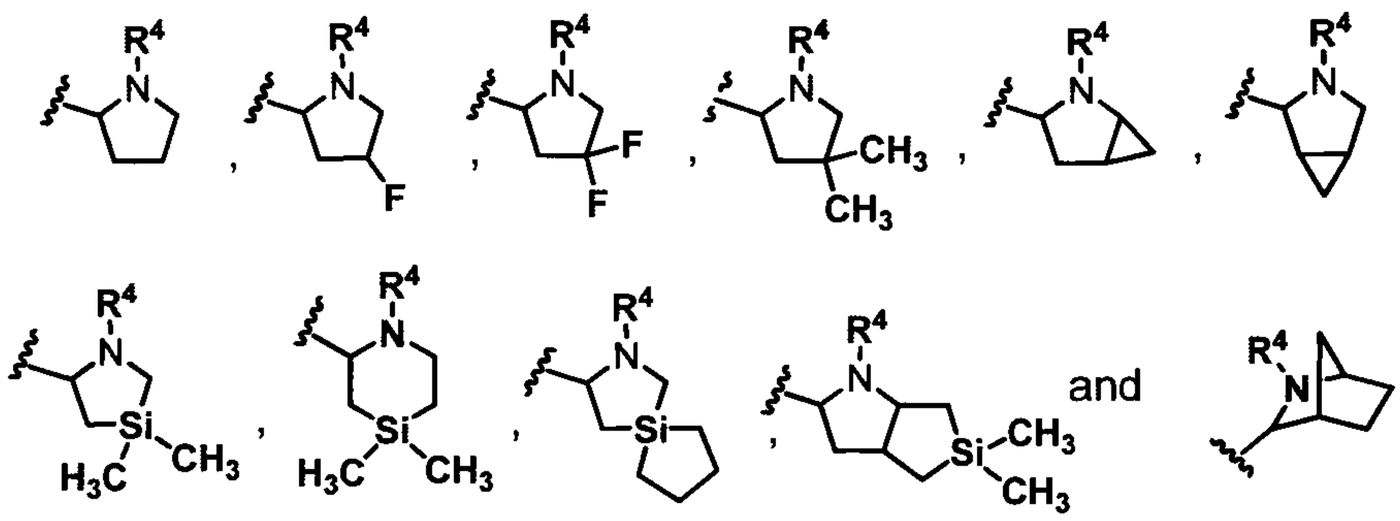
(I)

and pharmaceutically acceptable salts thereof, wherein A, A', G, R^1, U, V, V', W, W', X, X', Y and Y' are defined above for the Compounds of Formula (I).

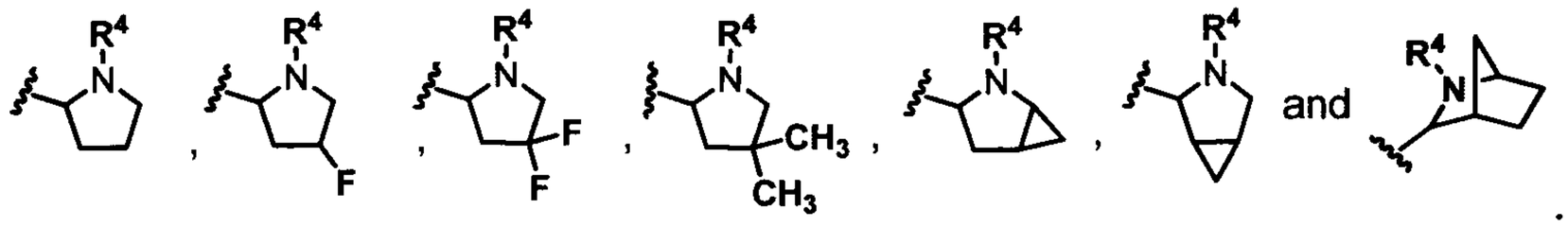
In one embodiment, A and A' are each a 5-membered heterocycloalkyl group.

In another embodiment, A and A' are each a 6-membered heterocycloalkyl group.

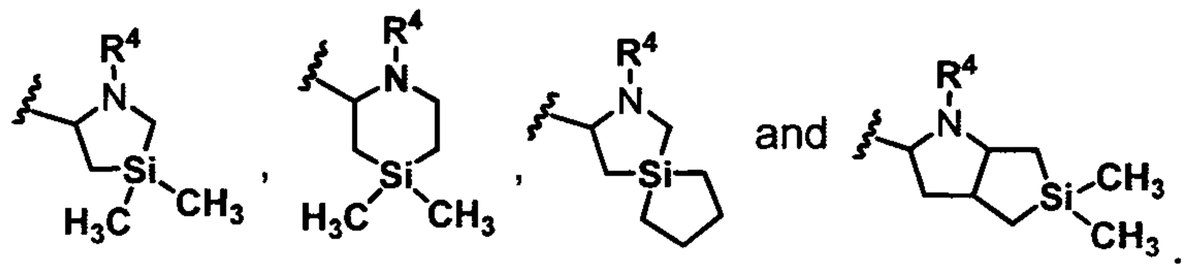
In another embodiment, A and A' are each independently selected from:



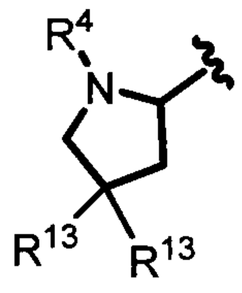
In still another embodiment, A and A' are each independently selected from:



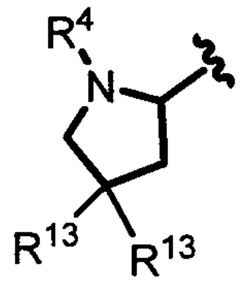
In another embodiment, A and A' are each independently selected from:



In another embodiment, A and A' are each independently:



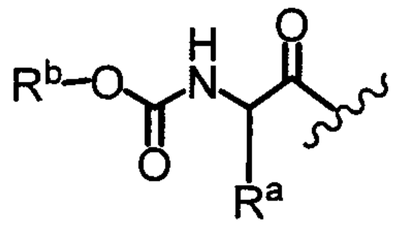
In another embodiment, A and A' are each independently:



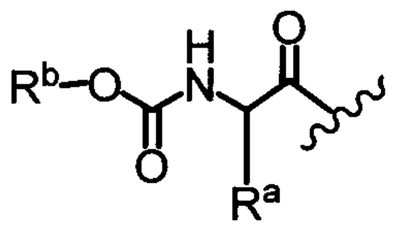
wherein each occurrence of R^{13} is independently H, CH_3, or F.

In one embodiment, each occurrence of R^4 is independently -C(O)-$[C(R^7)_2]_qN(R^6)C(O)O$-R^{11}.

In another embodiment, each occurrence of R^4 is independently:

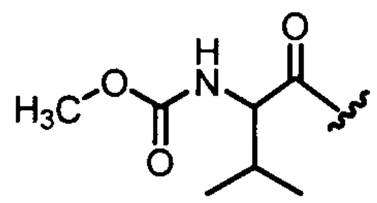

, wherein R^b is H, alkyl, haloalkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl or heteroaryl and R^a is alkyl, haloalkyl, silylalkyl, 3 to 6-membered cycloalkyl or 4 to 6-membered heterocycloalkyl, aryl or heteroaryl.

In another embodiment, each occurrence of R^4 is independently:

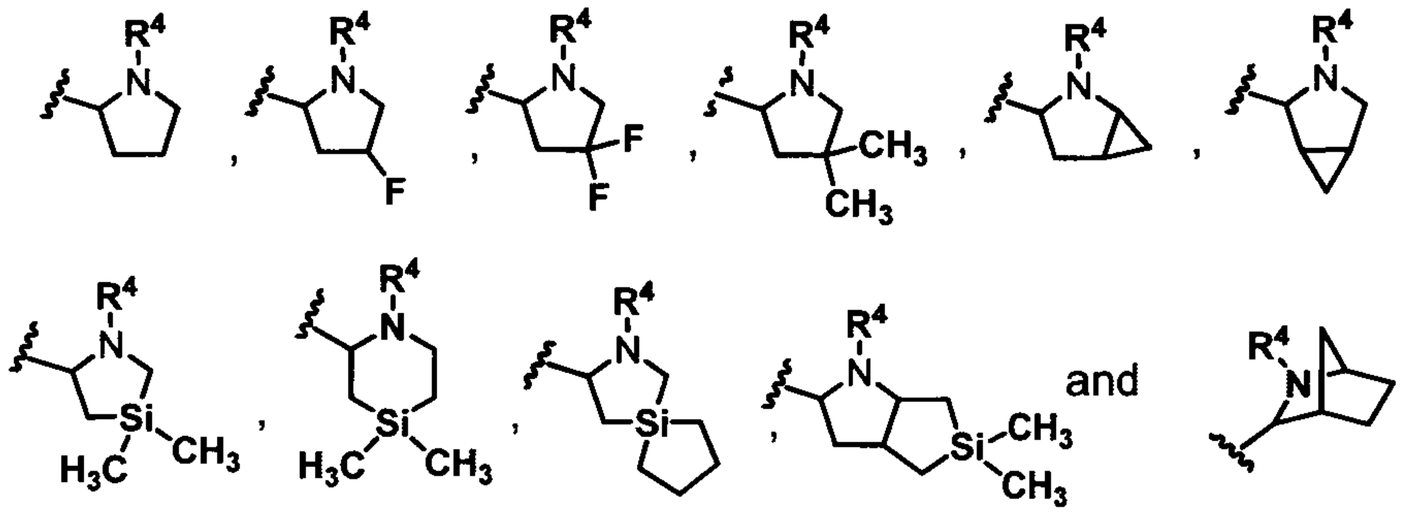

, wherein R^a is H, methyl, ethyl, propyl, isopropyl, t-butyl, cyclopropyl, $-CH_2CH_2Si(CH_3)_3$, $-CH_2CH_2CF_3$, pyranyl, benzyl or phenyl, and R^b is methyl, ethyl or isopropyl.

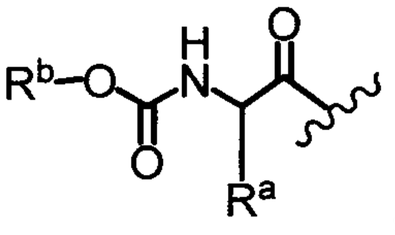
In still another embodiment, each occurrence of R^4 is independently –C(O)CH(alkyl)-NHC(O)Oalkyl.

In another embodiment, each occurrence of R^4 is independently:

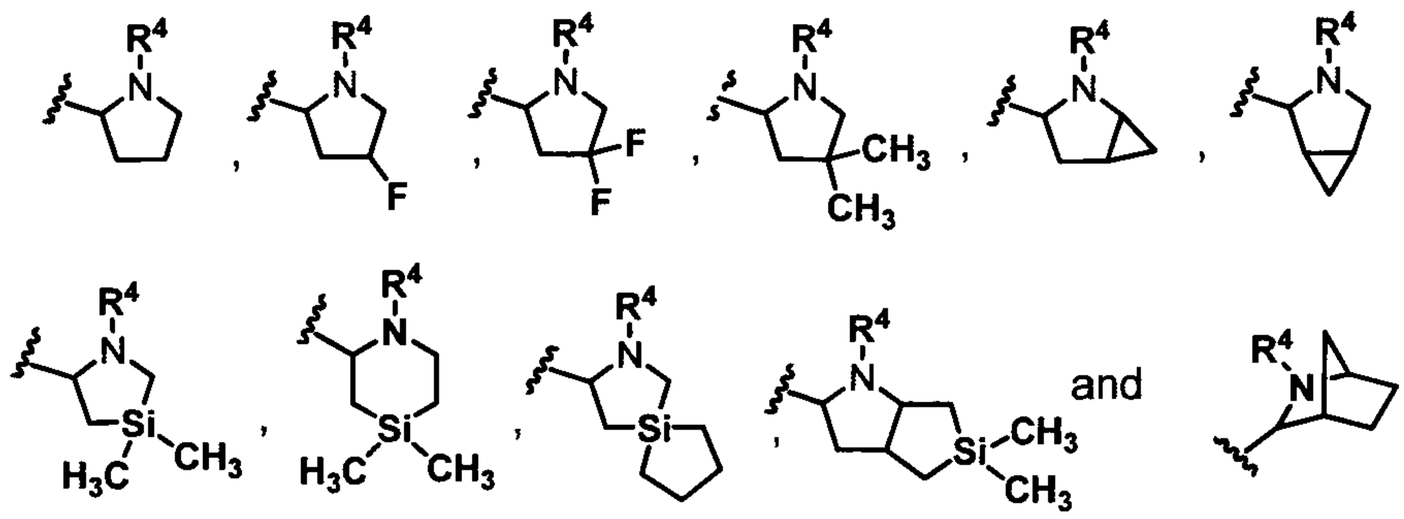


In one embodiment, A and A' are each independently selected from:

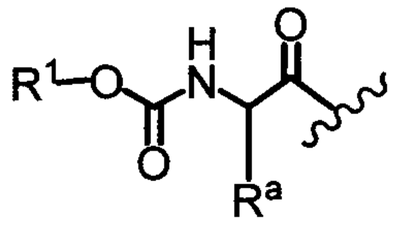

and R^4 is:


, wherein R^b is H, alkyl, haloalkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl or heteroaryl and R^a is alkyl, haloalkyl, silylalkyl, 3 to 6-membered cycloalkyl or 4 to 6-membered heterocycloalkyl, aryl or heteroaryl.

In another embodiment, A and A' are each independently selected from:

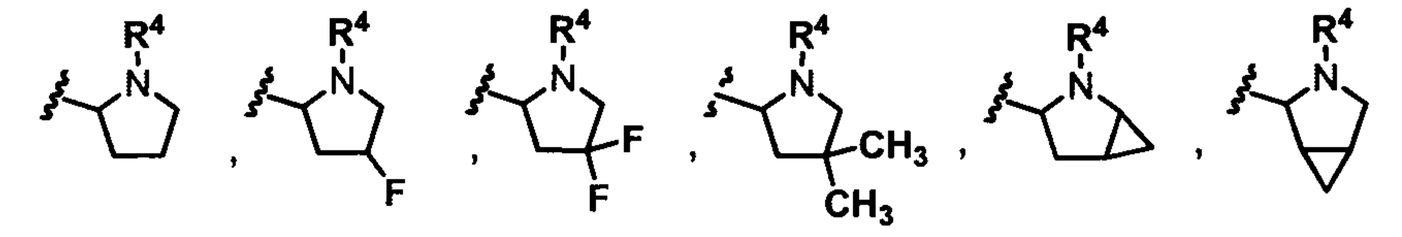


and R^4 is:

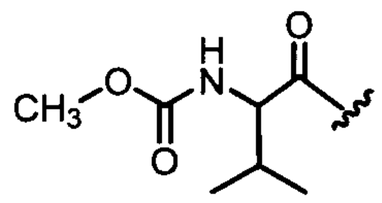


, wherein R^a is H, methyl, ethyl, propyl, isopropyl, t-butyl, cyclopropyl, $-CH_2CH_2Si(CH_3)_3$, $-CH_2CH_2CF_3$, pyranyl, benzyl or phenyl, and R^1 is methyl, ethyl or isopropyl.

In another embodiment, A and A' are each independently selected from:

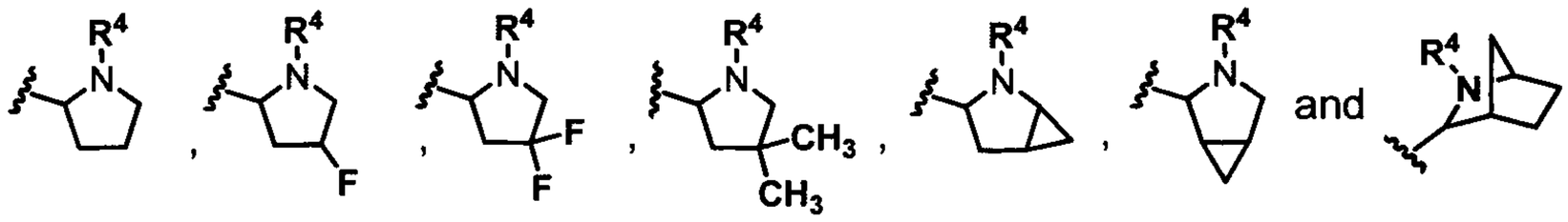


and R^4 is:

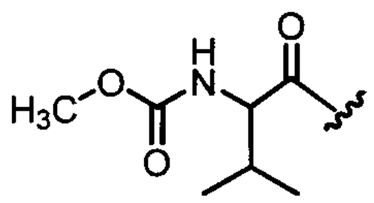


.

In another embodiment, A and A' are each independently selected from:

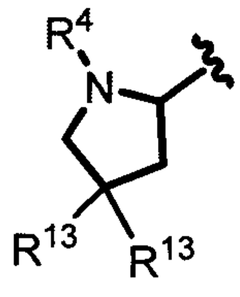


and R^4 is:



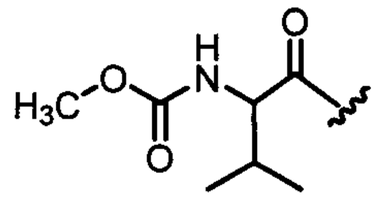
.

In yet another embodiment, A and A' are each:



, wherein each occurrence of R^{13} is independently H, CH_3, or F;

and R^4 is



.

In one embodiment, G is $-C(R^3)_2$-O-.

In another embodiment, G is $-C(R^{14})$=N-.

In another embodiment, G is $-C(R^3)_2-C(R^3)_2$- or $-C(R^{14})=C(R^{14})$-.

In still another embodiment, G is $-C(R^3)_2-C(R^3)_2$- or $-C(R^{14})=C(R^{14})$-.

In one embodiment, G is $-C(R_3)_2$-O- and each occurrence of R^3 is independently selected from H, C_1-C_6 alkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl and 5 or 6-membered monocyclic heteroaryl, wherein said 5 or 6-membered monocyclic heteroaryl group and said phenyl groups can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-C_1-C_6 haloalkyl.

In another embodiment, G is $-C(R_3)_2$-O-, wherein one occurrence of R^3 is H, and the other occurrence of R^3 is selected from C_1-C_6 alkyl, cycloalkyl and phenyl, wherein said phenyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-C_1-C_6 haloalkyl.

In one embodiment, G is $-C(R_3)_2$-O- and each occurrence of R^3 is independently selected from H, methyl, ethyl, isopropyl, cyclopropyl, 1'-methylcyclopropyl, methylenecyclopropyl, phenyl, pyridyl, and pyrimidyl wherein said phenyl, pyridyl and pyrimidinyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from F, Cl, -CN, CH_3, CF_3, OCF_3 and $OCH_2CH_2OCH_3$.

In one embodiment, G is $-CH(R^3)$-O-, wherein R^3 is selected from C_1-C_6 alkyl, phenyl, 5 or 6-membered monocyclic heteroaryl and 9 or 10-membered

bicyclic heteroaryl, wherein said phenyl group, said 5 or 6-membered monocyclic heteroaryl group and said 9 or 10-membered bicyclic heteroaryl group can be optionally substituted with a C_1-C_6 alkyl group.

In another embodiment, G is –CH(R^3)-O-, wherein R^3 is selected from methyl, phenyl, 5-methyl-thiophen-2-yl and benzothiophen-2-yl.

In another embodiment, G is –C(R_3)$_2$-O-, wherein one occurrence of R^3 is H, and the other occurrence of R^3 is selected from phenyl, methyl, thiophenyl or benzothiophenyl, wherein said benzothiophenyl can be optionally substituted witha C_1-C_6 alkyl, cycloalkyl and phenyl, wherein said phenyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-C_1-C_6 haloalkyl.

In one embodiment, G is –C(R_3)$_2$-O- and each occurrence of R^3 is independently selected from H, methyl, ethyl, isopropyl, cyclopropyl, 1'-methylcyclopropyl, methylenecyclopropyl, phenyl, pyridyl, and pyrimidyl wherein said phenyl, pyridyl and pyrimidinyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from F, Cl, -CN, CH_3, CF_3, OCF_3 and $OCH_2CH_2OCH_3$.

In another embodiment, G is –C(R_3)$_2$-O-, wherein one occurrence of R^3 is H, and the other occurrence of R^3 is selected from methyl, ethyl, isopropyl, cyclopropyl, 1'-methylcyclopropyl, methylenecyclopropyl, phenyl, pyridyl, and pyrimidyl wherein said phenyl, pyridyl and pyrimidinyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from F, Cl, -CN, CH_3, CF_3, OCF_3 and $OCH_2CH_2OCH_3$.

In one embodiment, G is –C(R_3)$_2$-O-, wherein both R^3 groups, together with the common carbon atom to which they are attached, join to form a carbonyl group, a 3 to 6-membered spirocyclic cycloalkyl group or a 3 to 6-membered spirocyclic heterocycloalkyl group.

In one embodiment, G is –C(R^{14})=N-, wherein R^{14} is selected from H, C_1-C_6 alkyl, cycloalkyl and phenyl, wherein said phenyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-C_1-C_6 haloalkyl.

In one embodiment, each occurrence of R^3 is independently selected from H, methyl, ethyl, isopropyl, cyclopropyl, 1'-methylcyclopropyl, methylenecyclopropyl, phenyl, pyridyl, and pyrimidyl wherein said phenyl, pyridyl and pyrimidinyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from F, Cl, -CN, CH_3, CF_3, OCF_3 and $OCH_2CH_2OCH_3$.

In another embodiment, two R^3 groups on the same carbon atom, together with the common carbon atom to which they are attached, join to form a carbonyl group, a 3 to 6-membered spirocyclic cycloalkyl group or a 3 to 6-membered spirocyclic heterocycloalkyl group.

In one embodiment, U is $C(R^2)$.

In another embodiment, U is CH.

In another embodiment, U is CF.

In one embodiment, V is $C(R^{15})$.

In another embodiment, V is CH.

In another embodiment, V is CF.

In another embodiment, V is N.

In one embodiment, V' is $C(R^{15})$.

In another embodiment, V' is CH.

In another embodiment, V' is CF.

In another embodiment, V' is N.

In still another embodiment, V and V' are each CH.

In one embodiment, W is $C(R^{15})$.

In another embodiment, W is CH.

In another embodiment, W is CF.

In another embodiment, W is N.

In one embodiment, W ' is $C(R^{15})$.

In another embodiment, W ' is CH.

In another embodiment, W ' is CF.

In another embodiment, W ' is N.

In still another embodiment, W and W' are each CH.

In a further embodiment, V, V' W and W' are each CH.

In one embodiment, R^1 is absent.

In another embodiment, R^1 is F.

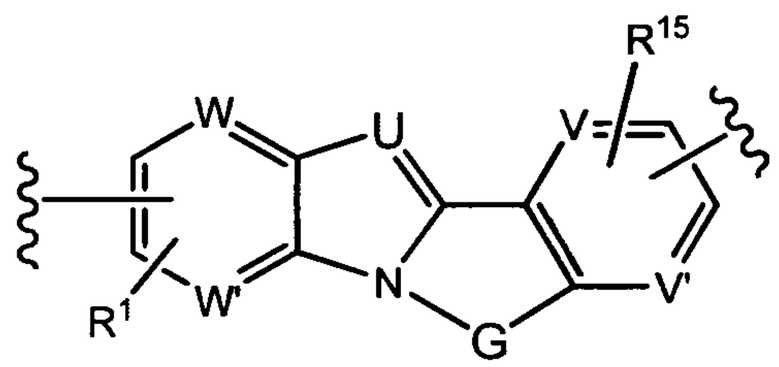
In one embodiment, each occurrence of R^3 is independently selected from H, methyl, ethyl, isopropyl, cyclopropyl, 1'-methylcyclopropyl, methylenecyclopropyl, phenyl, pyridyl, and pyrimidyl wherein said phenyl, pyridyl and pyrimidinyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from F, Cl, -CN, CH_3, CF_3, OCF_3 and $OCH_2CH_2OCH_3$.

In another embodiment, two R^3 groups on the same carbon atom, together with the common carbon atom to which they are attached, join to form a carbonyl group, a 3 to 6-membered spirocyclic cycloalkyl group or a 3 to 6-membered spirocyclic heterocycloalkyl group.

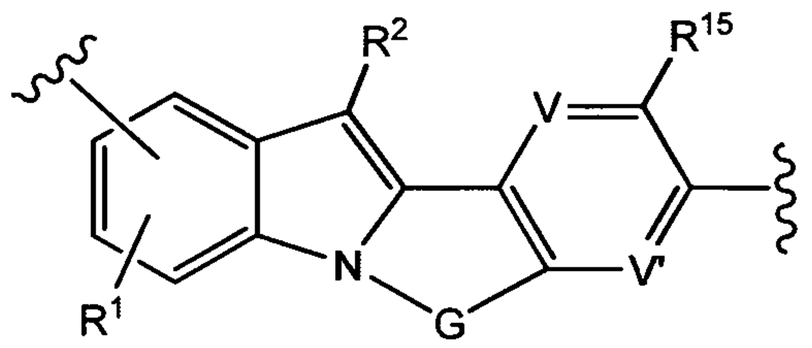
In one embodiment, each occurrence of R^{10} is independently H or F.

In another embodiment, each occurrence of R^{10} is H.

In one embodiment, the group:

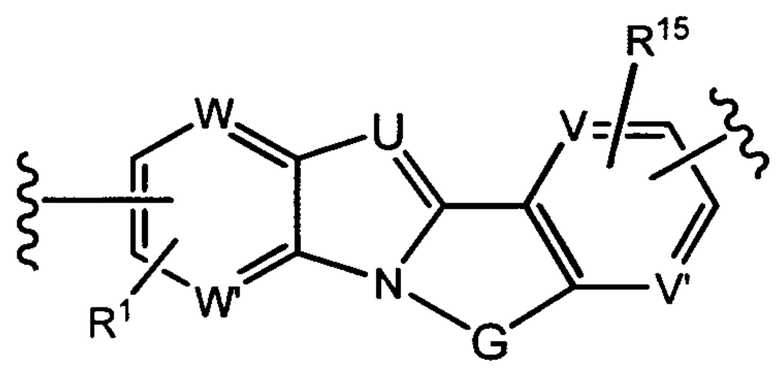


has the structure:

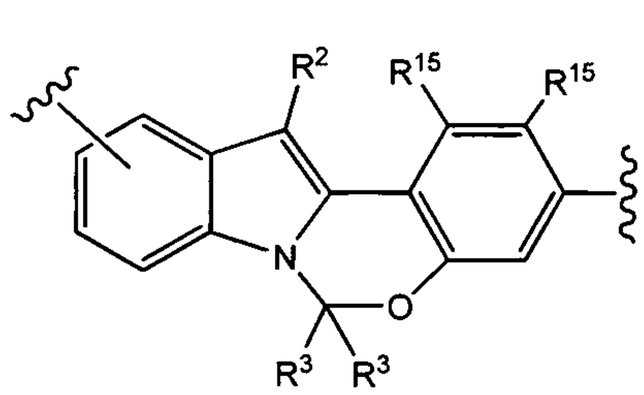
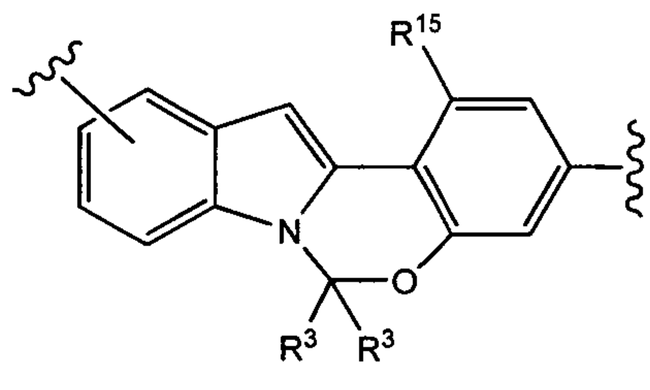


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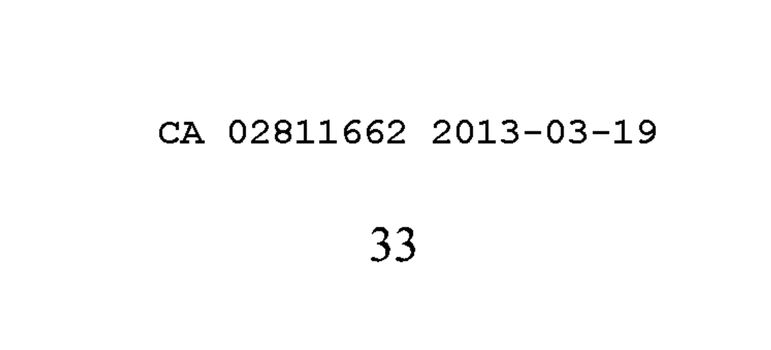
In another embodiment, the group:



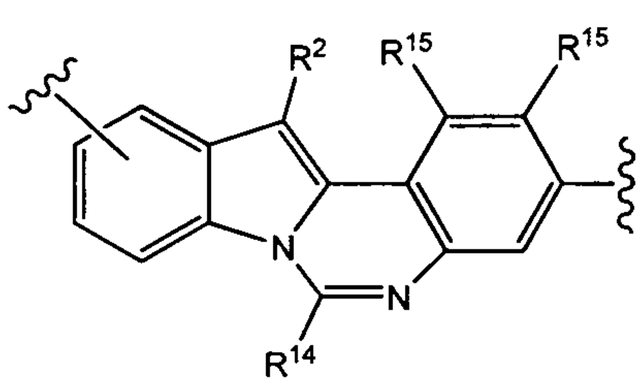
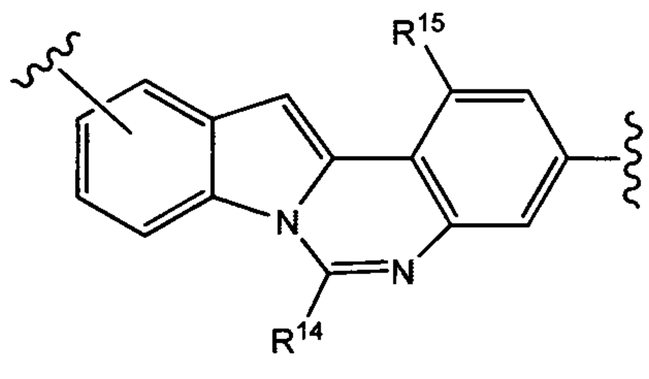
has the structure:

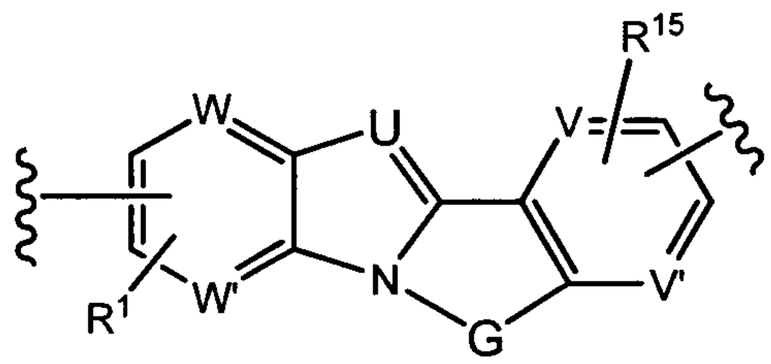
In another embodiment, the group:



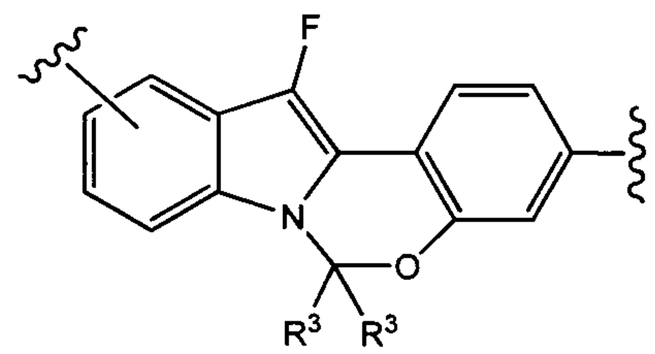
has the structure:

In still another embodiment, the group:



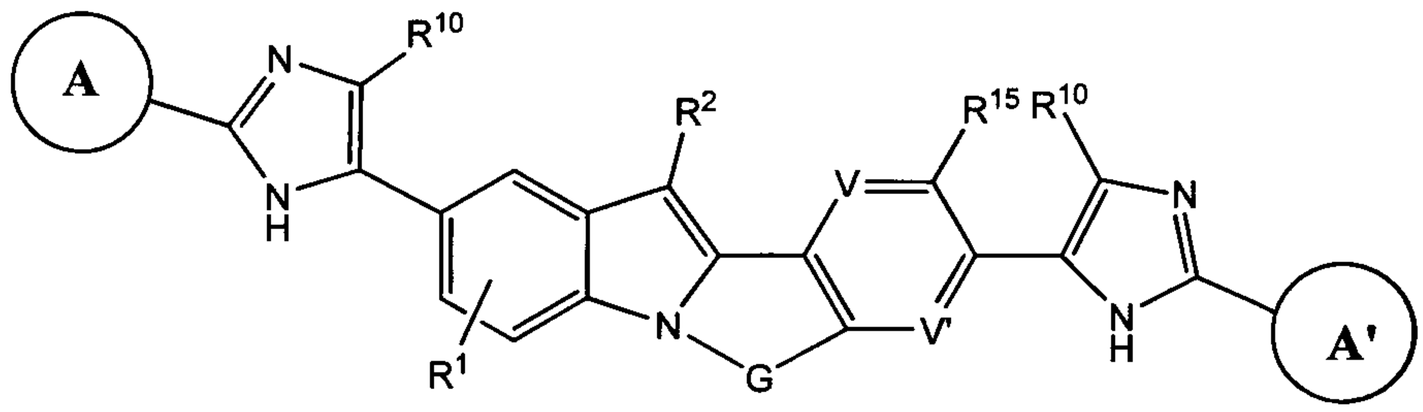
has the structure:



In one embodiment, variables A, A', G, R^1, U, V, V', W, W', X, X', Y and Y' for the Compounds of Formula (I) are selected independently of each other.

In another embodiment, the Compounds of Formula (I) are in substantially purified form.

In one embodiment, the Compounds of Formula (I) have the formula (Ia):



(Ia)

and pharmaceutically acceptable salts thereof, wherein:

A and A' are each independently a 5-membered monocyclic heterocycloalkyl, wherein said 5-membered monocyclic heterocycloalkyl group can be optionally and independently substituted on one or more ring carbon atoms with R^{13}, such that any two R^{13} groups on the same ring, together with the carbon atoms to which they are attached, can join to form a fused, bridged or spirocyclic 3 to 6-membered cycloalkyl group or a fused, bridged or spirocyclic 4 to 6-membered heterocycloalkyl group, wherein said 5-membered monocyclic heterocycloalkyl contains from 1 to 2 ring heteroatoms, each independently selected from $N(R^4)$ and $Si(R^{16})_2$;

G is selected from $-C(R^3)_2-$, $-C(R^3)_2-O-$, $-C(R^{14})=N-$, $-C(R^3)_2-C(R^3)_2-$ and $-C(R^{14})=C(R^{14})-$;

V and V' are each independently selected from N and $C(R^{15})$;

R^1 represents an optional ring substituent on the phenyl ring to which R^1 is attached, wherein said substituent is selected from C_1-C_6 alkyl and halo;

each occurrence of R^2 is independently selected from H, C_1-C_6 alkyl, 3 to 6 membered cycloalkyl, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl –O-(C_1-C_6 haloalkyl); halo, -OH, aryl, and heteroaryl

each occurrence of R^3 is independently selected from H, C_1-C_6 alkyl, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), 3 to 6-membered cycloalkyl, C_1-C_6 haloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl and benzyl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group or the phenyl group of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-(C_1-C_6 haloalkyl);

each occurrence of R^4 is independently -C(O)-[$C(R^7)_2$]N(R^6)C(O)O-R^{11};

each occurrence of R^6 is independently selected from H and C_1-C_6 alkyl;

each occurrence of R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl and 5 or 6-membered monocyclic heteroaryl, wherein said 3 to 6-membered cycloalkyl group, said 4 to 6-membered heterocycloalkyl group, said aryl group and said 5 or 6-membered monocyclic heteroaryl group can be optionally and independently substituted with up to three R^8 groups;

each occurrence of R^8 is independently selected from H, C_1-C_6 alkyl, halo, -C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -OH, -C(O)NH-(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -O-(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$ and -NHC(O)-(C_1-C_6 alkyl);

each occurrence of R^{10} is independently selected from H and halo;

each occurrence of R^{11} is independently C_1-C_6 alkyl;

each occurrence of R^{13} is independently selected from H and halo, wherein two R^{13} groups, together with the carbon atom(s) to which they are attached, can optionally join to form a 3 to 6-membered cycloalkyl group or 4 to 6-membered heterocycloalkyl group;

each occurrence of R^{14} is independently selected from H, halo, C_1-C_6 alkyl, -(C_1-C_6 alkylene)-O-C_1-C_6 alkyl, 3 to 6-membered cycloalkyl, C_1-C_6 haloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl and benzyl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group or the phenyl group of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-C_1-C_6 haloalkyl;

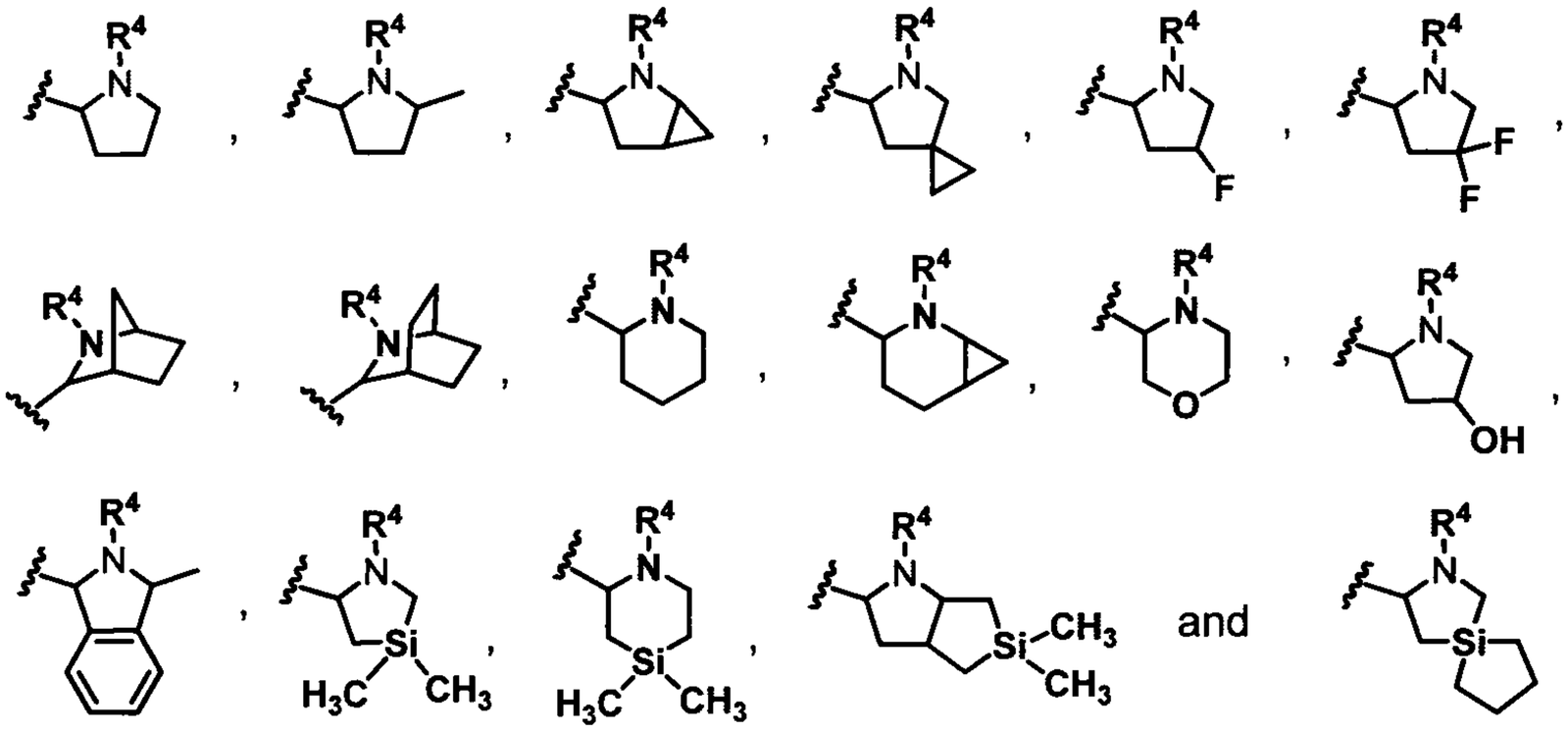
each occurrence of R^{15} is independently selected from H and halo; and

each occurrence of R^{16} is independently selected from C_1-C_6 alkyl.

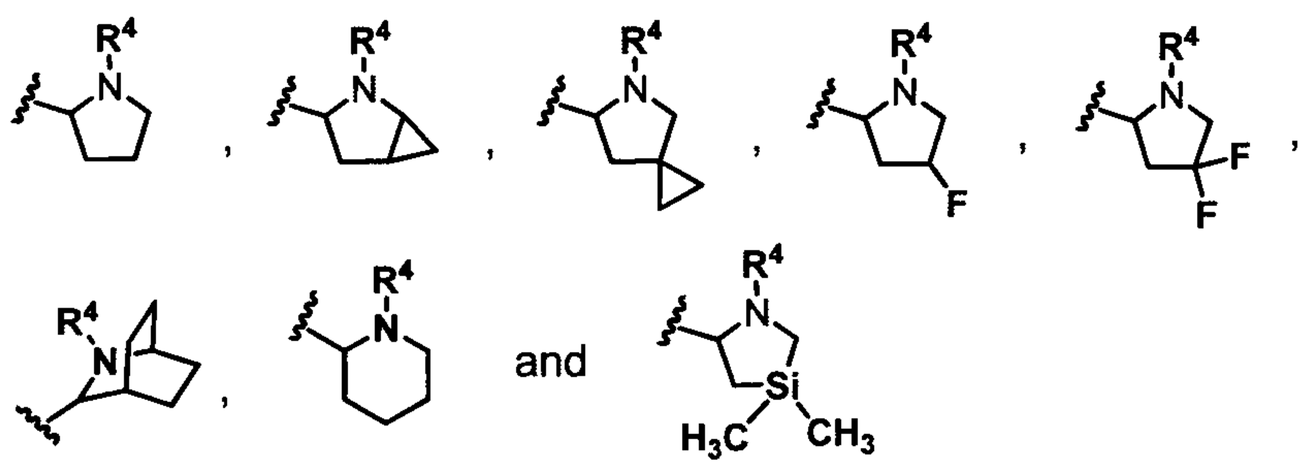
In one embodiment, for the Compounds of Formula (Ia), A and A' are each a 5-membered monocyclic heteroaryl group.

In another embodiment, for the Compounds of Formula (Ia), A and A' are each a 6-membered monocyclic heteroaryl group.

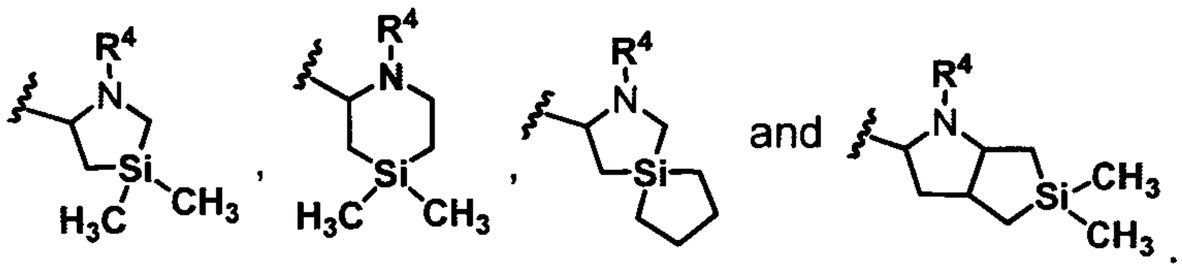
In another embodiment, for the Compounds of Formula (Ia), A and A' are each independently selected from:



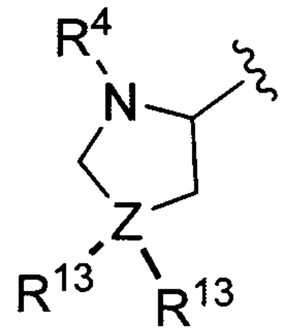
In still another embodiment, for the Compounds of Formula (Ia), A and A' are each independently selected from:



In another embodiment, for the Compounds of Formula (Ia), A and A' are each independently selected from:



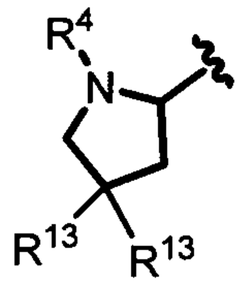
In one embodiment, for the Compounds of Formula (Ia), A and A' are each:



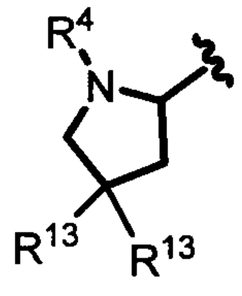
wherein each occurrence of Z is independently $-Si(R^{13})_2-$, $-C(R^{13})_2-$ or –S-,

and each occurrence of R^{13} is independently H, Me, F or two R^{13} groups together with Z, can combine to form a spirocyclic 3 to 6-membered cycloalkyl group or a spirocyclic 3 to 6-membered silyl-containing heterocycloalkyl group.

In another embodiment, for the Compounds of Formula (Ia), A and A' are each independently:



In another embodiment, for the Compounds of Formula (Ia), A and A' are each independently:



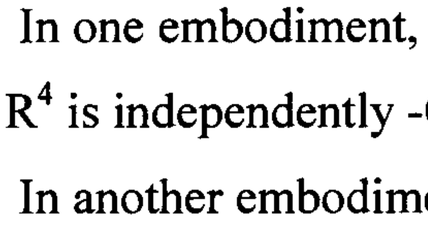
wherein each occurrence of R^{13} is independently H, CH_3, or F.

In one embodiment, for the Compounds of Formula (Ia), each occurrence of R^4 is independently $-C(O)C(R^7)_2NHC(O)O-R^{11}$ or $-C(O)C(R^7)_2N(R^6)_2$.

In another embodiment, for the Compounds of Formula (Ia), each occurrence of R^4 is independently $-C(O)-[C(R^7)_2]_qN(R^6)C(O)O-R^{11}$.

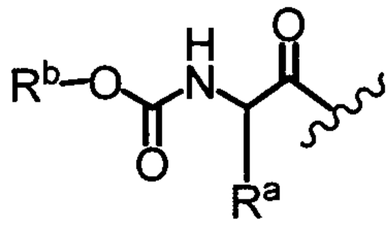
In another embodiment, for the Compounds of Formula (Ia), each occurrence of R^4 is independently –C(O)CH(alkyl)-NHC(O)Oalkyl, C(O)CH(cycloalkyl)-NHC(O)Oalkyl, C(O)CH(heterocycloalkyl)-NHC(O)Oalkyl, C(O)CH(aryl)-NHC(O)Oalkyl or $C(O)CH(aryl)-N(alkyl)_2$.

In another embodiment, for the Compounds of Formula (Ia), each occurrence of R^4 is independently:



, wherein R^b is H, alkyl, haloalkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl or heteroaryl and R^a is alkyl, haloalkyl, silylalkyl, 3 to 6-membered cycloalkyl or 4 to 6-membered heterocycloalkyl, aryl or heteroaryl.

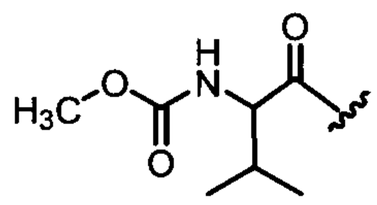
In another embodiment, for the Compounds of Formula (Ia), each occurrence of R^4 is independently:



, wherein R^a is H, methyl, ethyl, propyl, isopropyl, t-butyl, cyclopropyl, $-CH_2CH_2Si(CH_3)_3$, $-CH_2CH_2CF_3$, pyranyl, benzyl or phenyl, and R^b is methyl, ethyl or isopropyl.

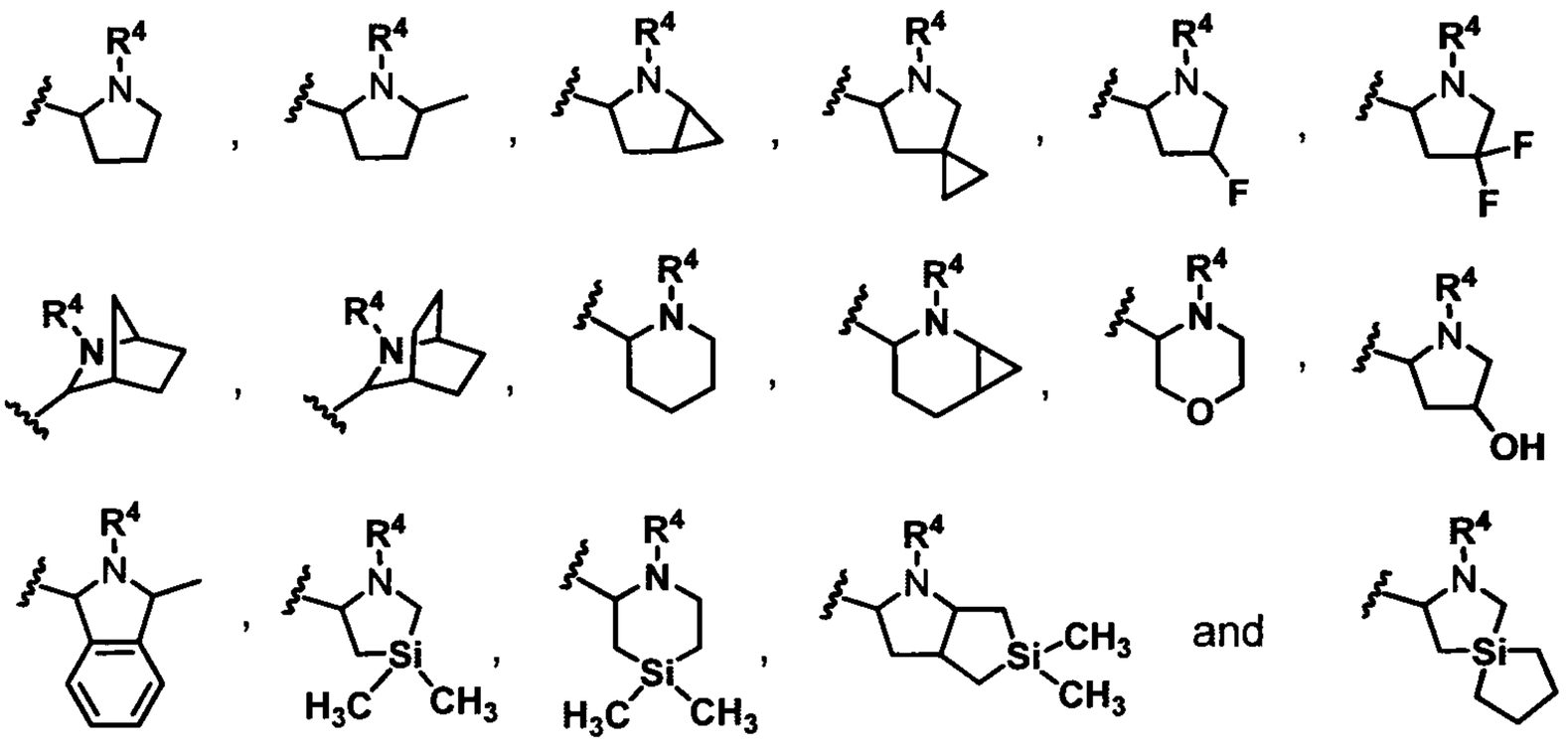
In still another embodiment, for the Compounds of Formula (Ia), each occurrence of R^4 is independently –C(O)CH(alkyl)-NHC(O)Oalkyl.

In another embodiment, for the Compounds of Formula (Ia), each occurrence of R^4 is independently:

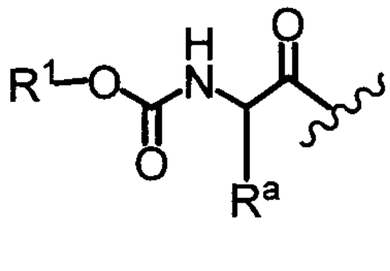


.

In one embodiment, for the Compounds of Formula (Ia), A and A' are each independently selected from:

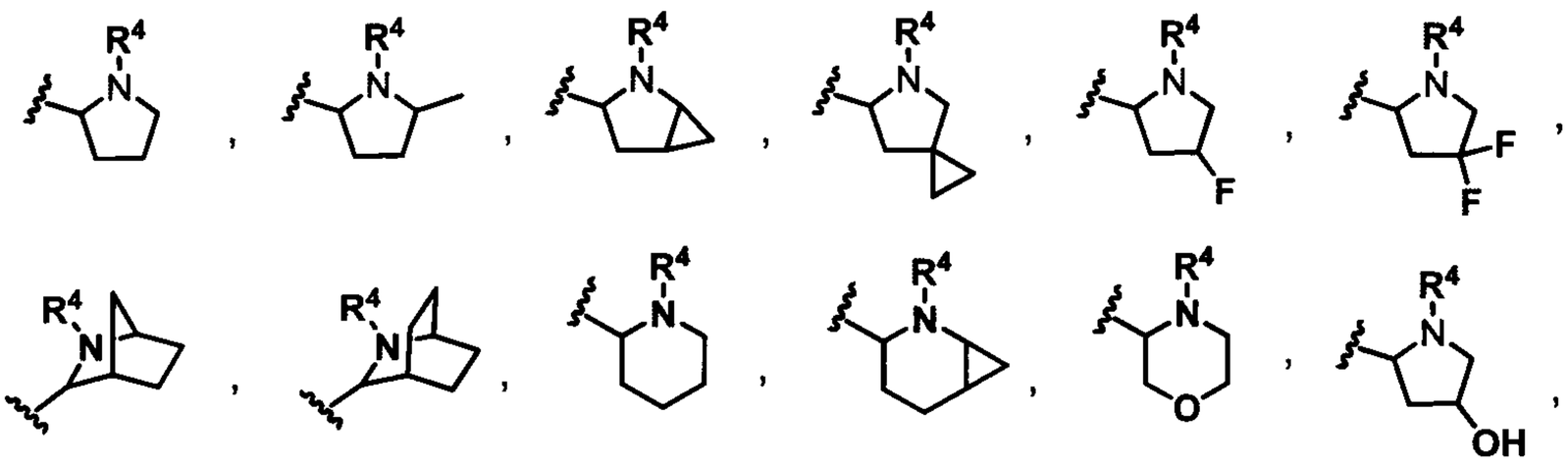


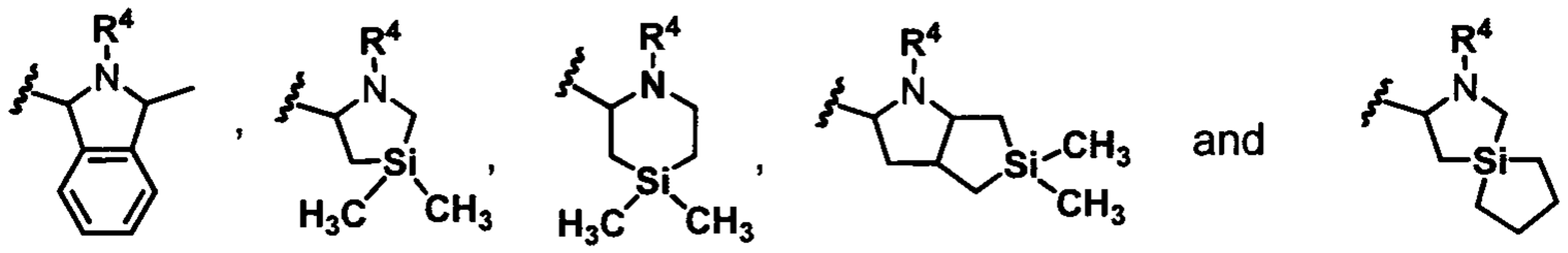
and R^4 is:



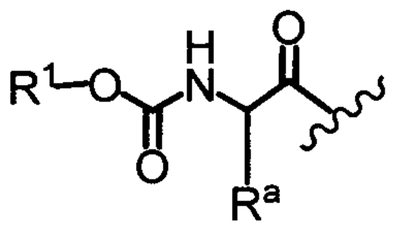
, wherein R^1 is H, alkyl, haloalkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl or heteroaryl and R^a is alkyl, haloalkyl, silylalkyl, 3 to 6-membered cycloalkyl or 4 to 6-membered heterocycloalkyl, aryl or heteroaryl.

In another embodiment, for the Compounds of Formula (Ia), A and A' are each independently selected from:



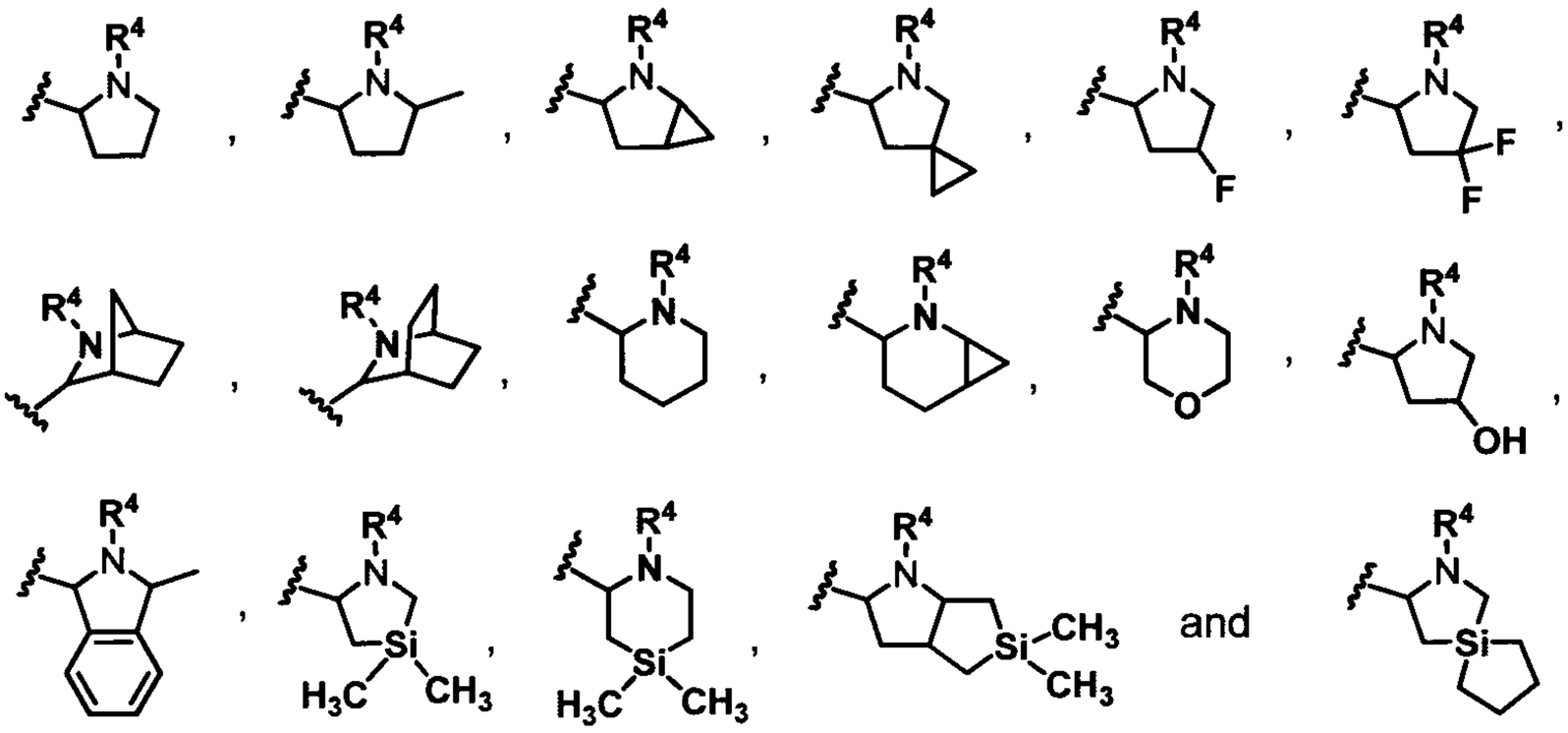


and R^4 is:

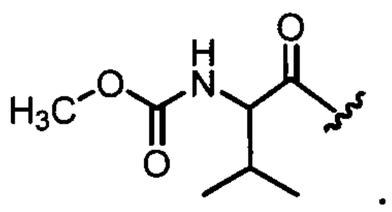


, wherein R^a is H, methyl, ethyl, propyl, isopropyl, t-butyl, cyclopropyl, $-CH_2CH_2Si(CH_3)_3$, $-CH_2CH_2CF_3$, pyranyl, benzyl or phenyl, and R^1 is methyl, ethyl or isopropyl.

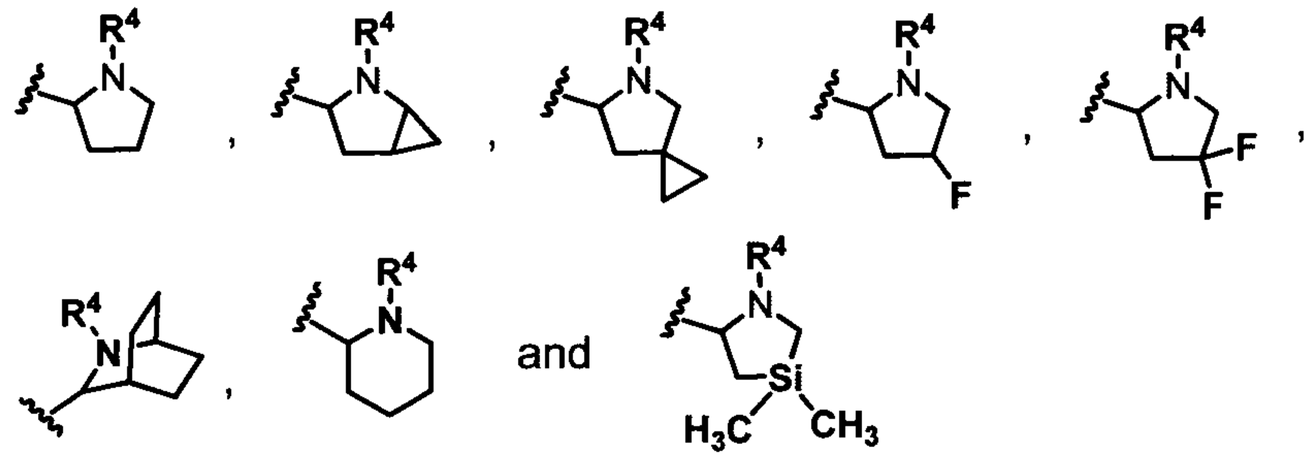
In another embodiment, for the Compounds of Formula (Ia), A and A' are each independently selected from:



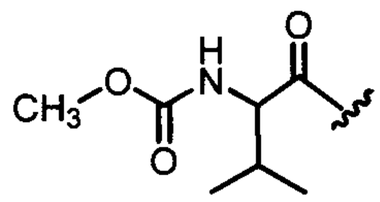
and R^4 is:



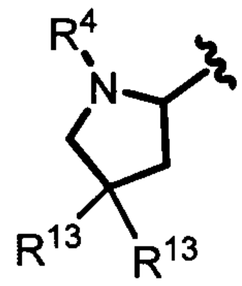
In another embodiment, for the Compounds of Formula (Ia), A and A' are each independently selected from:



and R^4 is:

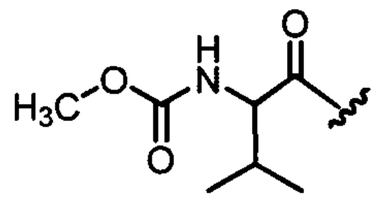


In yet another embodiment, for the Compounds of Formula (Ia), A and A' are each:



, wherein each occurrence of R^{13} is independently H, CH_3, or F;

and R^4 is



In one embodiment, for the Compounds of Formula (Ia), G is $-C(R^3)_2$-O-.

In another embodiment, for the Compounds of Formula (Ia), G is $-C(R^{14})=N-$.

In another embodiment, for the Compounds of Formula (Ia), G is $-C(R^3)_2-C(R^3)_2-$, $-C(R^{14})=C(R^{14})-$.

In still another embodiment, for the Compounds of Formula (Ia), G is $-C(R^3)_2-C(R^3)_2-$, $-C(R^{14})=C(R^{14})-$.

In one embodiment, for the Compounds of Formula (Ia), G is $-C(R_3)_2$-O- and each occurrence of R^3 is independently selected from H, C_1-C_6 alkyl, cycloalkyl and phenyl, wherein said phenyl group can be optionally substituted with

up to 2 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-C_1-C_6 haloalkyl.

In another embodiment, for the Compounds of Formula (Ia), G is –$C(R_3)_2$-O-, wherein one occurrence of R^3 is H, and the other occurrence of R^3 is selected from C_1-C_6 alkyl, cycloalkyl and phenyl, wherein said phenyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-C_1-C_6 haloalkyl.

In one embodiment, for the Compounds of Formula (Ia), G is –$C(R_3)_2$-O- and each occurrence of R^3 is independently selected from H, methyl, ethyl, isopropyl, cyclopropyl, 1'-methylcyclopropyl, methylenecyclopropyl, phenyl, pyridyl, and pyrimidyl wherein said phenyl, pyridyl and pyrimidinyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from F, Cl, -CN, CH_3, CF_3, OCF_3 and $OCH_2CH_2OCH_3$.

In another embodiment, for the Compounds of Formula (Ia), G is –$C(R_3)_2$-O-, wherein one occurrence of R^3 is H, and the other occurrence of R^3 is selected from methyl, ethyl, isopropyl, cyclopropyl, 1'-methylcyclopropyl, methylenecyclopropyl, phenyl, pyridyl, and pyrimidyl wherein said phenyl, pyridyl and pyrimidinyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from F, Cl, -CN, CH_3, CF_3, OCF_3 and $OCH_2CH_2OCH_3$.

In one embodiment, for the Compounds of Formula (Ia), G is –$C(R^{14})$=N-, wherein R^{14} is selected from H, C_1-C_6 alkyl, cycloalkyl and phenyl, wherein said phenyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-C_1-C_6 haloalkyl.

In one embodiment, for the Compounds of Formula (Ia), U is $C(R^2)$.

In another embodiment, for the Compounds of Formula (Ia), U is CH.

In another embodiment, for the Compounds of Formula (Ia), U is CF.

In one embodiment, for the Compounds of Formula (Ia), V is $C(R^{15})$.

In another embodiment, for the Compounds of Formula (Ia), V is CH.

In another embodiment, for the Compounds of Formula (Ia), V is N.

In one embodiment, for the Compounds of Formula (Ia), V' is $C(R^{15})$.

In another embodiment, for the Compounds of Formula (Ia), V' is CH.

In another embodiment, for the Compounds of Formula (Ia), V' is N.

In still another embodiment, for the Compounds of Formula (Ia), V and V' are each CH.

In one embodiment, for the Compounds of Formula (Ia), R^1 is absent.

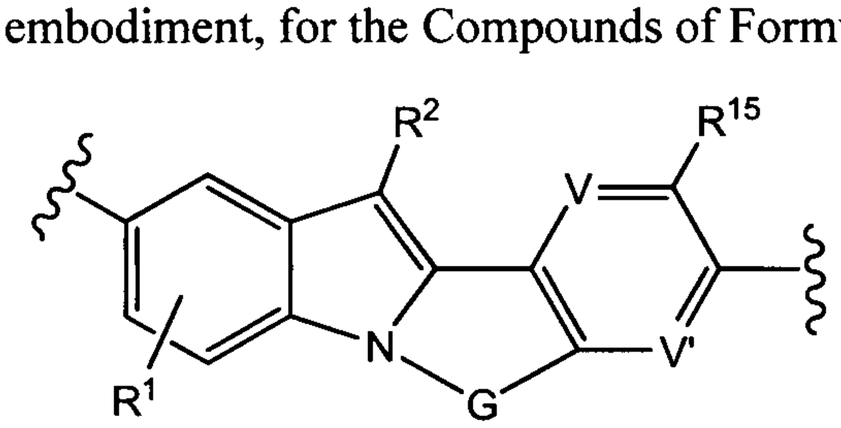
In another embodiment, for the Compounds of Formula (Ia), R^1 is F.

In one embodiment, each occurrence of R^3 is independently selected from H, methyl, ethyl, isopropyl, cyclopropyl, 1'-methylcyclopropyl, methylenecyclopropyl, phenyl, pyridyl, and pyrimidyl wherein said phenyl, pyridyl and pyrimidinyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from F, Cl, -CN, CH_3, CF_3, OCF_3 and $OCH_2CH_2OCH_3$.

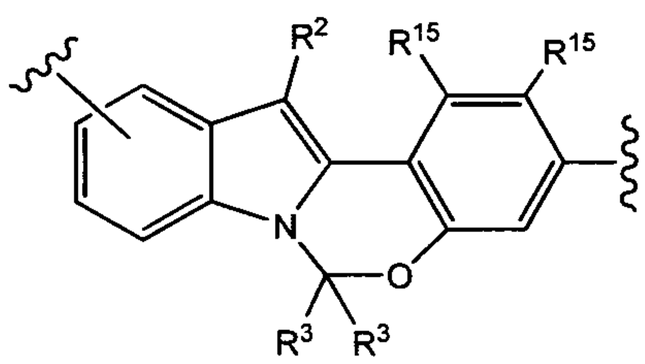
In one embodiment, for the Compounds of Formula (Ia), each occurrence of R^{10} is independently H or F.

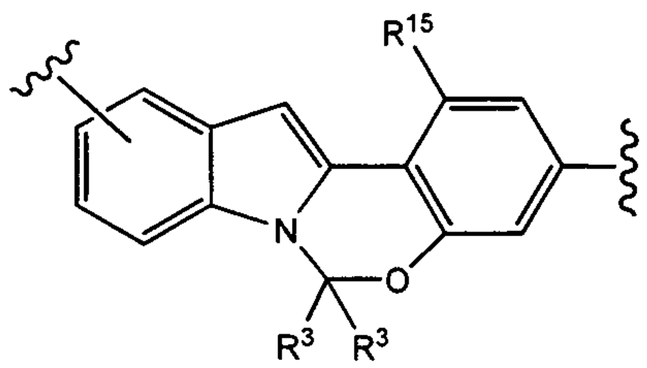
In another embodiment, for the Compounds of Formula (Ia), each occurrence of R^{10} is H.

In one embodiment, for the Compounds of Formula (Ia), the group:

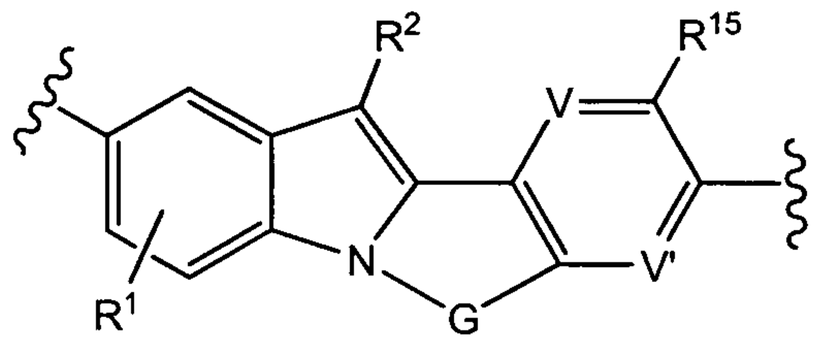


has the structure:

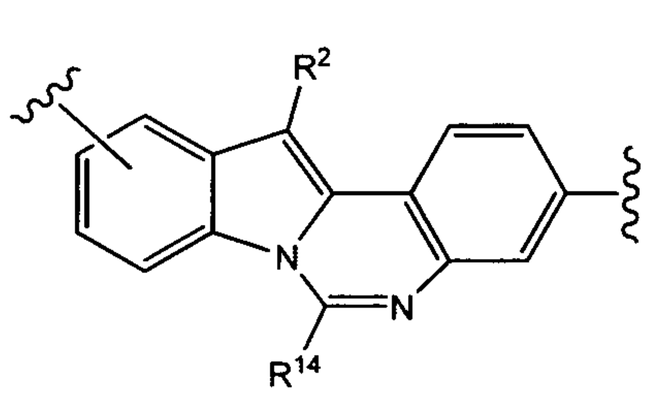


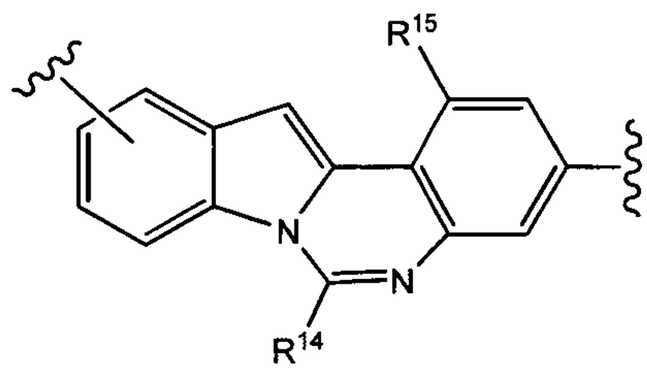


In another embodiment, for the Compounds of Formula (Ia), the group:

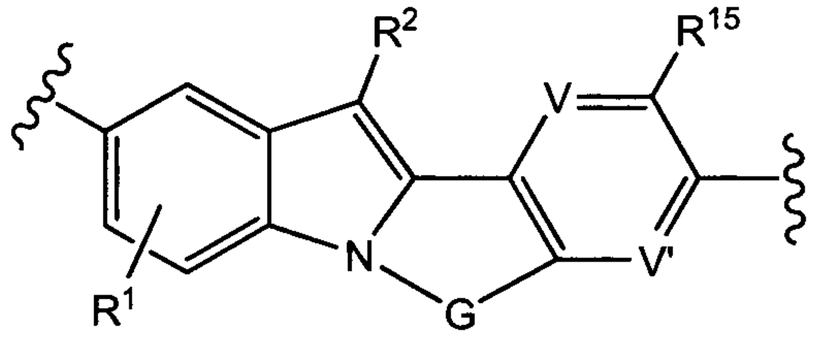


has the structure:

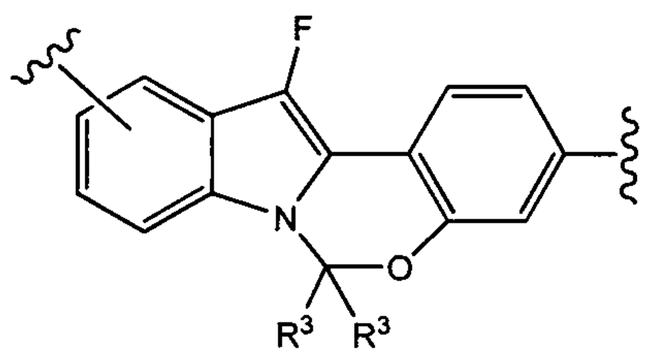




In another embodiment, for the Compounds of Formula (Ia), the group:



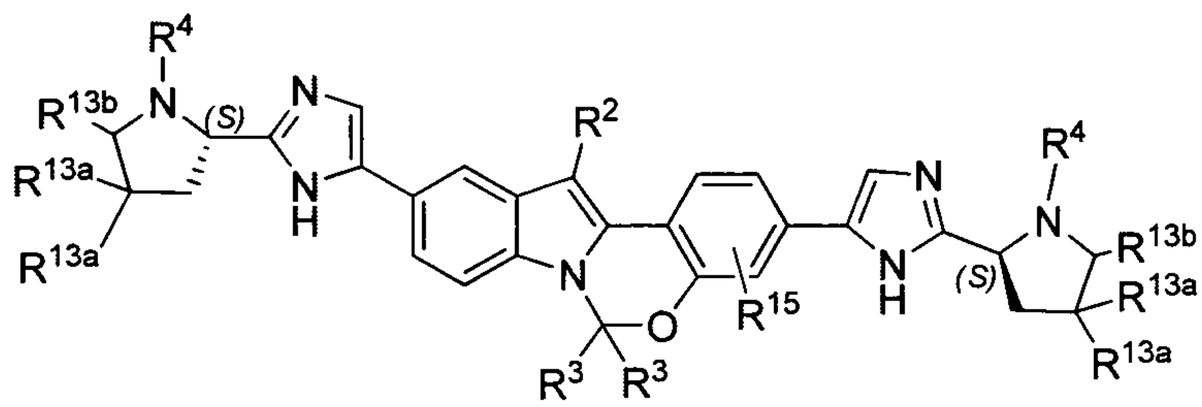
has the structure:



In one embodiment, variables A, A', G, R^1, R^2, R^{10}, R^{15}, U, V and V' for the Compounds of Formula (Ia) are selected independently of each other.

In another embodiment, the Compounds of Formula (Ia) are in substantially purified form.

In one embodiment, the Compounds of Formula (I) have the formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof, wherein:

R^2 is H or F;

each occurrence of R^3 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3 to 6 membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl,

5 or 6-membered monocyclic heteroaryl, 9 or 10-membered bicyclic heteroaryl, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkylene –O-(C_1-C_6 haloalkyl); -(C_1-C_6 alkylene)C(=O)NH-alkyl, -(C_1-C_6 alkylene)aryl, and -(C_1-C_6 alkylene)heteroaryl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group, said 9 or 10-membered bicyclic heteroaryl group or the phenyl group of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-(C_1-C_6 haloalkyl);

each occurrence of R^4 is independently selected from –C(O)O-(C_1-C_6 alkyl), –C(O)-CH(R^7)N(R^6)$_2$ and –C(O)-CH(R^7)C(O)O-R^{11};

each occurrence of R^6 is independently H or C_1-C_6 alkyl;

each occurrence of R^7 is independently selected from C_1-C_6 alkyl, phenyl, 4 to 6-membered heterocycloalkyl and 3 to 6 membered cycloalkyl;

each occurrence of R^{11} is independently C_1-C_6 alkyl;

each occurrence of R^{13a} is independently H, Me or F; or two R^{13a} groups that are attached to the same carbon atom, together with the common carbon atom to which they are attached, combine to form a spirocyclic 3 to 6 membered cycloalkyl group;

each occurrence of R^{13b} is independently H, or one or both R^{13b} groups and an R13^a group that are attached to same ring, together with the ring carbon atoms to which they are attached, can combine to form a fused 3 to 6 membered cycloalkyl group; and

R^{15} represents up to 2 substituents, each independently selected from H, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3 to 6 membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl, benzyl, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkylene –O-(C_1-C_6 haloalkyl) -(C_1-C_6 alkylene)C(=O)NH-alkyl, -(C_1-C_6 alkylene)aryl, and -(C_1-C_6 alkylene)heteroaryl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group or the phenyl group of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-(C_1-C_6 haloalkyl).

In one embodiment, for the Compounds of Formula (Ib), R^2 is H.

In another embodiment, for the Compounds of Formula (Ib), R^2 is F.

In one embodiment, for the Compounds of Formula (Ib), one occurrence of R^3 is H and the other occurrence of R^3 is selected from H, methyl, ethyl, isopropyl, cyclopropyl, 1'-methylcyclopropyl, methylenecyclopropyl, phenyl, pyridyl, and pyrimidyl wherein said phenyl, pyridyl and pyrimidinyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from F, Cl, -CN, CH_3, CF_3, OCF_3, $OCH_2CH_2OCH_3$.

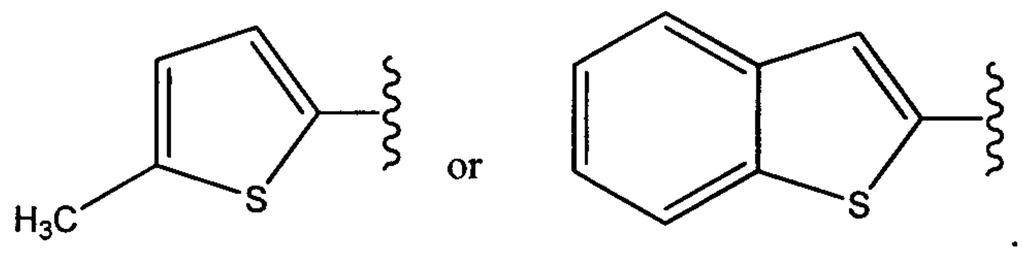
In another embodiment, for the Compounds of Formula (Ib), two R^3 groups that are attached to the same carbon atom, together with the common carbon atom that they are attached to, join to form a carbonyl group, a 3 to 6-membered spirocyclic cycloalkyl group or a 3 to 6-membered spirocyclic heterocycloalkyl group.

In one embodiment, for the Compounds of Formula (Ib), each occurrence of R^3 is C_1-C_6 alkyl.

In another embodiment, for the Compounds of Formula (Ib), one occurrence of R^3 is H.

In another embodiment, for the Compounds of Formula (Ib), one occurrence of R^3 is H and the other occurrence of R^3 is methyl, phenyl, 5 or 6-membered monocyclic heteroaryl or 9-membered bicyclic heteroaryl.

In still another embodiment, for the Compounds of Formula (Ib), one occurrence of R^3 is H and the other occurrence of R^3 is phenyl, methyl,



In one embodiment, for the Compounds of Formula (Ib), each occurrence of R^4 is $-C(O)CH(R^7)NHC(O)OR^{11}$.

In another embodiment, for the Compounds of Formula (Ib), each occurrence of R^4 is $-C(O)CH(R^7)NHC(O)OR^{11}$ and each occurrence of R^{11} is methyl.

In another embodiment, for the Compounds of Formula (Ib), each occurrence of R^4 is $-C(O)CH(R^7)NHC(O)OR^{11}$; each occurrence of R^7 is isopropyl, benzyl, cyclopropyl or tetrahyropyranyl; and each occurrence of R^{11} is methyl.

In still another embodiment, for the Compounds of Formula (Ib), each occurrence of R^4 is –C(O)CH(R^7)NHC(O)OR^{11}; each occurrence of R^7 is isopropyl or tetrahyropyranyl; and each occurrence of R^{11} is methyl.

In another embodiment, for the Compounds of Formula (Ib), each occurrence of R^4 is –C(O)CH(R^7)NHC(O)OR^{11}; each occurrence of R^7 is isopropyl; and each occurrence of R^{11} is methyl.

In yetanother embodiment, for the Compounds of Formula (Ib), each occurrence of R^4 is –C(O)CH(R^7)NHC(O)OR^{11}; each occurrence of R^7 is tetrahyropyranyl; and each occurrence of R^{11} is methyl.

In one embodiment, for the Compounds of Formula (Ib), each occurrence of R^{13a} is independently H, or F.

In another embodiment, for the Compounds of Formula (Ib), two R^{13a} groups that are attached to the same carbon atom, together with the common carbon atom to which they are attached, combine to form a spirocyclic 3 to 6 membered cycloalkyl group.

In another embodiment, for the Compounds of Formula (Ib), two R^{13a} groups that are attached to the same carbon atom, together with the common carbon atom to which they are attached, combine to form a spirocyclic cyclopropyl group.

In one embodiment, for the Compounds of Formula (Ib), each occurrence of R^{13b} is H.

In another embodiment, for the Compounds of Formula (Ib), one or both R^{13b} groups and an $R13^a$ group that are attached to same ring, together with the ring carbon atoms to which they are attached, can combine to form a fused 3 to 6 membered cycloalkyl group.

In another embodiment, for the Compounds of Formula (Ib), one or both R^{13b} groups and an $R13^a$ group that are attached to same ring, together with the ring carbon atoms to which they are attached, can combine to form a fused 3 to 6 membered cyclopropyl group.

In one embodiment, for the Compounds of Formula (Ib), each occurrence of R^{15} is independently selected from H and F.

In another embodiment, for the Compounds of Formula (Ib), each occurrence of R^{15} is H.

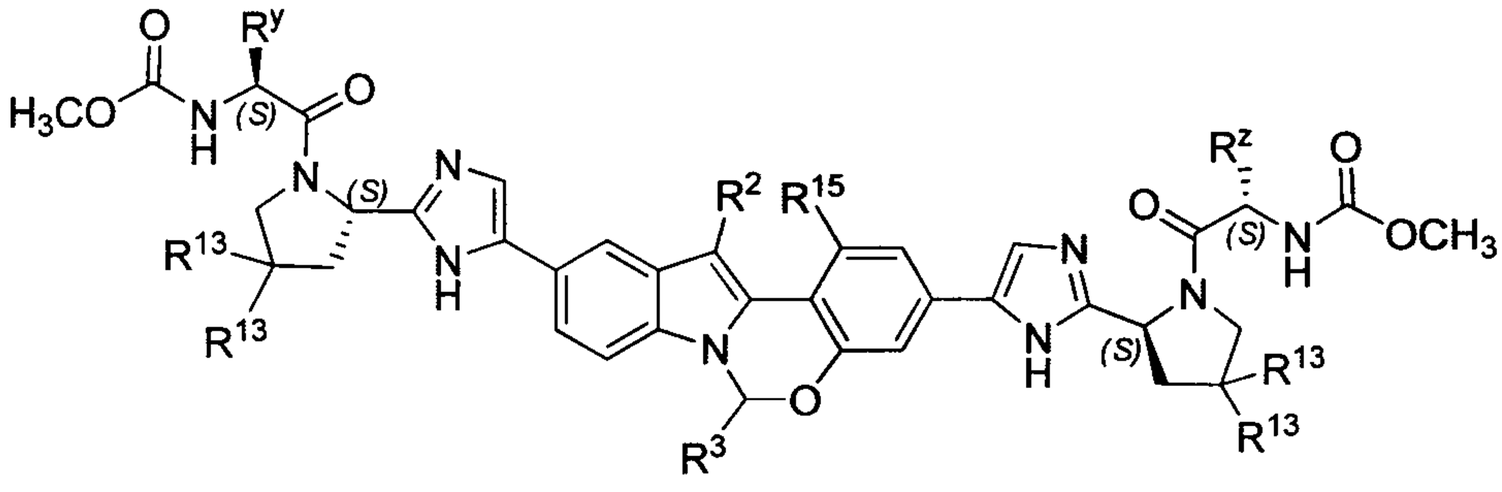
In one embodiment, for the Compounds of Formula (Ib), each occurrence of R^2, R^{13} and R^{15} is independently selected from H and F.

In another embodiment, for the Compounds of Formula (Ib), each occurrence of R^2, R^{13} and R^{15} is independently selected from H and F and one occurrence of R^3 is H.

In one embodiment, variables R^2, R^3, R^{13} and R^{15} for the Compounds of Formula (Ib) are selected independently of each other.

In another embodiment, the Compounds of Formula (Ib) are in substantially purified form.

In one embodiment, the Compounds of Formula (I) have the formula (Ic):



(Ic)

and pharmaceutically acceptable salts thereof, wherein:

R^y is isopropyl or tetrahydropyranyl;

R^z is isopropyl or tetrahydropyranyl;

R^2 is H or halo;

R^3 is selected from 3 to 6-membered cycloalkyl or phenyl, wherein said phenyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-C_1-C_6 haloalkyland

each occurrence of R^{13} is independently selected from H and halo; and

each occurrence of R^{15} is independently selected from H and halo.

In one embodiment, for the compounds of formula (Ic), R^3 is phenyl, wherein said phenyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from F, Cl, -CN, CH_3, CF_3, OCF_3, $OCH_2CH_2OCH_3$.

In another embodiment, for the compounds of formula (Ic), R^3 is cyclopropyl.

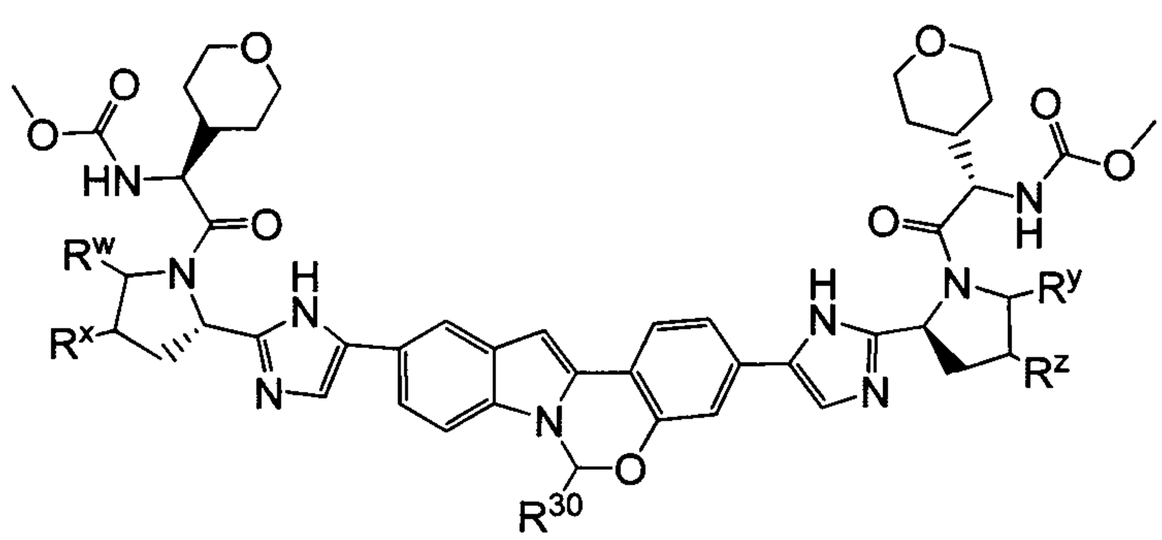
In another embodiment, for the compounds of formula (Ic), R^2 and R^{15} are each independently H or F.

In another embodiment, for the compounds of formula (Ic), each occurrence of R^{13} is independently H or F;

In one embodiment, for the compounds of formula (Ic), R^3 is phenyl; each occurrence of R^{13} is independently H or F; and R^2 and R^{15} are each independently H or F, wherein said phenyl group can be optionally substituted with up to 2 groups, which can be the same or different, and are selected from F, Cl, -CN, CH_3, CF_3, OCF_3, $OCH_2CH_2OCH_3$.

In another embodiment, for the compounds of formula (Ic), R^3 is cyclopropyl; each occurrence of R^{13} is independently H or F; and R^2 and R^{15} are each independently H or F.

In one embodiment, the Compounds of Formula (I) have the formula (Id):



(Id)

or a pharmaceutically acceptable salt thereof,

wherein:

R^{30} is C_1-C_6 alkyl, aryl, 5 or 6-membered monocyclic heteroaryl or 9-membered bicyclic heteroaryl;

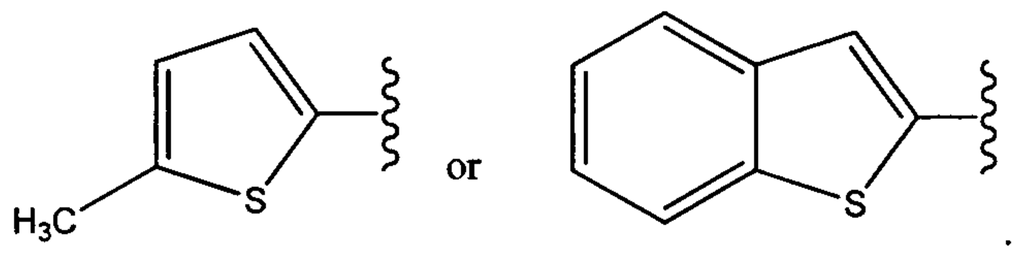
R^w is H, or R^w and R^x, together with the ring carbon atoms to which they are attached, combine to form a fused 3 to 6-membered cycloalkyl group;

R^x is H or F, or R^w and R^x, together with the ring carbon atoms to which they are attached, combine to form a fused 3 to 6-membered cycloalkyl group;

R^y is H, or R^y and R^z, together with the ring carbon atoms to which they are attached, combine to form a fused 3 to 6-membered cycloalkyl group; and

R^z is H or F, or R^y and R^z, together with the ring carbon atoms to which they are attached, combine to form a fused 3 to 6-membered cycloalkyl group.

In one embodiment, for the compounds of formula (Id), R^{30} is phenyl, methyl,



In another embodiment, for the compounds of formula (Id), R^w and R^x, together with the ring carbon atoms to which they are attached, combine to form a fused cyclopropyl group.

In another embodiment, for the compounds of formula (Id), R^y and R^z, together with the ring carbon atoms to which they are attached, combine to form a fused cyclopropyl group.

In still another embodiment, for the compounds of formula (Id), R^y and R^z, together with the ring carbon atoms to which they are attached, combine to form a fused cyclopropyl group and R^w and R^x, together with the ring carbon atoms to which they are attached, combine to form a fused cyclopropyl group.

In another embodiment, for the compounds of formula (Id), R^w, R^x, and R^y are each H and R^z is F.

In another embodiment, for the compounds of formula (Id), R^w and R^x, together with the ring carbon atoms to which they are attached, combine to form a fused cyclopropyl group; R^y is H and R^z is F.

In one embodiment, for the compounds of formula (Id), variables R^{30}, R^w, R^x, R^y, and R^z are selected independently of each other.

In another embodiment, the Compounds of Formula (Ic) are in substantially purified form.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a Compound of Formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(c) The pharmaceutical composition of (b), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(d) A pharmaceutical combination that is (i) a Compound of Formula (I) and (ii) a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents; wherein the Compound of Formula (I) and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HCV replication, or for treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection.

(e) The combination of (d), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(f) A method of inhibiting HCV replication in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula (I).

(g) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof which comprises administering to the subject an effective amount of a Compound of Formula (I).

(h) The method of (g), wherein the Compound of Formula (I) is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(i) The method of (h), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(j) A method of inhibiting HCV replication in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b) or (c) or the combination of (d) or (e).

(k) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b) or (c) or the combination of (d) or (e).

The present invention also includes a compound of the present invention for use (i) in, (ii) as a medicament for, or (iii) in the preparation of a medicament for: (a) medicine; (b) inhibiting HCV replication or (c) treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection. In these uses, the compounds of the present invention can optionally be employed in combination with one or more second therapeutic agents selected from HCV antiviral agents, anti-infective agents, and immunomodulators.

The present invention also includes the use of a compound of the present invention for (i) inhibiting HCV replication or (ii) treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(k) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt or hydrate as appropriate.

It is further to be understood that the embodiments of compositions and methods provided as (a) through (k) above are understood to include all embodiments of the compounds, including such embodiments as result from combinations of embodiments.

The Compounds of Formula (I) may be referred to herein by chemical structure and/or by chemical name. In the instance that both the structure and the name of a Compound of Formula (I) are provided and a discrepancy is found to exist between the chemical structure and the corresponding chemical name, it is understood that the chemical structure will predominate.

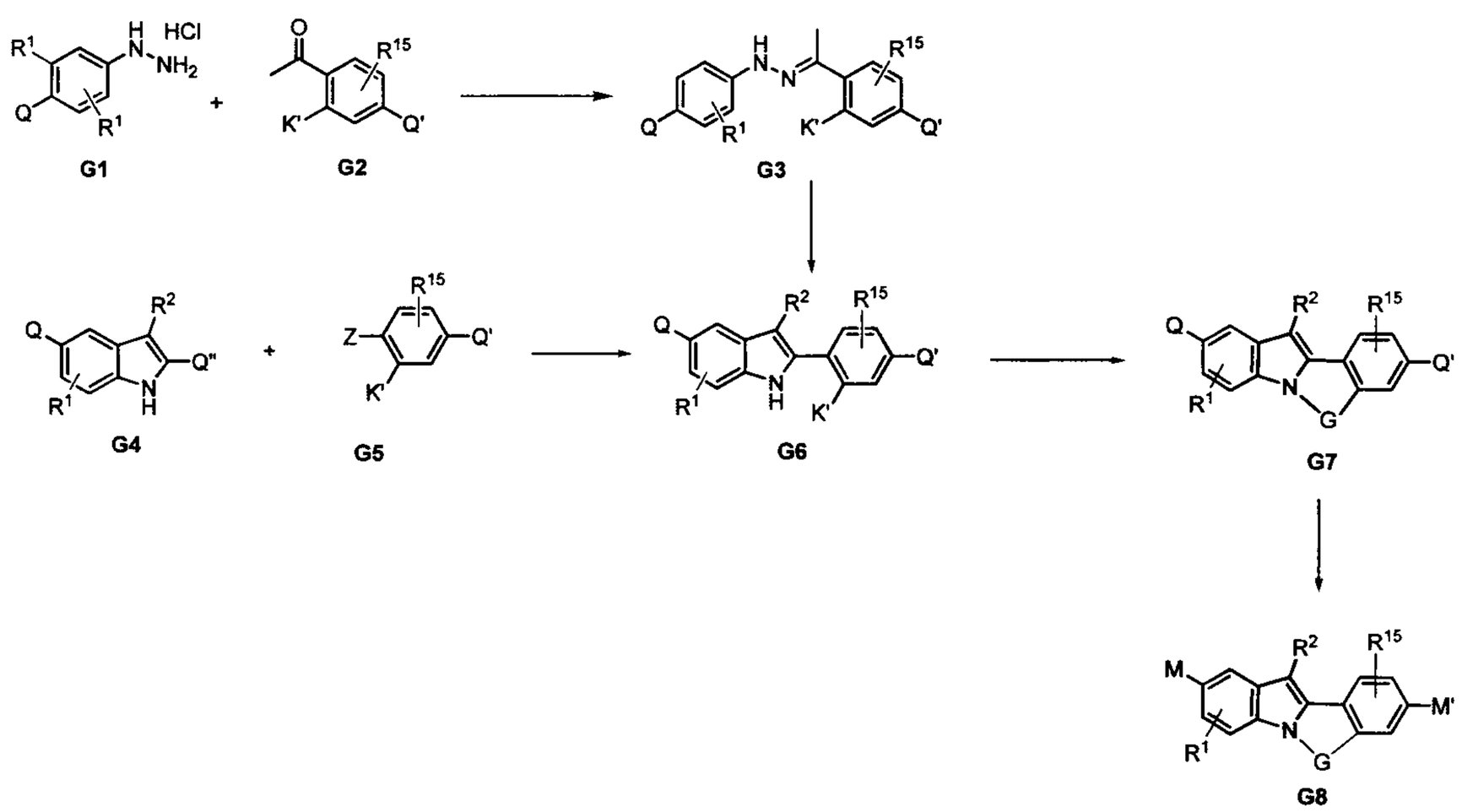
Non-limiting examples of the Compounds of Formula (I) include (i) compounds **1-1542**, as set forth in Tables 1 and 2 in the Examples Section below.

Methods For Making the Compounds of Formula (I)

The Compounds of Formula (I) may be prepared from known or readily prepared starting materials, following methods known to one skilled in the art of organic synthesis. Methods useful for making the Compounds of Formula (I) are set forth in the Examples below and generalized in Schemes 1-5 below. Alternative synthetic pathways and analogous structures will be apparent to those skilled in the art of organic synthesis.

Scheme 1 shows methods useful for making the Compounds of formula **G8**, which correspond to the Compounds of Formula (I), wherein B is phenyl and the group –U-V-W- is $–C(R^2)=CH-N-$.

Scheme 1



Wherein Q and Q' are each independently halo, hydroxy, or a protected hydroxy such as methoxy or benzyloxy; M, M', M" are each independently halo, hydroxy, or a protected hydroxy, triflate, boronic acid or boronic ester; K represents a group that can form a bond to the indole nitrogen. One skilled in the art of organic synthesis will recognize that when G is single or multiatom bridge, K should contain all the atoms of the bridge and a reactive group capable of forming a bond to nitrogen of the indole. Examples of reactive groups capable of forming a bond to nitrogen are

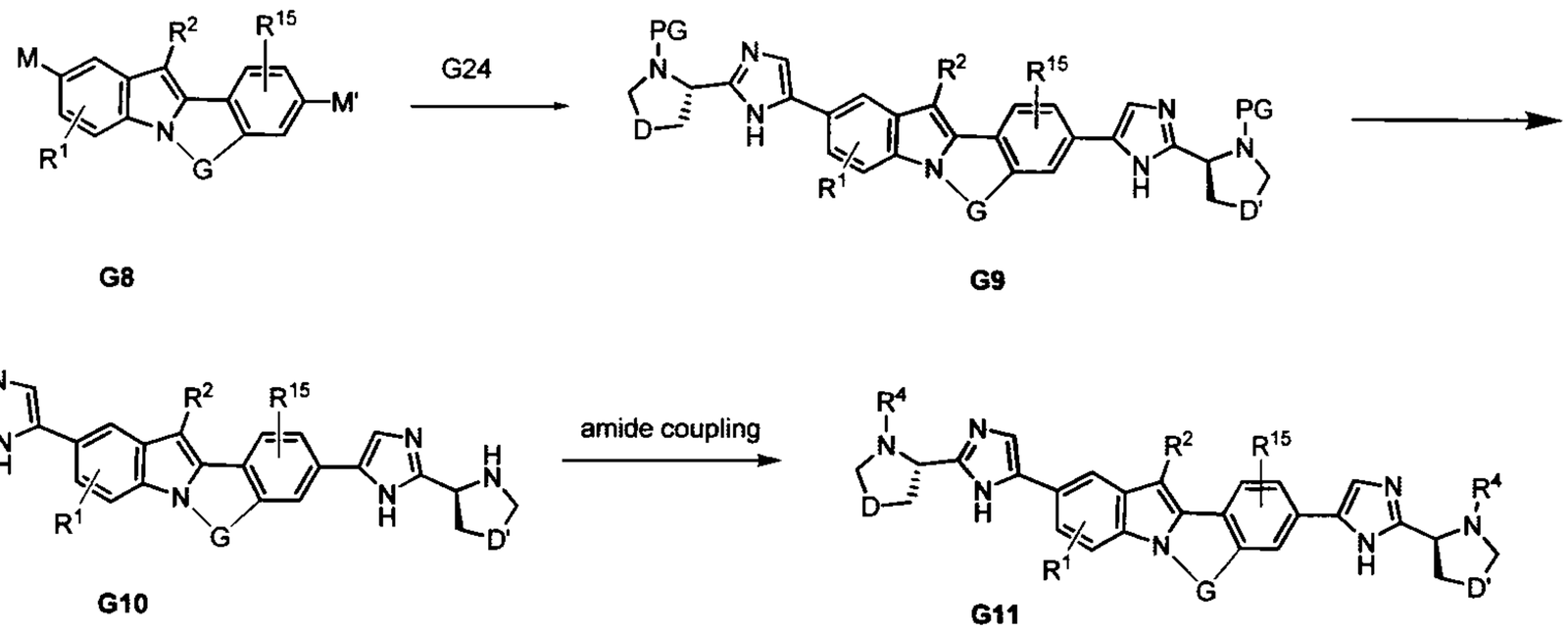
well known to one skilled in the art of organic synthesis and non-limiting examples include an alkyl halide, vinyl halide, aldehyde group or a vicinal dihalide. Z represents an appropriate aryl coupling partner which will be well known to one skilled in the art of organic chemistry. An example of aryl coupling partners include but are not limited to halide and triflate when the other partner is an arylboron or arylstannane derivative.

Tetracyclic Compounds of formula **G8** can be prepared from suitably substituted indole derivatives of formula **G6**. An indole derivative of formula **G6** is cyclized to provide tetracyclic Compounds of formula G7. Indole derivatives of formula **G6** may be obtained commercially or prepared by using methods known to those skilled in the art of organic synthesis. In an illustrative example, the Compounds of formula **G6** can be made via dehydration of a hydrazide of formula **G1** with a ketone of formula **G2** to provide hydrazones of formula **G3**, which can then be cyclized in the presence of a strong acid such as PPA or a Lewis acid such as aluminum chloride, to provide the hydroxyl-substituted indole Compounds of formula **G4**. A Compound of formula **G4** can then be reacted with an aldehyde of formula R^3-CHO to provide the cyclized Compounds of formula **G8**, wherein G is $-CHR^3-O-$.

Compounds of formula **G7** can be made, for example, via the arylation of the 2-position of an indole of formula **G5** with a coupling partner of formula **G6**. A Compound of formula **G7** can then be cyclized by reacting Y and K' to provide the Compounds of formula **G8**. It will be obvious to one skilled in the art of organic synthesis that the Compounds of formulas **G4** and **G7** may undergo further functional group manipulations prior to cyclization as necessary in order to provide the scope of the Compounds of Formula (I).

Scheme 2 shows a method useful for making the Compounds of formula **G12**, which correspond to the Compounds of Formula (I), wherein B is phenyl; X and X' are each CH; Y and Y' are each N; and the group –U-V-W- is $-C(R^2)=CH-N-$.

Scheme 2

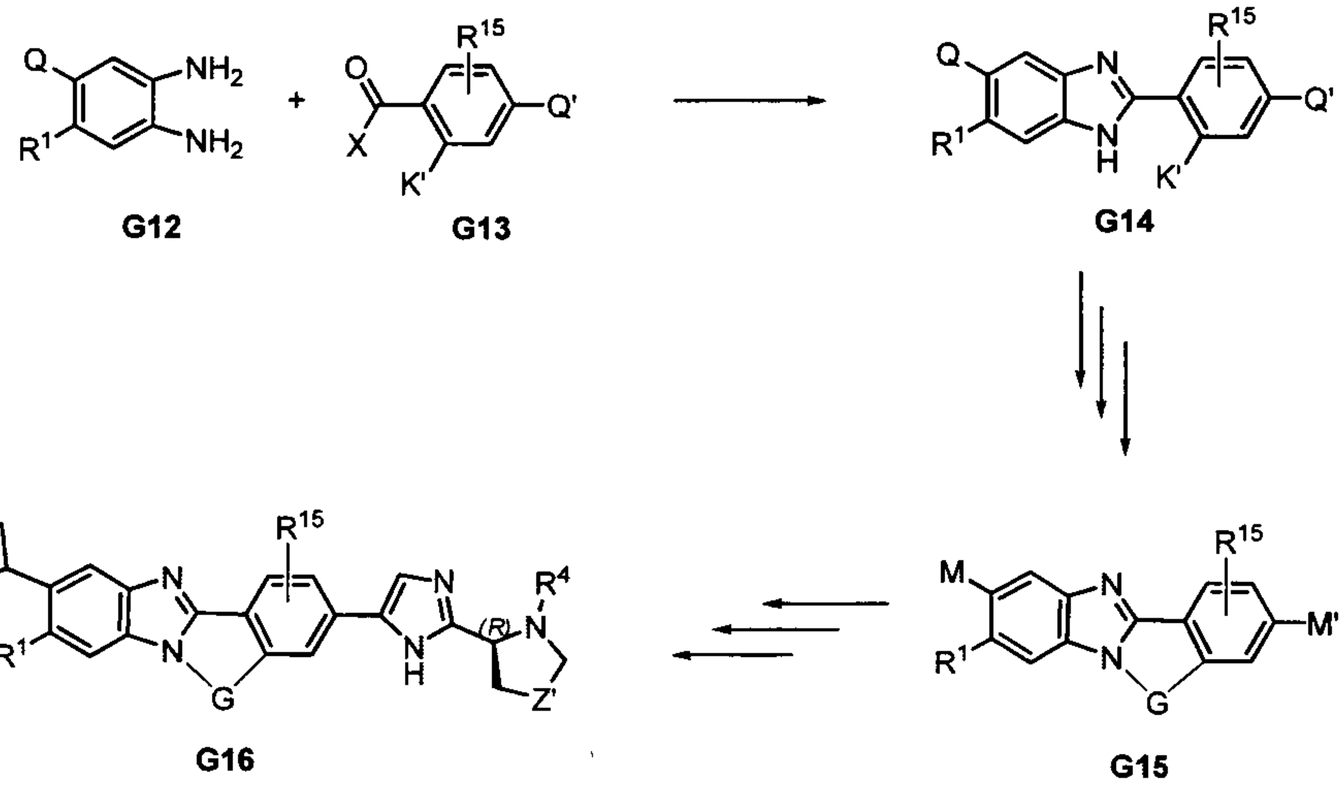


G8 G9 G10 G11

Wherein D and D' are each independently $C(R^{13})_2$, $N(R^4)$, S, O or $Si(R^{16})_2$; M and M' are each independently halo, triflate, boronic acid or boronic ester; PG is a protecting group, such as Boc or 4-methoxybenzyl; R^4 is $-C(O)R^{11}$, $-C(O)-[C(R^7)_2]_qN(R^6)_2$, $-C(O)-[C(R^7)_2]_q-R^{11}$, $-C(O)-[C(R^7)_2]_qN(R^6)C(O)-R^{11}$, $-C(O)[C(R^7)_2]_qN(R^6)SO_2-R^{11}$, $-C(O)-[C(R^7)_2]_qN(R^6)C(O)O-R^{11}$ or $-C(O)-[C(R^7)_2]_qC(O)O-R^{11}$; and G, R^1, R^2 and R^{15} are defined above for the Compounds of Formula (I).

Scheme 3 shows a method useful for making the Compounds of formula **G16**, which correspond to the Compounds of Formula (I), wherein B is phenyl; X and X' are each CH; Y and Y' are each N; and the group –U-V-W- is -N=CH-N-.

Scheme 3



G12 G13 G14 G16 G15

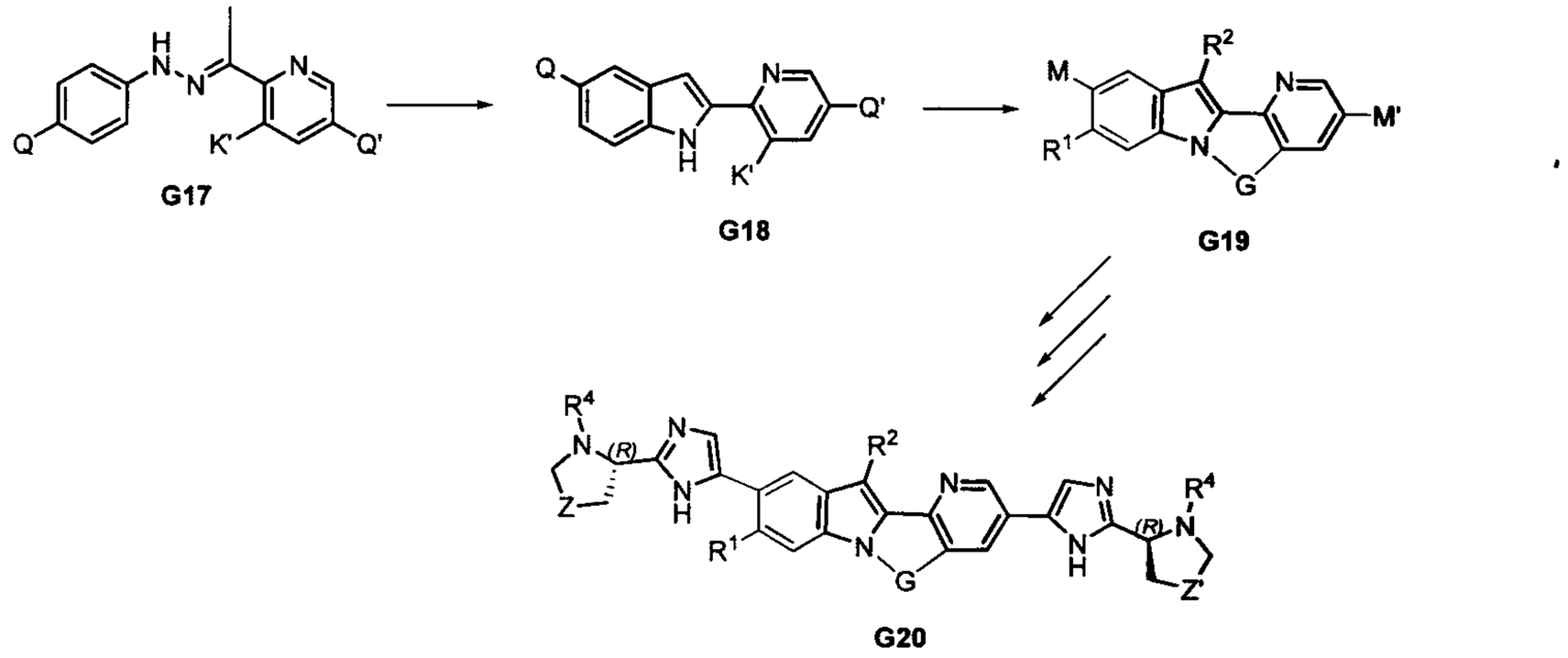
Wherein Z and Z' are each independently $C(R^{13})_2$, $N(R^4)$, S, O or $Si(R^{16})_2$; M and M' are each independently halo, triflate, boronic acid or boronic ester; X is halo; R^4 is $-C(O)R^{11}$, $-C(O)-[C(R^7)_2]_qN(R^6)_2$, $-C(O)-[C(R^7)_2]_q-R^{11}$, $-C(O)-$

$[C(R^7)_2]_qN(R^6)C(O)$-R^{11}, -$C(O)[C(R^7)_2]_qN(R^6)SO_2$-$R^{11}$, -C(O)-$[C(R^7)_2]_qN(R^6)C(O)O$-$R^{11}$ or -C(O)-$[C(R^7)_2]_qC(O)O$-R^{11}; K, Q and Q' are defined above in connection with Scheme 1; and G, R^2 and R^{15} are defined above for the Compounds of Formula (I).

A 2-amino aniline derivative of formula **G12** can be reacted with an acyl halide of formula **G13** to provide the 2-substituted benzimidazole Compounds of formula **G14**. The Compounds of formula **G14**.can be cyclized and derivatized to provide Compounds of formula **G15**, using at methods analogous to those described in Scheme 1 for the conversion of **G6** to **G8**. A Compound of formula **G15** can then be carried forth to the Compounds of formula **G16** using methods analogous to those described in Scheme 2.

Scheme 4 shows a method useful for making the Compounds of formula **G20**, which correspond to the Compounds of Formula (I), wherein B is pyridyl; X and X' are each CH; Y and Y' are each N; and the group –U-V-W- is –$C(R^2)$=CH-N-.

Scheme 4



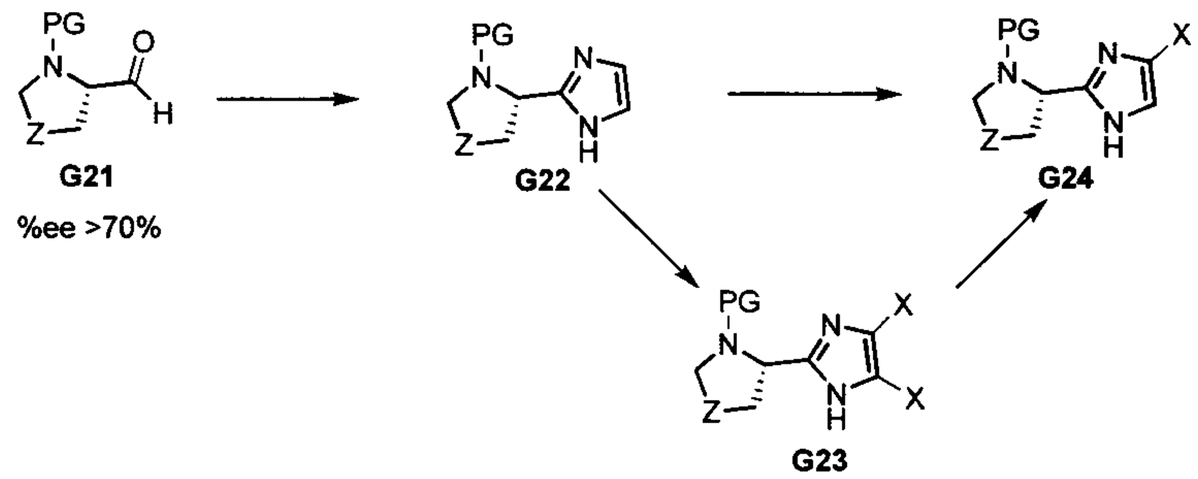
Wherein Z and Z' are each independently $C(R^{13})_2$, $N(R^4)$, S, O or $Si(R^{16})_2$; M and M' are each independently halo, triflate, boronic acid or boronic ester; R^4 is -$C(O)R^{11}$, -C(O)-$[C(R^7)_2]_qN(R^6)_2$, -C(O)-$[C(R^7)_2]_q$-R^{11}, -C(O)-$[C(R^7)_2]_qN(R^6)C(O)$-R^{11}, -$C(O)[C(R^7)_2]_qN(R^6)SO_2$-$R^{11}$, -C(O)-$[C(R^7)_2]_qN(R^6)C(O)O$-$R^{11}$ or -C(O)-$[C(R^7)_2]_qC(O)O$-R^{11}; and G, R^1 and R^2 are defined above for the Compounds of Formula (I).

A pyridyl hydrazone of formula **G17** can be converted to the tetracyclic Compounds of formula **G19** using methods analogous to those described in Scheme 1 for the conversion of **G3** to **G8**. A Compound of formula **G19** can then

be carried forth to the Compounds of **G20** using methods analogous to those described in Scheme 2.

Scheme 5 shows methods useful for making the Compounds of formula **G24**, which are useful intermediates for making the Compounds of Formula (I) wherein X and X' are each CH and Y and Y' are each N.

Scheme 5



Wherein Z or Z' is $C(R^{13})_2$, $N(R^4)$, S, O or $Si(R^{16})_2$; X is halo or triflate; and PG is a amino protecting group, such as Boc or 4-methoxybenzyl..

An appropriately functionalized aldehyde of formula **G21** can be reacted with glyoxal and ammonia to provide a substituted imidazole of formula **G22**. A Compound of formula **G22** can subsequently be selectively mono-halogenated to provide a mono-halogenated imidazole Compound of formula **G24**. Alternatively, a Compound of formula **G24** can subsequently be di-halogenated to provide a Compound of formula **G23**, which is then selectively reduced to provide a mono-halogenated imidazole Compound of formula **G24**.

In some of the Compounds of Formula (I) contemplated in Schemes 1-5, amino acids (such as, but not limited to proline, 4-(R)-fluoroproline, 4-(S)-fluoroproline, 4,4-difluoroproline, 4,4-dimethylsilylproline, aza-bicyclo[2.2.1]heptane carboxylic acid, aza-bicyclo[2.2.2]octane carboxylic acid, (S)-2-piperidine carboxylic acid, valine, alanine, norvaline, etc.) are incorporated as part of the structures. Methods have been described in the organic chemistry literature as well as in Banchard US 2009/0068140 (Published March 9th 2009) for the preparation of such amino acid-derived intermediates.

One skilled in the art of organic synthesis will recognize that the synthesis of fused tetracyclic cores contained in Compounds of Formula (I) may require protection of certain functional groups (*i.e.*, derivatization for the purpose of

chemical compatibility with a particular reaction condition). Suitable protecting groups for the various functional groups of these Compounds and methods for their installation and removal are well known in the art of organic chemistry. A summary of many of these methods can be found in Greene *et al.*, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, (1999).

One skilled in the art of organic synthesis will also recognize that one route for the synthesis of the fused tetracyclic cores of the Compounds of Formula (I) may be more desirable depending on the choice of appendage substituents. Additionally, one skilled in the art will recognize that in some cases the order of reactions may differ from that presented herein to avoid functional group incompatibilities and thus adjust the synthetic route accordingly.

One skilled in the art of organic synthesis will recognize that the synthesis of certain fused tetracyclic cores of the Compounds of Formula (I) require the construction of an amide bond. Methods useful for making such amide bonds, include but are not limited to, the use of a reactive carboxy derivative (*e.g.*, an acid halide, or ester at elevated temperatures) or the use of an acid with a coupling reagent (*e.g.*, HOBt, EDCI, DCC, HATU, PyBrop) with an amine.

The preparation of multicyclic intermediates useful for making the fused tetracyclic ring systems of the Compounds of Formula (I) have been described in the literature and in compendia such as "Comprehensive Heterocyclic Chemistry" editions I, II and III, published by Elsevier and edited by A.R. Katritzky & R. JK Taylor. Manipulation of the required substitution patterns have also been described in the available chemical literature as summarized in compendia such as "Comprehensive Organic Chemistry" published by Elsevier and edited by DH R. Barton and W. D. Ollis; "Comprehensive Organic Functional Group Transformations" edited by edited by A.R. Katritzky & R. JK Taylor and "Comprehensive Organic Transformation" published by Wily-CVH and edited by R. C. Larock.

The Compounds Formula (I) may contain one or more silicon atoms. The Compounds contemplated in this invention in general can be prepared using the carba-analog methodology unless otherwise noted. A recent review of the synthesis of silicon containing Compounds can be found in “Silicon Chemistry: from Atom to Extended Systems”, Ed P. Jutzi & U. Schubet; ISBN 978-3-527-30647-3. Preparation of silyl containing amino acids has been described. See Bolm *et al.*, *Angew. Chem. Int Ed.*, 39:2289 (2000). Descriptions of improved cellular update

(Giralt, J. Am. Chem. Soc., 128:8479 (2006)) and reduced metabolic processing of silyl containing Compounds have been described (Johansson *et al.*, *Drug Metabolism & Disposition*, 38:73 (2009)).

The starting materials used and the intermediates prepared using the methods set forth in Schemes 1-5 may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and alike. Such materials can be characterized using conventional means, including physical constants and spectral data.

Uses of the Tetracyclic Indole Derivatives

The Tetracyclic Indole Derivatives are useful in human and veterinary medicine for treating or preventing a viral infection in a patient. In one embodiment, the Tetracyclic Indole Derivatives can be inhibitors of viral replication. In another embodiment, the Tetracyclic Indole Derivatives can be inhibitors of HCV replication. Accordingly, the Tetracyclic Indole Derivatives are useful for treating viral infections, such as HCV. In accordance with the invention, the Tetracyclic Indole Derivatives can be administered to a patient in need of treatment or prevention of a viral infection.

Accordingly, in one embodiment, the invention provides methods for treating a viral infection in a patient comprising administering to the patient an effective amount of at least one Tetracyclic Indole Derivative or a pharmaceutically acceptable salt thereof.

Treatment or Prevention of a Flaviviridae Virus

The Tetracyclic Indole Derivatives can be useful for treating or preventing a viral infection caused by the Flaviviridae family of viruses.

Examples of Flaviviridae infections that can be treated or prevented using the present methods include but are not limited to, dengue fever, Japanese encephalitis, Kyasanur Forest disease, Murray Valley encephalitis, St. Louis encephalitis, Tick-borne encephalitis, West Nile encephalitis, yellow fever and Hepatitis C Virus (HCV) infection.

In one embodiment, the Flaviviridae infection being treated is hepatitis C virus infection.

Treatment or Prevention of HCV Infection

The Tetracyclic Indole Derivatives are useful in the inhibition of HCV (e.g., HCV NS5A), the treatment of HCV infection and/or reduction of the likelihood or severity of symptoms of HCV infection and the inhibition of HCV viral replication and/or HCV viral production in a cell-based system. For example, the Tetracyclic Indole Derivatives are useful in treating infection by HCV after suspected past exposure to HCV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery or other medical procedures.

In one embodiment, the hepatitis C infection is acute hepatitis C. In another embodiment, the hepatitis C infection is chronic hepatitis C.

Accordingly, in one embodiment, the invention provides methods for treating HCV infection in a patient, the methods comprising administering to the patient an effective amount of at least one Tetracyclic Indole Derivative or a pharmaceutically acceptable salt thereof. In a specific embodiment, the amount administered is effective to treat or prevent infection by HCV in the patient. In another specific embodiment, the amount administered is effective to inhibit HCV viral replication and/or viral production in the patient.

The Tetracyclic Indole Derivatives are also useful in the preparation and execution of screening assays for antiviral compounds. For example the Tetracyclic Indole Derivatives are useful for identifying resistant HCV replicon cell lines harboring mutations within NS5A, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the Tetracyclic Indole Derivatives are useful in establishing or determining the binding site of other antivirals to the HCV replicase.

The compositions and combinations of the present invention can be useful for treating a patient suffering from infection related to any HCV genotype. HCV types and subtypes may differ in their antigenicity, level of viremia, severity of disease produced, and response to interferon therapy as described in Holland *et al.*, *Pathology*, 30(2):192-195 (1998). The nomenclature set forth in Simmonds *et al.*, *J Gen Virol*, 74(Pt11):2391-2399 (1993) is widely used and classifies isolates into six major genotypes, 1 through 6, with two or more related subtypes, *e.g.*, 1a and 1b. Additional genotypes 7-10 and 11 have been proposed, however the phylogenetic basis on which this classification is based has been questioned, and thus types 7, 8, 9 and 11 isolates have been reassigned as type 6, and type 10 isolates as type 3 (see

Lamballerie *et al., J Gen Virol*, 78(Pt1):45-51 (1997)). The major genotypes have been defined as having sequence similarities of between 55 and 72% (mean 64.5%), and subtypes within types as having 75%-86% similarity (mean 80%) when sequenced in the NS-5 region (see Simmonds *et al., J Gen Virol*, 75(Pt 5):1053-1061 (1994)).

Combination Therapy

In another embodiment, the present methods for treating or preventing HCV infection can further comprise the administration of one or more additional therapeutic agents which are not Tetracyclic Indole Derivatives.

In one embodiment, the additional therapeutic agent is an antiviral agent.

In another embodiment, the additional therapeutic agent is an immunomodulatory agent, such as an immunosuppressive agent.

Accordingly, in one embodiment, the present invention provides methods for treating a viral infection in a patient, the method comprising administering to the patient: (i) at least one Tetracyclic Indole Derivative, or a pharmaceutically acceptable salt thereof, and (ii) at least one additional therapeutic agent that is other than a Tetracyclic Indole Derivative, wherein the amounts administered are together effective to treat or prevent a viral infection.

When administering a combination therapy of the invention to a patient, therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or same amounts (same dosage amounts). Thus, for non-limiting illustration purposes, a Tetracyclic Indole Derivative and an additional therapeutic agent may be present in fixed amounts (dosage amounts) in a single dosage unit (*e.g.*, a capsule, a tablet and the like).

In one embodiment, the at least one Tetracyclic Indole Derivative is administered during a time when the additional therapeutic agent(s) exert their prophylactic or therapeutic effect, or *vice versa*.

In another embodiment, the at least one Tetracyclic Indole Derivative and the additional therapeutic agent(s) are administered in doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In another embodiment, the at least one Tetracyclic Indole Derivative and the additional therapeutic agent(s) are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In still another embodiment, the at least one Tetracyclic Indole Derivative and the additional therapeutic agent(s) act synergistically and are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In one embodiment, the at least one Tetracyclic Indole Derivative and the additional therapeutic agent(s) are present in the same composition. In one embodiment, this composition is suitable for oral administration. In another embodiment, this composition is suitable for intravenous administration. In another embodiment, this composition is suitable for subcutaneous administration. In still another embodiment, this composition is suitable for parenteral administration.

Viral infections and virus-related disorders that can be treated or prevented using the combination therapy methods of the present invention include, but are not limited to, those listed above.

In one embodiment, the viral infection is HCV infection.

The at least one Tetracyclic Indole Derivative and the additional therapeutic agent(s) can act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of therapy without reducing the efficacy of therapy.

In one embodiment, the administration of at least one Tetracyclic Indole Derivative and the additional therapeutic agent(s) may inhibit the resistance of a viral infection to these agents.

Non-limiting examples of additional therapeutic agents useful in the present compositions and methods include an interferon, an immunomodulator, a viral replication inhibitor, an antisense agent, a therapeutic vaccine, a viral polymerase inhibitor, a nucleoside inhibitor, a viral protease inhibitor, a viral helicase inhibitor, a

virion production inhibitor, a viral entry inhibitor, a viral assembly inhibitor, an antibody therapy (monoclonal or polyclonal), and any agent useful for treating an RNA-dependent polymerase-related disorder.

In one embodiment, the additional therapeutic agent is a viral protease inhibitor.

In another embodiment, the additional therapeutic agent is a viral replication inhibitor.

In another embodiment, the additional therapeutic agent is an HCV NS3 protease inhibitor.

In still another embodiment, the additional therapeutic agent is an HCV NS5B polymerase inhibitor.

In another embodiment, the additional therapeutic agent is a nucleoside inhibitor.

In another embodiment, the additional therapeutic agent is an interferon.

In yet another embodiment, the additional therapeutic agent is an HCV replicase inhibitor.

In another embodiment, the additional therapeutic agent is an antisense agent.

In another embodiment, the additional therapeutic agent is a therapeutic vaccine.

In a further embodiment, the additional therapeutic agent is a virion production inhibitor.

In another embodiment, the additional therapeutic agent is an antibody therapy.

In another embodiment, the additional therapeutic agent is an HCV NS2 inhibitor.

In still another embodiment, the additional therapeutic agent is an HCV NS4A inhibitor.

In another embodiment, the additional therapeutic agent is an HCV NS4B inhibitor.

In another embodiment, the additional therapeutic agent is an HCV NS5A inhibitor

In yet another embodiment, the additional therapeutic agent is an HCV NS3 helicase inhibitor.

In another embodiment, the additional therapeutic agent is an HCV IRES inhibitor.

In another embodiment, the additional therapeutic agent is an HCV p7 inhibitor.

In a further embodiment, the additional therapeutic agent is an HCV entry inhibitor.

In another embodiment, the additional therapeutic agent is an HCV assembly inhibitor.

In one embodiment, the additional therapeutic agents comprise a viral protease inhibitor and a viral polymerase inhibitor.

In still another embodiment, the additional therapeutic agents comprise a viral protease inhibitor and an immunomodulatory agent.

In yet another embodiment, the additional therapeutic agents comprise a polymerase inhibitor and an immunomodulatory agent.

In another embodiment, the additional therapeutic agents comprise a viral protease inhibitor and a nucleoside.

In another embodiment, the additional therapeutic agents comprise an immunomodulatory agent and a nucleoside.

In one embodiment, the additional therapeutic agents comprise an HCV protease inhibitor and an HCV polymerase inhibitor.

In another embodiment, the additional therapeutic agents comprise a nucleoside and an HCV NS5A inhibitor.

In another embodiment, the additional therapeutic agents comprise a viral protease inhibitor, an immunomodulatory agent and a nucleoside.

In a further embodiment, the additional therapeutic agents comprise a viral protease inhibitor, a viral polymerase inhibitor and an immunomodulatory agent.

In another embodiment, the additional therapeutic agent is ribavirin.

HCV polymerase inhibitors useful in the present compositions and methods include, but are not limited to, VP-19744 (Wyeth/ViroPharma), PSI-7851 (Pharmasset), RG7128 (Roche/Pharmasset), PSI-938 (Pharmasset), PSI-7977 (Pharmasset), PF-868554/filibuvir (Pfizer), VCH-759 (ViroChem Pharma), HCV-796 (Wyeth/ViroPharma), IDX-184 (Idenix), IDX-375 (Idenix), NM-283

(Idenix/Novartis), R-1626 (Roche), MK-0608 (Isis/Merck), INX-8014 (Inhibitex), INX-8018 (Inhibitex), INX-189 (Inhibitex), GS 9190 (Gilead), A-848837 (Abbott), ABT-333 (Abbott), ABT-072 (Abbott), A-837093 (Abbott), BI-207127 (Boehringer-Ingelheim), BILB-1941 (Boehringer-Ingelheim), MK-3281 (Merck), VCH222 (ViroChem), VCH916 (ViroChem), VCH716(ViroChem), GSK-71185 (Glaxo SmithKline), ANA598 (Anadys), GSK-625433 (Glaxo SmithKline), XTL-2125 (XTL Biopharmaceuticals), and those disclosed in Ni *et al.*, *Current Opinion in Drug Discovery and Development*, 7(4):446 (2004); Tan *et al.*, *Nature Reviews*, 1:867 (2002); and Beaulieu *et al.*, *Current Opinion in Investigational Drugs*, 5:838 (2004).

Other HCV polymerase inhibitors useful in the present compositions and methods include, but are not limited to, those disclosed in International Publication Nos. WO 08/082484, WO 08/082488, WO 08/083351, WO 08/136815, WO 09/032116, WO 09/032123, WO 09/032124 and WO 09/032125.

Interferons useful in the present compositions and methods include, but are not limited to, interferon alfa-2a, interferon alfa-2b, interferon alfacon-1 and PEG-interferon alpha conjugates. "PEG-interferon alpha conjugates" are interferon alpha molecules covalently attached to a PEG molecule. Illustrative PEG-interferon alpha conjugates include interferon alpha-2a (Roferon™, Hoffman La-Roche, Nutley, New Jersey) in the form of pegylated interferon alpha-2a (*e.g.*, as sold under the trade name Pegasys™), interferon alpha-2b (Intron™, from Schering-Plough Corporation) in the form of pegylated interferon alpha-2b (*e.g.*, as sold under the trade name PEG-Intron™ from Schering-Plough Corporation), interferon alpha-2b-XL (*e.g.*, as sold under the trade name PEG-Intron™), interferon alpha-2c (Berofor Alpha™, Boehringer Ingelheim, Ingelheim, Germany), PEG-interferon lambda (Bristol-Myers Squibb and ZymoGenetics), interferon alfa-2b alpha fusion polypeptides, interferon fused with the human blood protein albumin (Albuferon™, Human Genome Sciences), Omega Interferon (Intarcia), Locteron controlled release interferon (Biolex/OctoPlus), Biomed-510 (omega interferon), Peg-IL-29 (ZymoGenetics), Locteron CR (Octoplus), IFN-α-2b-XL (Flamel Technologies), and consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (Infergen™, Amgen, Thousand Oaks, California).

Antibody therapy agents useful in the present compositions and methods include, but are not limited to, antibodies specific to IL-10 (such as those disclosed in US Patent Publication No. US2005/0101770, humanized 12G8, a

humanized monoclonal antibody against human IL-10, plasmids containing the nucleic acids encoding the humanized 12G8 light and heavy chains were deposited with the American Type Culture Collection (ATCC) as deposit numbers PTA-5923 and PTA-5922, respectively), and the like).

Examples of viral protease inhbitors useful in the present compositions and methods include, but are not limited to, an HCV protease inhibitor.

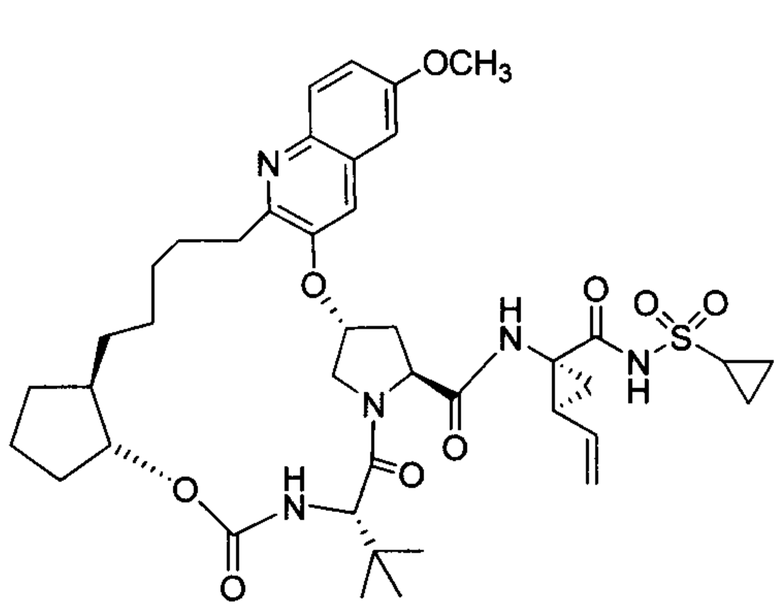
HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, those disclosed in U.S. Patent Nos. 7,494,988, 7,485,625, 7,449,447, 7,442,695, 7,425,576, 7,342,041, 7,253,160, 7,244,721, 7,205,330, 7,192,957, 7,186,747, 7,173,057, 7,169,760, 7,012,066, 6,914,122, 6,911,428, 6,894,072, 6,846,802, 6,838,475, 6,800,434, 6,767,991, 5,017,380, 4,933,443, 4,812,561 and 4,634,697; U.S. Patent Publication Nos. US20020068702, US20020160962, US20050119168, US20050176648, US20050209164, US20050249702 and US20070042968; and International Publication Nos. WO 03/006490, WO 03/087092, WO 04/092161 and WO 08/124148.

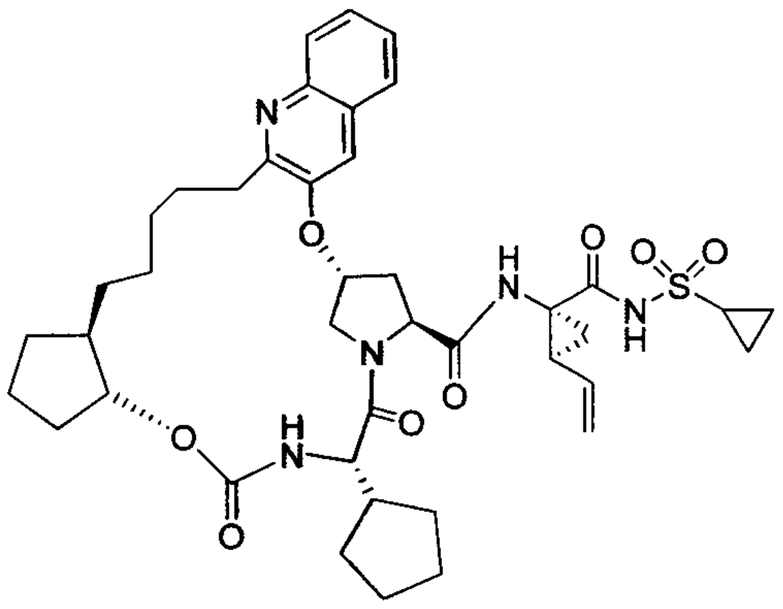
Additional HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, SCH503034 (Boceprevir, Schering-Plough), SCH900518 (Schering-Plough), VX-950 (Telaprevir, Vertex), VX-500 (Vertex), VX-813 (Vertex), VBY-376 (Virobay), MK-7009 (Merck), MK-5172 (Merck), BI-201335 (Boehringer Ingelheim), TMC-435 (Medivir/Tibotec), ABT-450 (Abbott), TMC-435350 (Medivir), ITMN-191/R7227 (InterMune/Roche), EA-058 (Abbott/Enanta), EA-063 (Abbott/Enanta), GS-9132 (Gilead/Achillion), ACH-1095 (Gilead/Achillon), IDX-136 (Idenix), IDX-316 (Idenix), ITMN-8356 (InterMune), ITMN-8347 (InterMune), ITMN-8096 (InterMune), ITMN-7587 (InterMune), BMS-650032 (Bristol-Myers Squibb), VX-985 (Vertex) and PHX1766 (Phenomix).

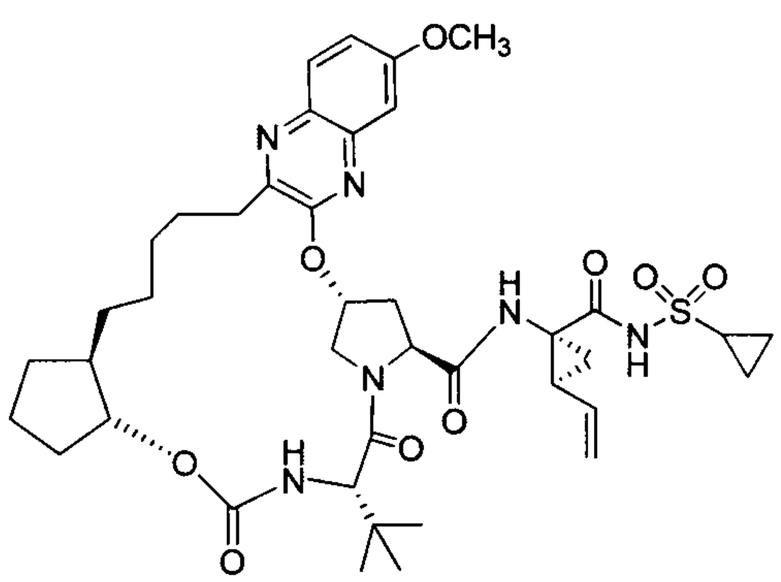
Further examples of HCV protease inhbitors useful in the present compositions and methods include, but are not limited to, those disclosed in Landro *et al.*, *Biochemistry*, 36(31):9340-9348 (1997); Ingallinella *et al.*, *Biochemistry*, 37(25):8906-8914 (1998); Llinàs-Brunet *et al.*, *Bioorg Med Chem Lett*, 8(13):1713-1718 (1998); Martin *et al.*, *Biochemistry*, 37(33):11459-11468 (1998); Dimasi *et al.*, *J Virol*, 71(10):7461-7469 (1997); Martin *et al.*, *Protein Eng*, 10(5):607-614 (1997); Elzouki *et al.*, *J Hepat*, 27(1):42-48 (1997); *BioWorld Today*, 9(217):4 (November 10, 1998); U.S. Patent Publication Nos. US2005/0249702 and US 2007/0274951; and

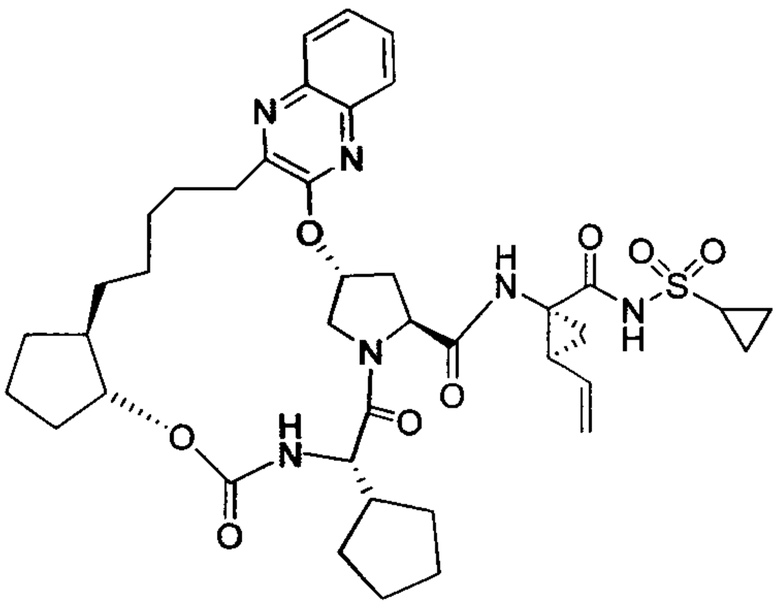
International Publication Nos. WO 98/14181, WO 98/17679, WO 98/17679, WO 98/22496 and WO 99/07734 and WO 05/087731.

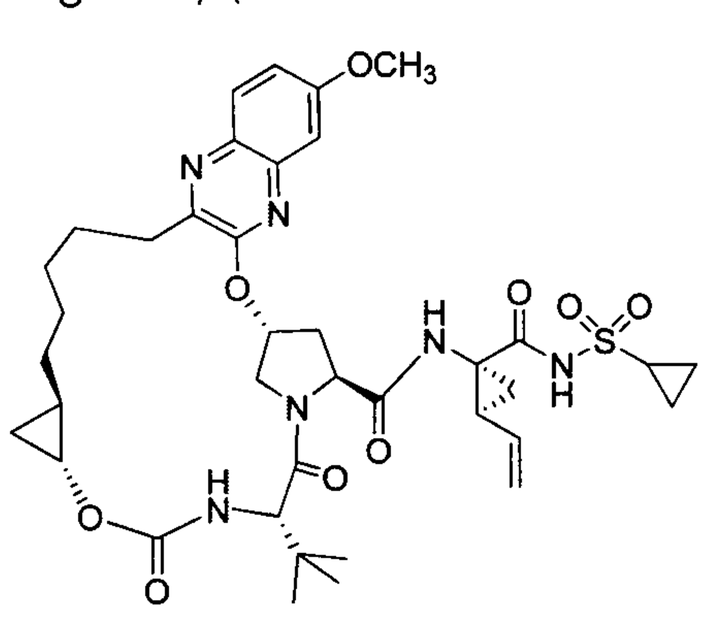
Further examples of HCV protease inhibitors useful in the present compositions and methods include, but are not limited to, the following compounds:

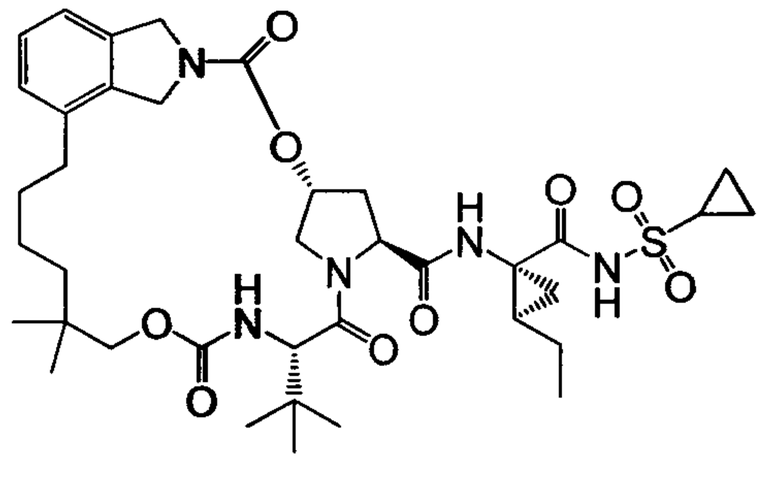


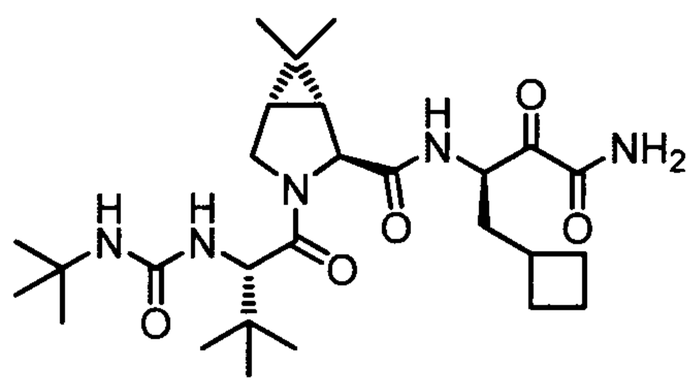


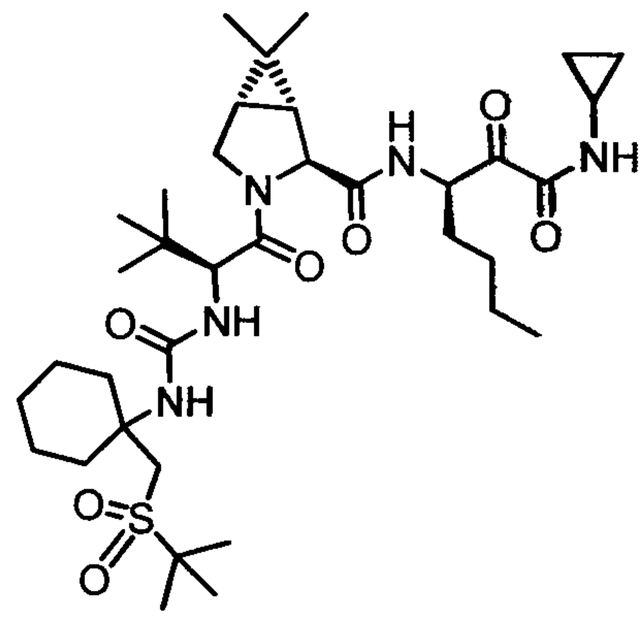


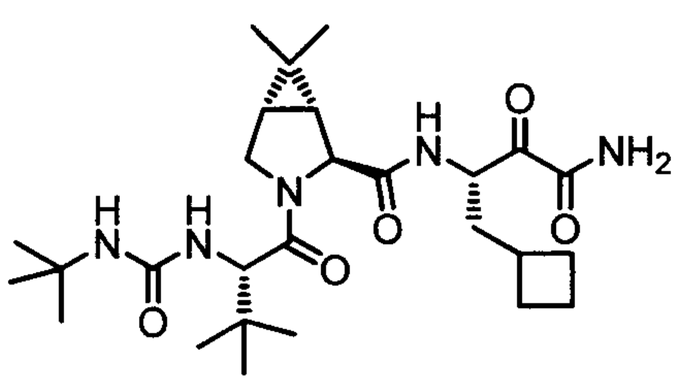


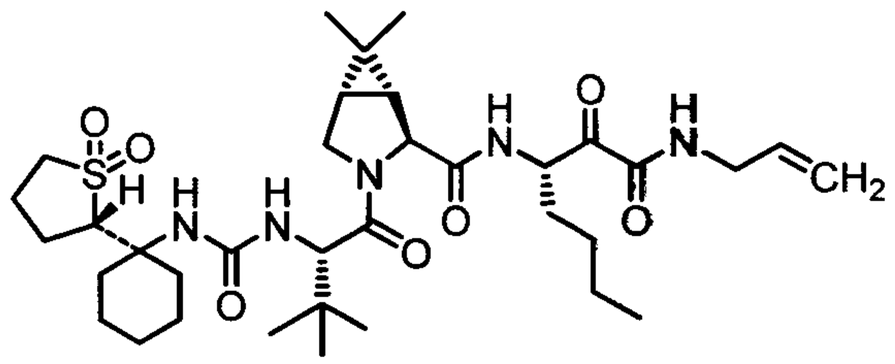


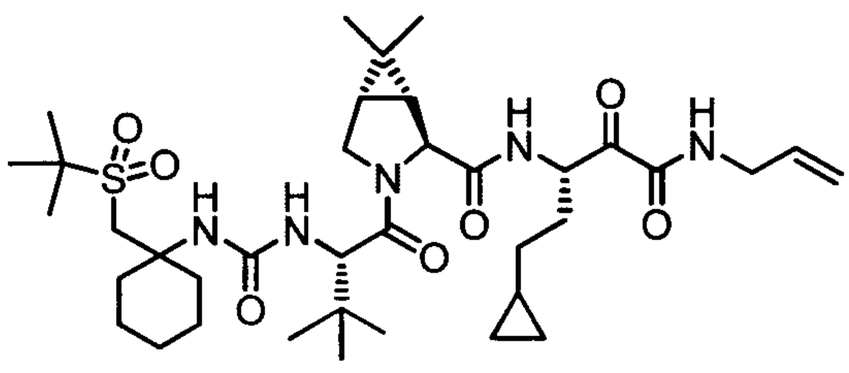


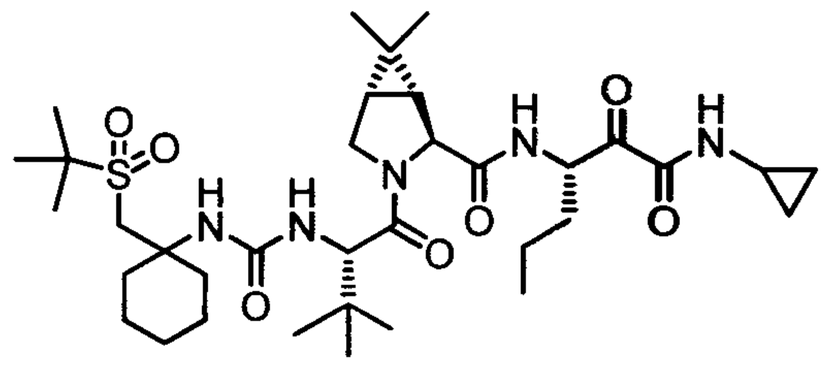


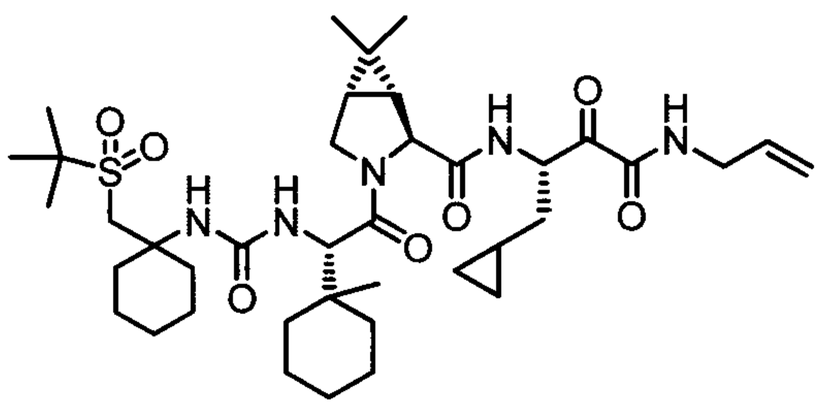


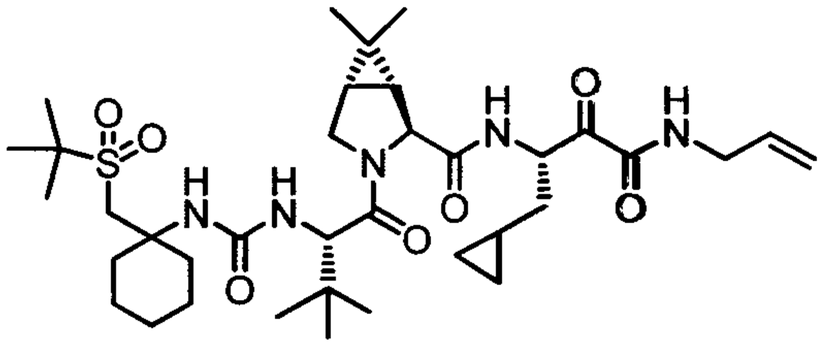


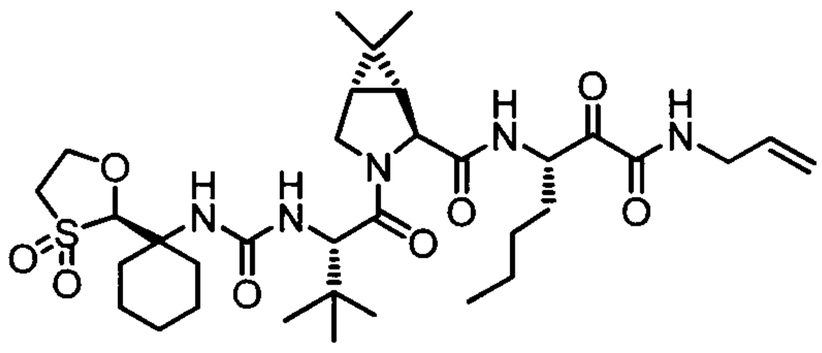


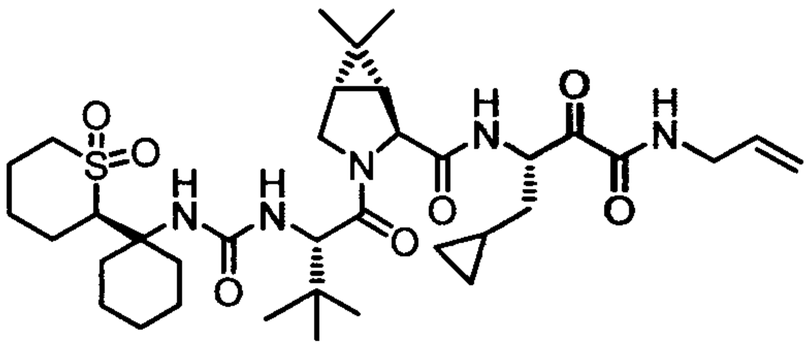


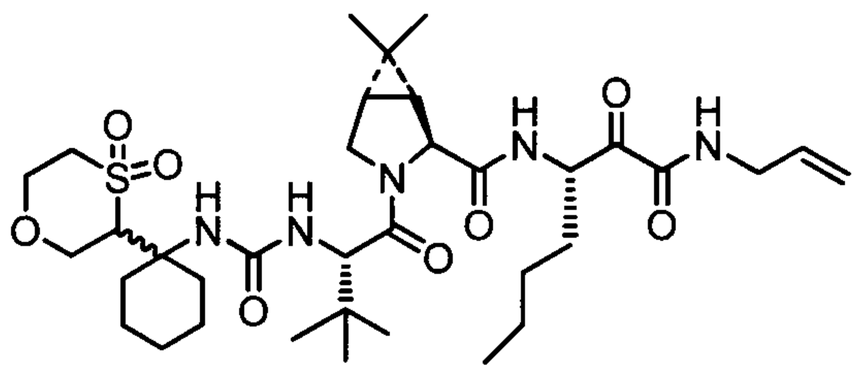


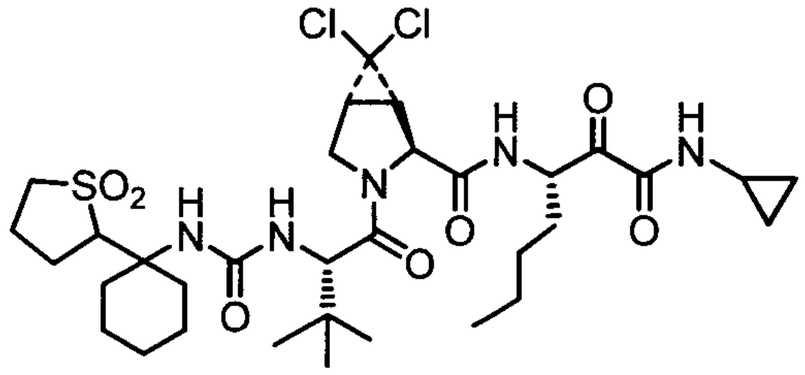


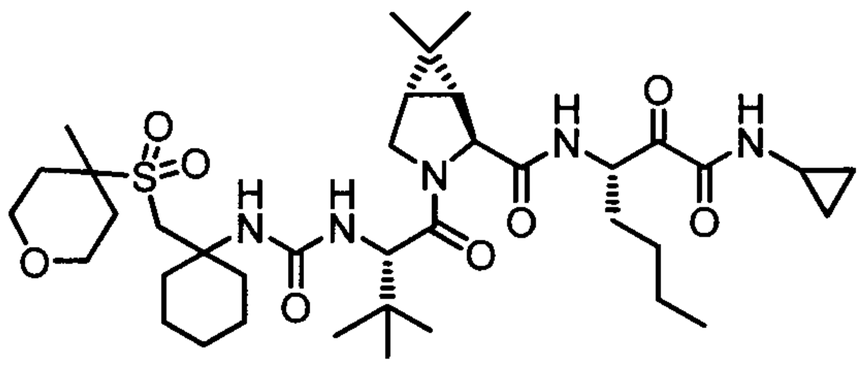


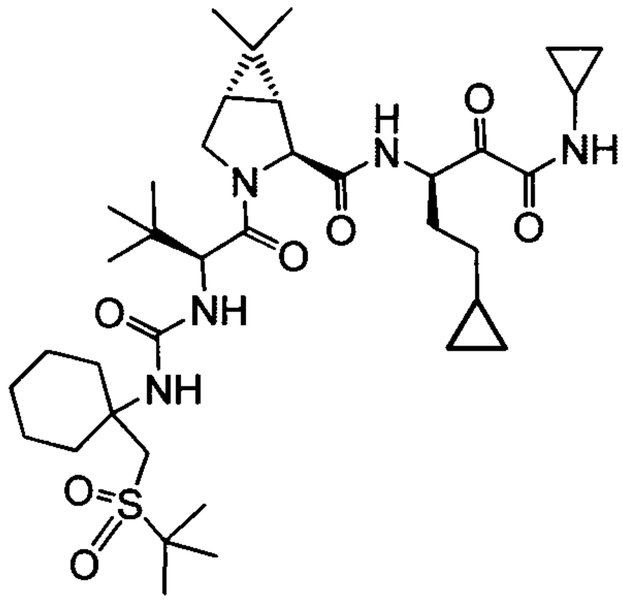


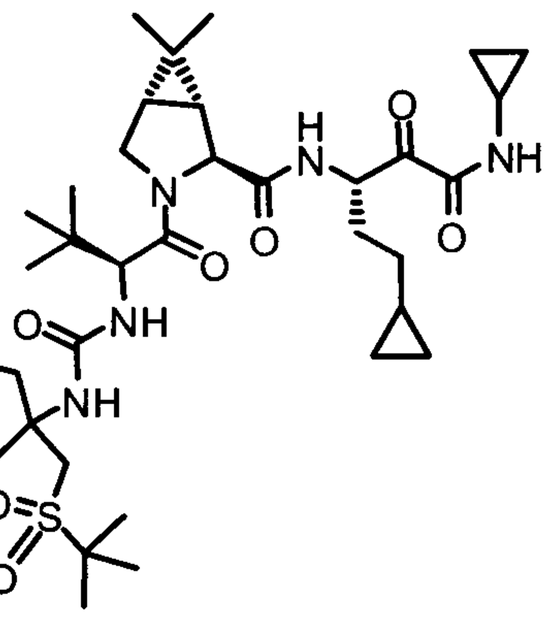


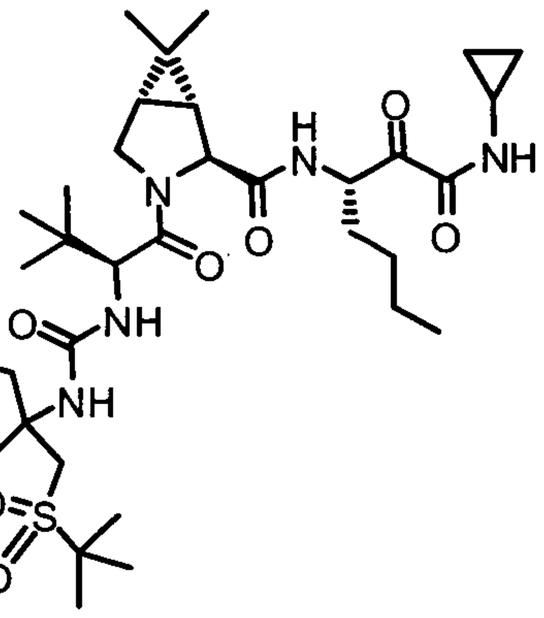


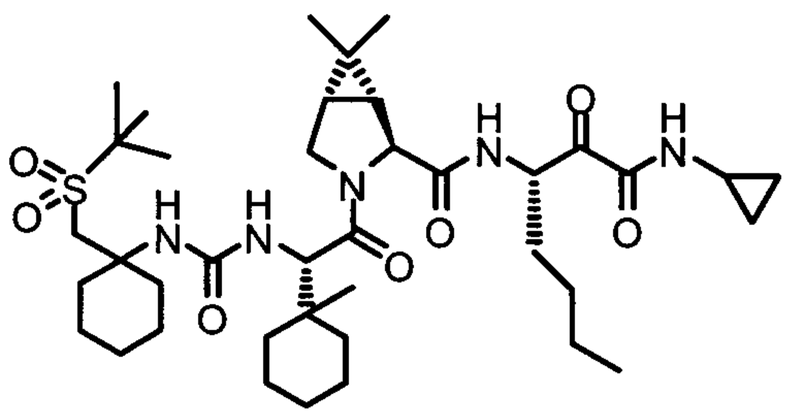




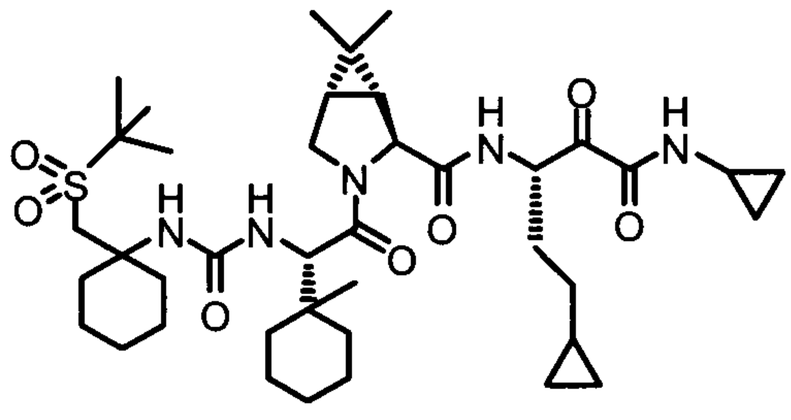








and



Viral replication inhibitors useful in the present compositions and methods include, but are not limited to, HCV replicase inhibitors, IRES inhibitors, NS4A inhibitors, NS3 helicase inhibitors, NS5A inhibitors, NS5B inhibitors, ribavirin, AZD-2836 (Astra Zeneca), BMS-790052 (Bristol-Myers Squibb, see Gao *et al.*, *Nature*, 465:96-100 (2010)), viramidine, A-831 (Arrow Therapeutics); an antisense agent or a therapeutic vaccine.

HCV NS4A inhibitors useful in the useful in the present compositions and methods include, but are not limited to, those disclosed in U.S. Patent Nos. 7,476,686 and 7,273,885; U.S. Patent Publication No. US20090022688; and International Publication Nos. WO 2006/019831 and WO 2006/019832. Additional HCV NS4A inhibitors useful in the useful in the present compositions and methods include, but are not limited to, AZD2836 (Astra Zeneca) and ACH-806 (Achillon Pharmaceuticals, New Haven, CT).

HCV replicase inhibitors useful in the useful in the present compositions and methods include, but are not limited to, those disclosed in U.S. Patent Publication No. US20090081636.

Therapeutic vaccines useful in the present compositions and methods include, but are not limited to, IC41 (Intercell Novartis), CSL123 (Chiron/CSL), GI 5005 (Globeimmune), TG-4040 (Transgene), GNI-103 (GENimmune), Hepavaxx C (ViRex Medical), ChronVac-C (Inovio/Tripep), PeviPROTM (Pevion Biotect), HCV/MF59 (Chiron/Novartis) and Civacir (NABI).

Examples of further additional therapeutic agents that may be useful in the present compositions and methods include, but are not limited to, Ritonavir (Abbott), TT033 (Benitec/Tacere Bio/Pfizer), Sirna-034 (Sirna Therapeutics), GNI-104 (GENimmune), GI-5005 (GlobeImmune), IDX-102 (Idenix), Levovirin™ (ICN Pharmaceuticals, Costa Mesa, California); Humax (Genmab), ITX-2155 (Ithrex/Novartis), PRO 206 (Progenics), HepaCide-I (NanoVirocides), MX3235 (Migenix), SCY-635 (Scynexis); KPE02003002 (Kemin Pharma), Lenocta (VioQuest Pharmaceuticals), IET – Interferon Enhancing Therapy (Transition Therapeutics), Zadaxin (SciClone Pharma), VP 50406™ (Viropharma, Incorporated, Exton, Pennsylvania); Taribavirin (Valeant Pharmaceuticals); Nitazoxanide (Romark); Debio 025 (Debiopharm); GS-9450 (Gilead); PF-4878691 (Pfizer); ANA773 (Anadys); SCV-07 (SciClone Pharmaceuticals); NIM-881 (Novartis); ISIS 14803™ (ISIS Pharmaceuticals, Carlsbad, California); Heptazyme™ (Ribozyme Pharmaceuticals, Boulder, Colorado); Thymosin™ (SciClone Pharmaceuticals, San Mateo, California); Maxamine™ (Maxim Pharmaceuticals, San Diego, California); NKB-122 (JenKen Bioscience Inc., North Carolina); Alinia (Romark Laboratories), INFORM-1 (a combination of R7128 and ITMN-191); and mycophenolate mofetil (Hoffman-LaRoche, Nutley, New Jersey).

The doses and dosage regimen of the other agents used in the combination therapies of the present invention for the treatment or prevention of HCV infection can be determined by the attending clinician, taking into consideration the approved doses and dosage regimen in the package insert; the age, sex and general health of the patient; and the type and severity of the viral infection or related disease or disorder. When administered in combination, the Tetracyclic Indole Derivative(s) and the other agent(s) can be administered simultaneously (*i.e.,* in the same composition or in separate compositions one right after the other) or sequentially. This particularly useful when the components of the combination are given on different dosing schedules, *e.g.*, one component is administered once daily and another component is administered every six hours, or when the preferred pharmaceutical compositions are different, *e.g.,* one is a tablet and one is a capsule. A kit comprising the separate dosage forms is therefore advantageous.

Generally, a total daily dosage of the at least one Tetracyclic Indole Derivative(s) alone, or when administered as combination therapy, can range from about 1 to about 2500 mg per day, although variations will necessarily occur depending on the target of therapy, the patient and the route of administration. In one embodiment, the dosage is from about 10 to about 1000 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 1 to about 500 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 1 to about 100 mg/day, administered in a single dose or in 2-4 divided doses. In yet another embodiment, the dosage is from about 1 to about 50 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 500 to about 1500 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 500 to about 1000 mg/day, administered in a single dose or in 2-4 divided doses. In yet another embodiment, the dosage is from about 100 to about 500 mg/day, administered in a single dose or in 2-4 divided doses.

In one embodiment, when the additional therapeutic agent is INTRON-A interferon alpha 2b (commercially available from Schering-Plough Corp.), this agent is administered by subcutaneous injection at 3MIU(12 mcg)/0.5mL/TIW for 24 weeks or 48 weeks for first time treatment.

In another embodiment, when the additional therapeutic agent is PEG-INTRON interferon alpha 2b pegylated (commercially available from Schering-

Plough Corp.), this agent is administered by subcutaneous injection at 1.5 mcg/kg/week, within a range of 40 to 150 mcg/week, for at least 24 weeks.

In another embodiment, when the additional therapeutic agent is ROFERON A interferon alpha 2a (commercially available from Hoffmann-La Roche), this agent is administered by subcutaneous or intramuscular injection at 3MIU(11.1 mcg/mL)/TIW for at least 48 to 52 weeks, or alternatively 6MIU/TIW for 12 weeks followed by 3MIU/TIW for 36 weeks.

In still another embodiment, when the additional therapeutic agent is PEGASUS interferon alpha 2a pegylated (commercially available from Hoffmann-La Roche), this agent is administered by subcutaneous injection at 180 mcg/1mL or 180 mcg/0.5mL, once a week for at least 24 weeks.

In yet another embodiment, when the additional therapeutic agent is INFERGEN interferon alphacon-1 (commercially available from Amgen), this agent is administered by subcutaneous injection at 9 mcg/TIW is 24 weeks for first time treatment and up to 15 mcg/TIW for 24 weeks for non-responsive or relapse treatment.

In a further embodiment, when the additional therapeutic agent is Ribavirin (commercially available as REBETOL ribavirin from Schering-Plough or COPEGUS ribavirin from Hoffmann-La Roche), this agent is administered at a daily dosage of from about 600 to about 1400 mg/day for at least 24 weeks.

In one embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from: an interferon, an immunomodulator, a viral replication inhibitor, an antisense agent, a therapeutic vaccine, a viral polymerase inhibitor, a nucleoside inhibitor, a viral protease inhibitor, a viral helicase inhibitor, a viral polymerase inhibitor a virion production inhibitor, a viral entry inhibitor, a viral assembly inhibitor, an antibody therapy (monoclonal or polyclonal), and any agent useful for treating an RNA-dependent polymerase-related disorder.

In another embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from an HCV protease inhibitor, an HCV polymerase inhibitor, an HCV replication inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin. The combination therapies can include any combination of these additional therapeutic agents.

In another embodiment, one or more compounds of the present invention are administered with one additional therapeutic agent selected from an HCV protease inhibitor, an interferon, a pegylated interferon and ribavirin.

In still another embodiment, one or more compounds of the present invention are administered with two additional therapeutic agents selected from an HCV protease inhibitor, an HCV replication inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin.

In another embodiment, one or more compounds of the present invention are administered with an HCV protease inhibitor and ribavirin. In another specific embodiment, one or more compounds of the present invention are administered with a pegylated interferon and ribavirin.

In another embodiment, one or more compounds of the present invention are administered with three additional therapeutic agents selected from an HCV protease inhibitor, an HCV replication inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin.

In one embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, an interferon, and a viral replication inhibitor. In another embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, an interferon, and a viral replication inhibitor. In another embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, an interferon, and ribavirin.

In one embodiment, one or more compounds of the present invention are administered with one additional therapeutic agent selected from an HCV polymerase inhibitor, a viral protease inhibitor, an interferon, and a viral replication inhibitor. In another embodiment, one or more compounds of the present invention are administered with ribavirin.

In one embodiment, one or more compounds of the present invention are administered with two additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, an interferon, and a viral replication inhibitor.

In another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and another therapeutic agent.

In another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and another therapeutic agent, wherein the additional therapeutic agent is selected from an HCV polymerase inhibitor, a viral protease inhibitor, and a viral replication inhibitor.

In still another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and a viral protease inhibitor.

In another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and an HCV protease inhibitor.

In another embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and boceprevir or telaprevir.

In a further embodiment, one or more compounds of the present invention are administered with ribavirin, interferon and an HCV polymerase inhibitor.

In another embodiment, one or more compounds of the present invention are administered with pegylated-interferon alpha and ribavirin.

In one embodiment, one or more compounds of the present invention are administered with from one to three additional therapeutic agents, wherein the additional therapeutic agents are each independently selected from HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

In one embodiment, one or more compounds of the present invention are administered with MK-5172.

In another embodiment, one or more compounds of the present invention are administered with MK-7009.

In another embodiment, one or more compounds of the present invention are administered with boceprevir.

In still another embodiment, one or more compounds of the present invention are administered with telaprevir.

In another embodiment, one or more compounds of the present invention are administered with PSI-938.

In another embodiment, one or more compounds of the present invention are administered with PSI-7977.

In yet another embodiment, one or more compounds of the present invention are administered with RG-7128.

In one embodiment, one or more compounds of the present invention are administered with (i) a compound selected from PSI-7977, PSI-938 RG-7128; and (ii) a compound selected from boceprevir, telaprevir, MK-7009 and MK-5172.

In another embodiment, one or more compounds of the present invention are administered with PSI-7977 and MK-5172.

Compositions and Administration

Due to their activity, the Tetracyclic Indole Derivatives are useful in veterinary and human medicine. As described above, the Tetracyclic Indole Derivatives are useful for treating or preventing HCV infection in a patient in need thereof.

When administered to a patient, the Tetracyclic Indole Derivatives can be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. The present invention provides pharmaceutical compositions comprising an effective amount of at least one Tetracyclic Indole Derivative and a pharmaceutically acceptable carrier. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, *i.e.,* oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. Powders and tablets may be comprised of from about 0.5 to about 95 percent inventive composition. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture.

Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum, and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate.

Liquid form preparations include solutions, suspensions and emulsions and may include water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize therapeutic effects, *i.e.*, antiviral activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

In one embodiment, the one or more Tetracyclic Indole Derivatives are administered orally.

In another embodiment, the one or more Tetracyclic Indole Derivatives are administered intravenously.

In another embodiment, the one or more Tetracyclic Indole Derivatives are administered topically.

In still another embodiment, the one or more Tetracyclic Indole Derivatives are administered sublingually.

In one embodiment, a pharmaceutical preparation comprising at least one Tetracyclic Indole Derivative is in unit dosage form. In such form, the preparation is subdivided into unit doses containing effective amounts of the active components.

Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present compositions can contain, in one embodiment, from about 0.1% to about 99% of the Tetracyclic Indole Derivative(s) by weight or volume. In various embodiments, the present compositions can contain, in one embodiment, from about 1% to about 70% or from about 5% to about 60% of the Tetracyclic Indole Derivative(s) by weight or volume.

The quantity of Tetracyclic Indole Derivative in a unit dose of preparation may be varied or adjusted from about 1 mg to about 2500 mg. In various embodiments, the quantity is from about 10 mg to about 1000 mg, 1 mg to about 500 mg, 1 mg to about 100 mg, and 1 mg to about 100 mg.

For convenience, the total daily dosage may be divided and administered in portions during the day if desired. In one embodiment, the daily dosage is administered in one portion. In another embodiment, the total daily dosage is administered in two divided doses over a 24 hour period. In another embodiment, the total daily dosage is administered in three divided doses over a 24 hour period. In still another embodiment, the total daily dosage is administered in four divided doses over a 24 hour period.

The amount and frequency of administration of the Tetracyclic Indole Derivatives will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. Generally, a total daily dosage of the Tetracyclic Indole Derivatives range from about 0.1 to about 2000 mg per day, although variations will necessarily occur depending on the target of therapy, the patient and the route of administration. In one embodiment, the dosage is from about 1 to about 200 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 10 to about 2000 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 100 to about 2000 mg/day, administered in a single dose or in 2-4 divided doses. In still another

embodiment, the dosage is from about 500 to about 2000 mg/day, administered in a single dose or in 2-4 divided doses.

The compositions of the invention can further comprise one or more additional therapeutic agents, selected from those listed above herein. Accordingly, in one embodiment, the present invention provides compositions comprising: (i) at least one Tetracyclic Indole Derivative or a pharmaceutically acceptable salt thereof; (ii) one or more additional therapeutic agents that are not a Tetracyclic Indole Derivative; and (iii) a pharmaceutically acceptable carrier, wherein the amounts in the composition are together effective to treat HCV infection.

In one embodiment, the present invention provides compositions comprising a Compound of Formula (I) and a pharmaceutically acceptable carrier.

In another embodiment, the present invention provides compositions comprising a Compound of Formula (I), a pharmaceutically acceptable carrier, and a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

In another embodiment, the present invention provides compositions comprising a Compound of Formula (I), a pharmaceutically acceptable carrier, and wto additional therapeutic agents, each of which are independently selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

Kits

In one aspect, the present invention provides a kit comprising a therapeutically effective amount of at least one Tetracyclic Indole Derivative, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

In another aspect the present invention provides a kit comprising an amount of at least one Tetracyclic Indole Derivative, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and an amount of at least one additional therapeutic agent listed above, wherein the amounts of the two or more active ingredients result in a desired therapeutic effect. In one embodiment, the one or more Tetracyclic Indole Derivatives and the one or more additional therapeutic agents are provided in the same container. In one embodiment, the one or more

Tetracyclic Indole Derivatives and the one or more additional therapeutic agents are provided in separate containers.

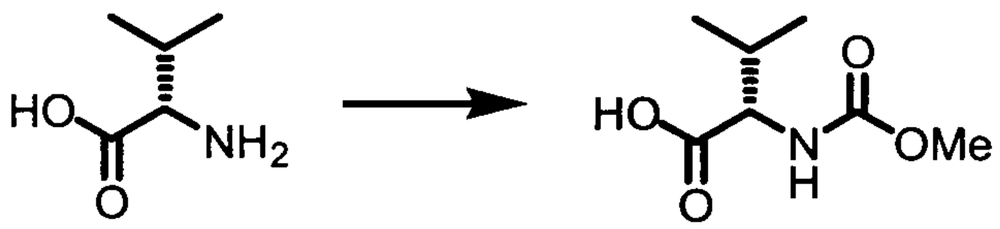
EXAMPLES

General Methods

Solvents, reagents, and intermediates that are commercially available were used as received. Reagents and intermediates that are not commercially available were prepared in the manner as described below. ^{1}H NMR spectra when reported, were obtained on either a Varian VNMR System 400 (400 MHz) or a Bruker Avance 500 (500 MHz) and resonances are reported as ppm downfield from Me_4Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Agilent 6110A MSD or an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Alltech platinum C18 column, 3 micron, 33 mm x 7mm ID; typical gradient flow: 0 minutes – 10% CH_3CN, 5 minutes – 95% CH_3CN, 5-7 minutes – 95% CH_3CN, 7 minutes – stop. The retention time and observed parent ion are given. Chromatography was performed using partially automated systems manufactured by Gilson, ISCO or Biotage. Unless otherwise indicated, chromatography was performed using a gradient elution of hexanes/ethyl acetate, from 100% hexanes to 100% ethyl acetate.

EXAMPLE 1

Preparation of Compound **Int-1a**

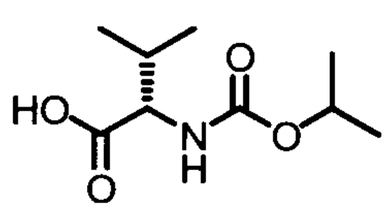


Int-1a

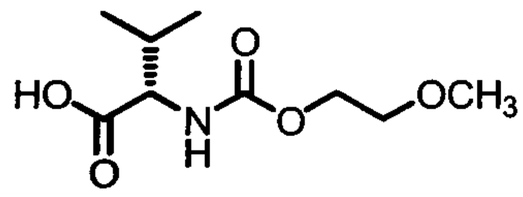
To a solution of L-valine (10.0 g, 85.3 mmol) in 1M aqueous NaOH solution (86 mL) at room temperature was added solid sodium carbonate (4.60 g, 43.4 mmol). The reaction mixture was cooled to 0 °C (ice bath) and then methyl chloroformate (7.20 mL, 93.6 mmol) was added dropwise over 20 minutes. The reaction mixture was then allowed to warm to room temperature, and allowed to stir at room temperature for an additional 4 hours. The reaction mixture was then diluted with diethyl

ether (100 mL), the resulting solution was cooled to at 0 °C, and then concentrated hydrochloric acid (18 mL, 216 mmol) was added slowly. The reaction was extracted with EtOAc (3 x 100 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide Compound **Int-1a** (13.5 g, 90%), which was used without further purification.

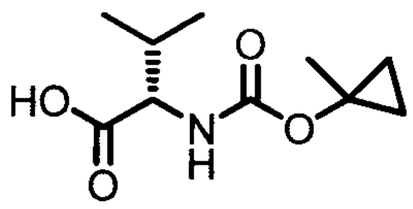
The following intermediates can be prepared by the reaction of L-valine or L- threonine with isopropyl chloroformate, 2-methoxyethyl chloroformate or with 1-methylcyclopropyl hydroxysuccinimide respectively as above.



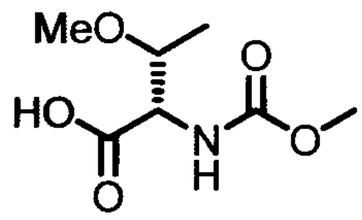
Int-1b



Int-1c



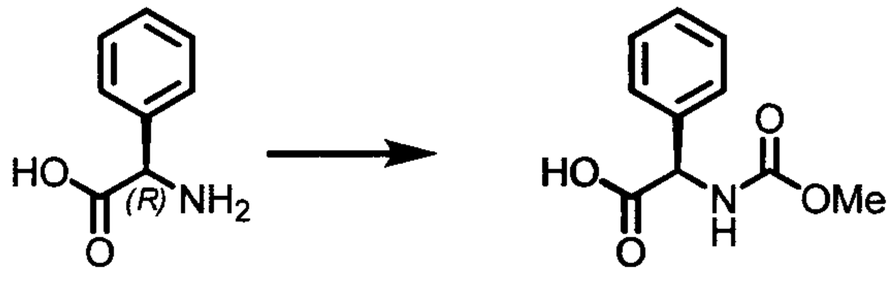
Int-1d



Int-1e

EXAMPLE 2

Preparation of Intermediate Compound **Int-2a**

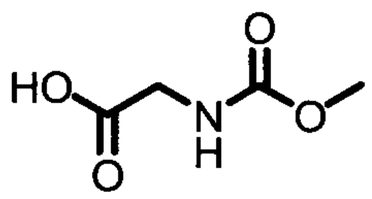


Int-2a

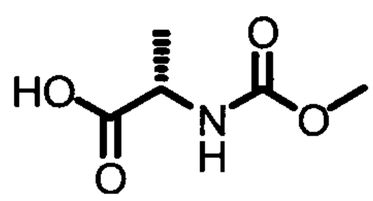
To a solution of D-phenylglycine (10.0 g, 66.1 mmol) and NaOH (21.2 g, 265 mmol) in water (60 mL) at 0 °C was added methyl chloroformate (10.2 mL, 133 mmol) dropwise over 20 minutes. The resulting mixture was allowed to stir at 0 °C for 1 hour, then was acidified using concentrated hydrochloric acid (25 mL, 300 mmol). The acidic solution was extracted with EtOAc (3 x 100 mL) and the combined organics were

dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide Compound **Int-2a** (12.6 g, 91%), which was used without further purification.

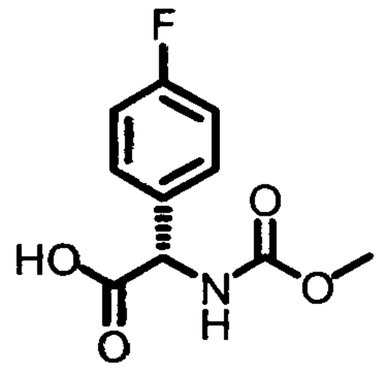
The following intermediates can be prepared by the reaction of glycine, L-Alanine and 4-F phenylglycine respectively with methyl chloroformate (Aldrich Inc.) using the method described above:



Int- 2b



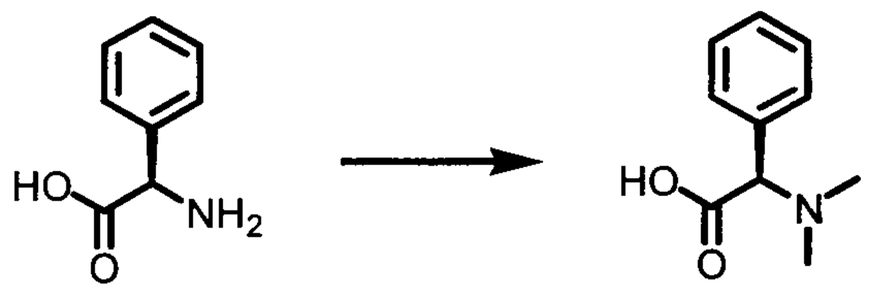
Int-2c



Int-2d

EXAMPLE 3

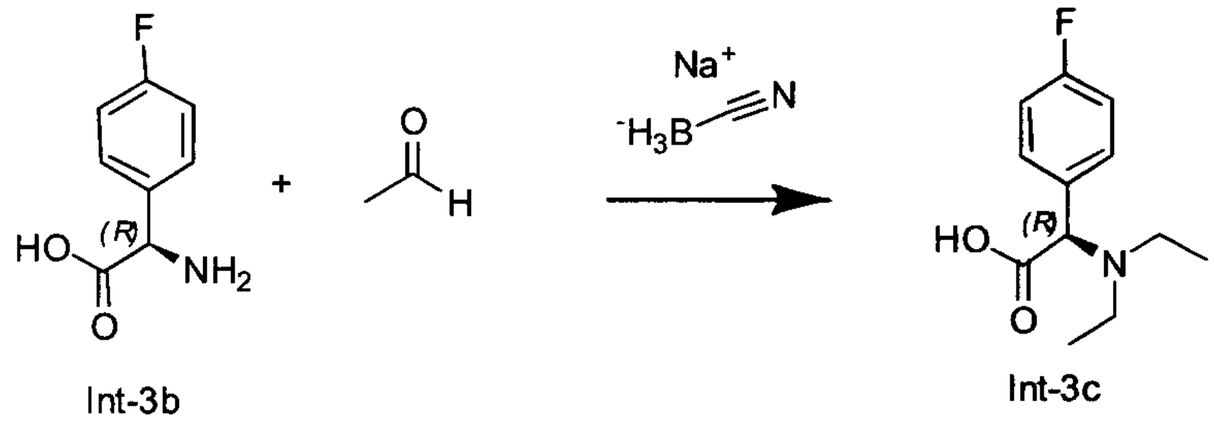
Preparation of Intermediate Compound **Int-3a**



Int-3a

A solution of D-phenylglycine (20.0 g, 132 mmol), **37%** aqueous formaldehyde (66 mL, 814 mmol) and 5 % Pd on carbon (8.0 g, **mmol)** in a mixture of methanol (80 mL) and 1 N HCl (60 mL) was placed on a hydrogenation shaker and shook under an atmosphere of 35-40 psi hydrogen for 4 hours. The reaction was then flushed with nitrogen, filtered through a Celite pad and concentrated *in vacuo* to provide Compound **Int-3a** (29.7 g, quant.) as a white solid, which was used without further purification.

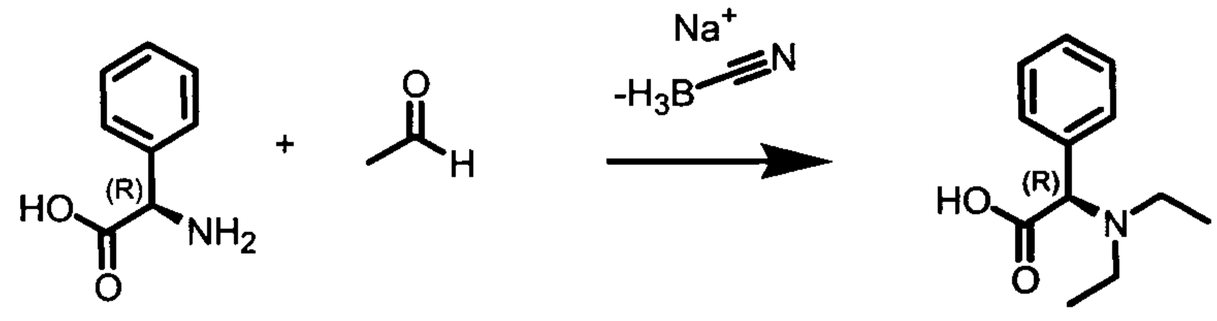
EXAMPLE 3A



Int-3b Int-3c

To a solution of (R)-2-amino-2-(4-fluorophenyl)acetic acid (**Int 3b**) in MeOH (20 mL) at 0 °C was added sodium cyanoborohydride portionwise over ~ 20 minutes. The resulting mixture was allowed to stir for 10 minutes and then acetaldehyde was added dropwise via syringe over ~10 minutes. The resulting solution was allowed to stir for 1 hour at 0 °C, and then allowed to warm to room temperature. After 12h, LC-MS indicated disappearance of **Int-3b**, and the mixture was recooled to 0 °C, carefully treated with water (3 mL) followed by addition of conc HCl over ~40 minutes (pH ~2.0). The cooling bath was removed and the mixture was allowed to stand for about 15 hours. The precipitate was collected by filtration to provide **Int-3c**.

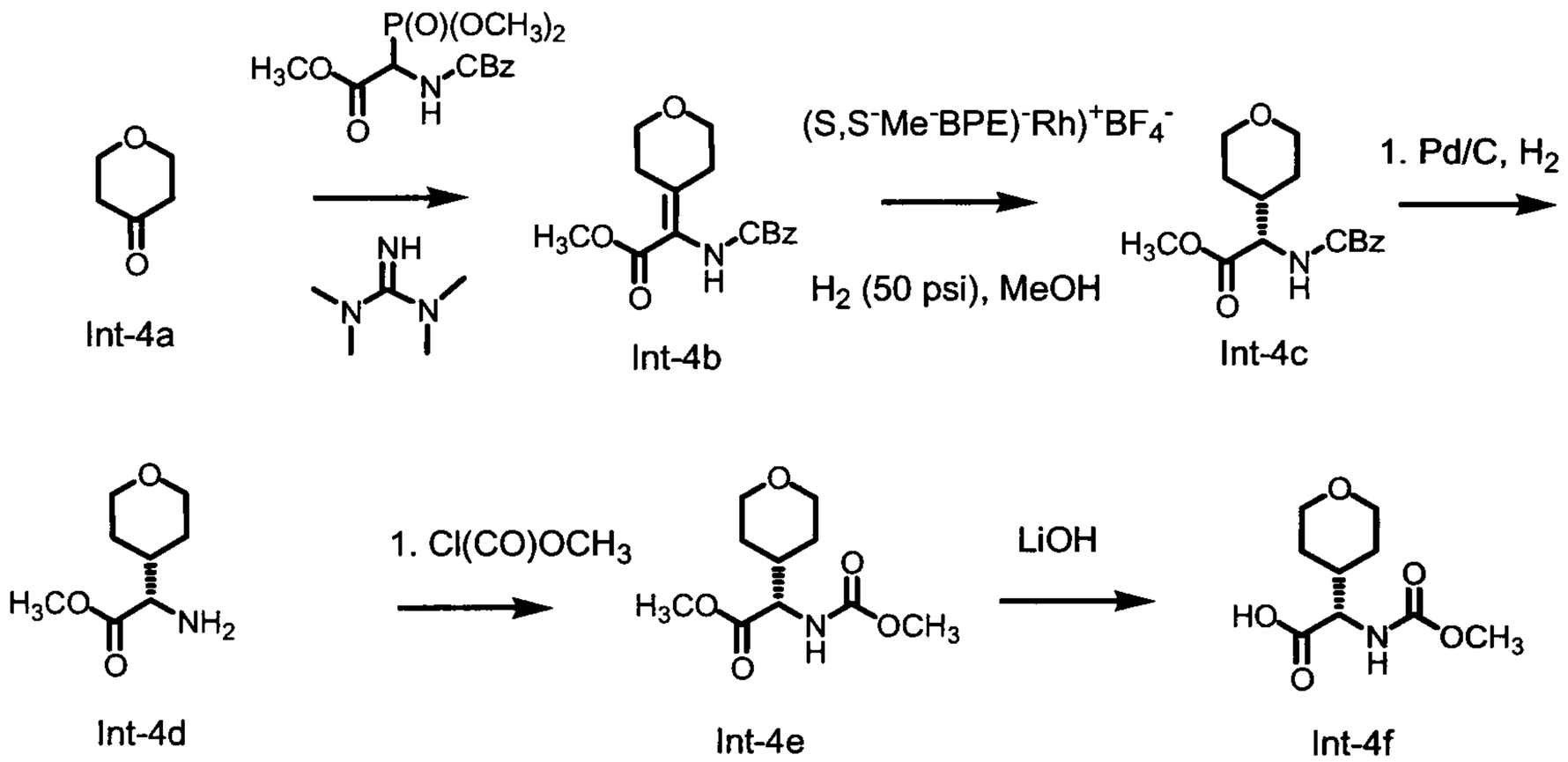
Intermediate **Int-3d** can be prepared using the procedure above from R-Phenyl glycine.



Phenylglycine **Int-3d**

EXAMPLE 4

Preparation of Intermediate Compound **Int-4f**



Step A – Preparation of Compound ***Int-4b***

To a solution of methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl) acetate (10.0 g, 30.2 mmol, made as decribed in Hamada *et al.*, *Organic Letters*; English, 20:4664-4667 (2009)) in THF (100 mL) at –20 °C was added tetramethylguanidine (4.20 mL, 33.2 mmol). The reaction mixture was allowed to stir at –20 °C for 1 hour then dihydro-2*H*-pyran-4(3*H*)-one (**4a**) was added (3.1 mL, 33.2 mmol) in THF (5 mL) and the reaction mixture was warmed to room temperature and allowed to stir for about 15 hours. EtOAc (200 mL) was added and the organic mixture was washed with water (3 × 50 mL) and brine (50 mL). The organic layers were combined and dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified using flash chromatography on an ISCO 330 g Redi-Sep column using 0 35% EtOAc/hexanes as the eluent to provide Compound **Int-4b** as a white solid (615 mg, 45%). ^{1}H NMR ($CDCl_3$) δ 7.40 7.30 (m, 5H), 6.00 (br s, 1H), 5.12 (s, 2H), 3.80 3.65 (m, 7H), 2.92 (m, 2H), 2.52 2.48 (m, 2H).

Step B – Preparation of Compound ***Int-4c***

To a solution of **Int-4b** (2.43 g, 7.96 mmol) in methanol (160 mL) previously purged with N_2 was added (–)-1,2-Bis((2*S*,5*S*)-2,5-dimethylphospholano)

ethane (cyclooctadiene)rhodium(I) tetrafluoroborate (487 mg, 0.880 mmol) under N_2. The mixture was shaken in a Parr shaker apparatus for 18 hours at 50 psi of H_2. After evacuating the hydrogen, the suspension was filtered and the filtrate was concentrated *in vacuo* to provide Compound **Int-4c** as a white solid (1.30 g, 53%). ^{1}H NMR ($CDCl_3$) δ 7.40 7.30 (m, 5H), 5.32 (br s, 1H), 5.12 (s, 2H), 4.40 4.30 (m, 1H), 4.00 3.95 (m, 2H), 3.75 (s, 3H), 3.40 3.25 (m, 2H), 2.10 1.95 (m, 1H), 1.50 1.45 (m, 4H).

Step C – Preparation of Compound ***Int-4d***

To a suspension of 50% palladium on carbon (10% wet, 200 mg) in absolute ethanol (20 mL) under nitrogen was added **Int-4c** (1.06 g, 3.45 mmol). With stirring, the solution was placed *in vacuo* for 30 seconds and then was opened to a hydrogen gas balloon for 2 hours. After evacuating the hydrogen, the suspension was filtered through a Celite pad and the pad was washed with ethanol (2 × 20 mL). The filtrate was concentrated *in vacuo* to provide Compound **Int-4d** as a colorless oil (585 mg, 98%). ^{1}H NMR ($CDCl_3$) δ 4.06 3.96 (m, 2H), 3.73 (s, 3H), 3.48 3.28 (m, 3H), 1.92 1.78 (m, 1H), 1.61 1.47 (m, 6H).

Step D – Preparation of Compound ***Int-4e***

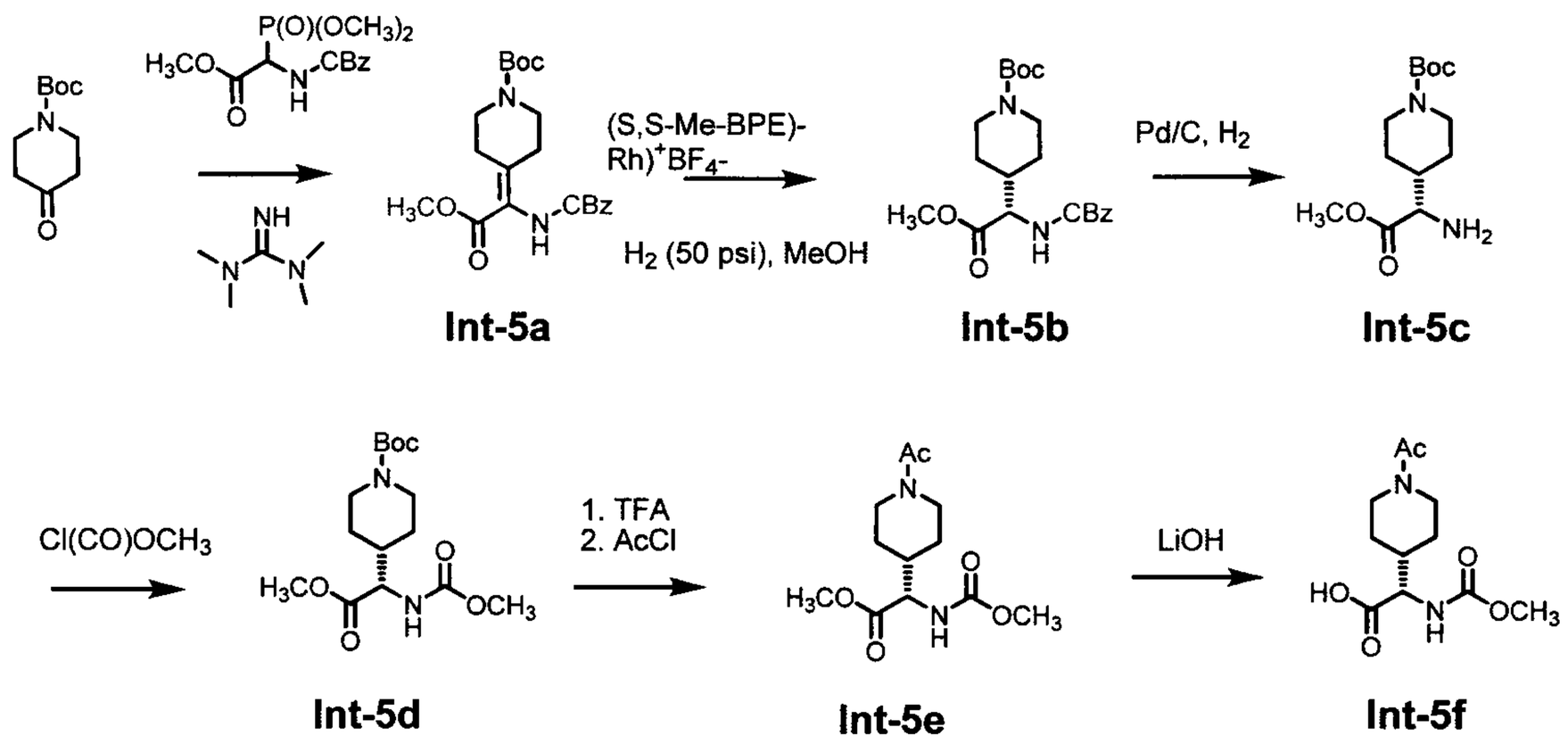
To a solution of Compound **Int-4d** (585 mg, 3.37 mmol) and triethylamine (0.710 mL, 5.09 mmol) in CH_2Cl_2 (6 mL) was added methyl chloroformate (0.290 mL, 3.76 mmol). The reaction was allowed to stir at room temperature for about 15 hours, then water (15 mL) was added and the aqueous mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified using flash chromatography on an ISCO 24 g Redi-Sep column using 0 3% MeOH/CH_2Cl_2 as the eluent to provide Compound **Int-4e** as a colorless oil (600 mg, 77%). ^{1}H NMR ($CDCl_3$) δ 5.27 5.18 (m, 1H), 4.38 4.28 (m, 1H), 4.06 3.96 (m, 2H), 3.75 (s, 3H), 3.69 (s, 3H), 3.39 3.30 (m, 2H), 2.09 1.94 (m, 1H), 1.59 1.48 (m, 4H).

Step E – Preparation of Compound ***Int-4f***

To a solution of Compound **Int-4e** (600 mg, 2.59 mmol) in THF (5 mL) was added lithium hydroxide monohydrate (218 mg, 5.19 mmol) in water (5 mL). The reaction was allowed to stir at room temperature for 2 hours then was concentrated *in vacuo* to half of its original volume. The concentrated mixture was then acidified with 6N HCl and extracted with EtOAc (7 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide Compound **Int-4f** as an off-white solid (485 mg, 86%). ^{1}H NMR (CD_3OD) δ 4.09 4.07 (m, 1H), 3.96 3.92 (m, 2H), 3.65 (s, 3H), 3.40 3.34 (m, 2H), 2.10 1.99 (m, 1H), 1.56 1.47 (m, 4H).

EXAMPLE 5

Preparation of Intermediate Compound **Int-5f**



*Step A – Preparation of Compound **Int-5a***

To a solution of methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl) acetate (1.50 g, 4.52 mmol) in THF (5 mL) at –20 °C was added tetramethylguanidine (625 µL, 4.98 mmol). The reaction mixture was allowed to stir at –20 °C for 1 hour then *tert*-butyl 4-oxopiperidine-1-carboxylate was added (992 mg, 4.97 mmol) in THF (2 mL) and the reaction mixture was warmed to room temperature and allowed to stir for about 15 hours. EtOAc (90 mL) was added and the organic mixture was washed with water (3 × 20 mL) and brine (25 mL). The combined organic extracts

were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified using flash chromatography on an ISCO 40 g Redi-Sep column using 0 35% EtOAc/hexanes as the eluent to provide Compound **Int-5a** as a white semi-solid (1.1 g, 61%). ^{1}H NMR ($CDCl_3$) δ 7.40 7.30 (m, 5H), 6.02 (br s, 1H), 5.12 (s, 2H), 3.80 3.40 (m, 7H), 2.90 2.80 (m, 2H), 2.45 2.35 (m, 2H), 1.45 (s, 9H).

Step B – Preparation of Compound ***Int-5b***

To a solution of **Int-5a** (1.30 g, 3.21 mmol) in methanol (90 mL) previously purged with N_2 was added (–)-1,2-Bis((2S,5S)-2,5-dimethylphospholano) ethane(cyclooctadiene)rhodium(I) tetrafluoroborate (197 mg, 0.354 mmol) under N_2. The mixture was then shaken in a Parr shaker apparatus for 18 hours at 50 psi of H_2. After evacuating the hydrogen, the suspension was filtered and the filtrate was concentrated *in vacuo* to provide Compound **Int-5b** as colorless oil (1.00 g, 77%). ^{1}H NMR ($CDCl_3$) δ 7.40 7.30 (m, 5H), 5.35 5.25 (m, 1H), 5.10 (s, 2H), 4.40 4.35 (m, 1H), 4.20 4.10 (m, 2H), 3.70 (s, 3H), 2.70 2.55 (m, 2H), 2.00 1.90 (m, 1H), 1.65 1.40 (m, 11H), 1.30 1.20 (m, 2H).

Step C – Preparation of Compound ***Int-5c***

To a solution of 50% palladium on carbon (10% wet, 250 mg) in absolute ethanol (20 mL) under nitrogen was added **Int-5b** (1.00 g, 2.46 mmol). The reaction was evacuated, then put under an H_2 atmosphere using a hydrogen-filled balloon and allowed to stir for 2 hours. The hydrogen was evacuated and the resulting suspension was filtered through a Celite pad and the pad washed with ethanol (2 × 20 mL). The filtrate and ethanol washings were combined and concentrated *in vacuo* to provide Compound **Int-5c** as a colorless oil (670 mg, quant.). ^{1}H NMR ($CDCl_3$) δ 4.21 4.08 (m, 2H), 3.73 (s, 3H), 3.31 (d, J = 6.0 Hz, 1H), 2.75 2.57 (m, 2H), 1.84 1.70 (m, 1H), 1.68 1.56 (m, 1H), 1.45 (s, 9H), 1.45 1.20 (m, 5H).

Step D – Preparation of Compound ***Int-5d***

To a solution of Compound **Int-5c** (670 mg, 2.46 mmol) and triethylamine (0.520 mL, 3.73 mmol) in CH_2Cl_2 (10 mL) was added methyl chloroformate (0.210 mL,

2.72 mmol). The reaction mixture was allowed to stir at room temperature for about 15 hours. Water (20 mL) was added and the aqueous mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified using flash chromatography on an ISCO 24 g Redi-Sep column using 0 3% MeOH/CH_2Cl_2 as the eluent to provide Compound **Int-5d** as an off-white solid (515 mg, 63%). ^{1}H NMR ($CDCl_3$) δ 5.26 5.17 (m, 1H), 4.38 4.30 (m, 1H), 4.20 4.07 (m, 2H), 3.75 (s, 3H), 3.68 (s, 3H), 2.71 2.57 (m, 2H), 2.00 1.85 (m, 1H), 1.87 1.48 (m, 2H), 1.44 (s, 9H), 1.35 1.18 (m, 2H).

*Step E – Preparation of Compound **Int-5e***

Compound **Int-5d** (300 mg, 0.908 mmol) was dissolved in a mixture of TFA (2 mL) and CH_2Cl_2 (10 mL) and the solution was allowed to stir at room temperature for 1 hour, then was concentrated *in vacuo*. To the resulting residue was added triethylamine (0.760 mL, 5.45 mmol) in CH_2Cl_2 (10 mL), then acetic anhydride (0.086 mL, 0.915 mmol). The reaction was allowed to stir at room temperature for about 15 hours then concentrated *in vacuo*. The residue obtained was purified using flash chromatography on an ISCO 12 g Redi-Sep column using 0 4% MeOH/CH_2Cl_2 as the eluent to provide Compound **Int-5e** as colorless oil (247 mg, 99%). ^{1}H NMR ($CDCl_3$) δ 5.27 5.21 (m, 1H), 4.73 4.62 (m, 1H), 4.42 4.32 (m, 1H), 3.69 (s, 3H), 3.18 (s, 3H), 3.18 3.09 (m, 1H), 3.07 2.95 (m ,1H), 2.55 2.41 (m, 1H), 2.07 (s, 3H), 1.78 1.49 (m, 3H), 1.38 1.21 (m, 2H).

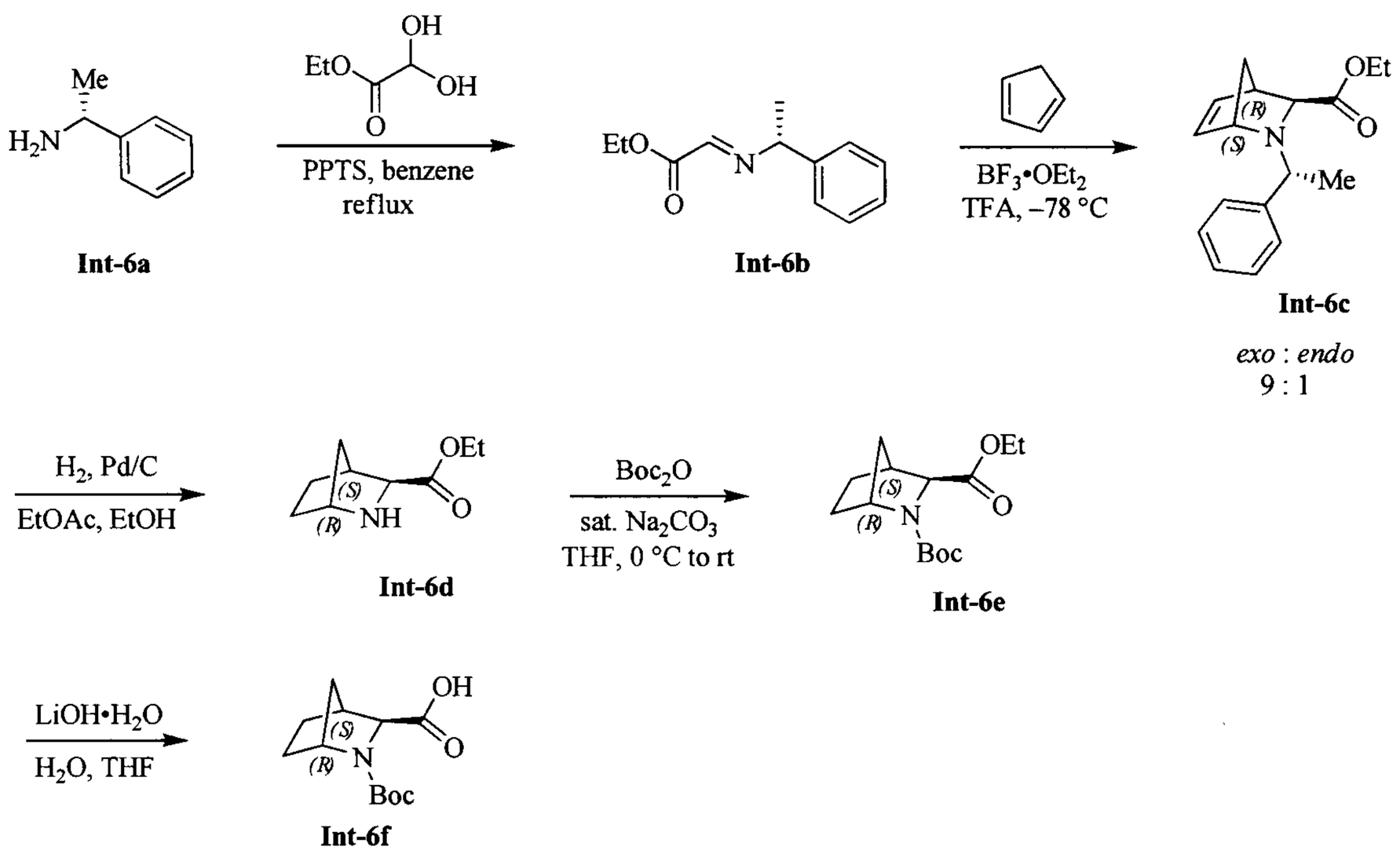
*Step F – Preparation of Compound **Int-5f***

To a solution of Compound **Int-5e** (247 mg, 2.59 mmol) in THF (3 mL) was added lithium hydroxide monohydrate (77 mg, 1.83 mmol) in water (3 mL). The reaction mixture was allowed to stir at room temperature for about 15 hours then concentrated *in vacuo* to 50% of its original volume. The concentrated solution was then acidified with 1N HCl to pH 4 and extracted with EtOAc (7 × 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide Compound **Int-5f** as an off-white solid (106 mg, 45%). ^{1}H NMR (CD_3OD) δ 5.52 5.43

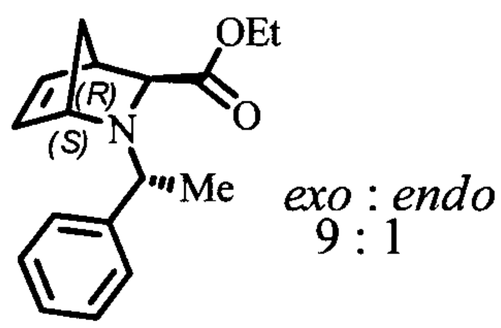
(m, 1H), 4.71 4.62 (m, 1H), 4.44 4.31 (m, 1H), 3.91 3.81 (M, 1H), 3.70 (s, 3H), 3.12 2.99 (m, 1H), 2.58 2.46 (m, 1H), 2.10 (m, 4H), 1.86 1.54 (m, 2H), 1.50 1.21 (m, 3H).

EXAMPLE 6

Preparation of Intermediate Compound **Int-6f**



Step A – Preparation of Compound **Int-6c**



Int-6c

A stirred mixture of D-(+)-α-methylbenzyl amine **Int-6a** (50.0 g, 0.412 mol), ethyl glyoxylate (81.5 mL, 50% in toluene, 0.412 mol) and PPTS (0.50 g, 2.00 mmol) in benzene (600 mL) was heated to reflux in a Dean-Stark apparatus and allowed to remain at reflux until no further water (~8 mL) azeotroped from the reaction (~ 4 hours). The resulting mixture was concentrated *in vacuo* to provide Compound **Int-6b**,

which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.36 7.24 (m, 5H), 4.61 (q, *J* = 6.9 Hz, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 1.62 (d, *J* = 6.6 Hz, 3H), 1.34 (t, *J* = 7.2 Hz, 3H).

To a stirred solution of crude **Int-6b** in methylene chloride (600 mL) at –78 °C were added the following in 10 minutesute intervals: TFA (31.0 mL, 0.416 mol), boron trifluoride etherate (51.3 mL, 0.416 mol) and freshly distilled cyclopentadiene (32.7 g, 0.494 mol). After less than 2 minutes following the addition of cyclopentadiene, the reaction mixture formed a thick brown mass, which was allowed to stir for 6 hours at –78 °C. The reaction mixture was then allowed to warm to room temperature on its own and stir for an additional 15 hours. The resulting dark brown reaction mixture was quenched with sat. aq. Na_2CO_3 (~ 900 mL) and allowed to stir for 30 minutes. The resultant suspension was filtered through a pad of Celite® and the filtrate was extracted with methylene chloride (3 × 100 mL). The combined organic extracts were washed with sat. aq. NaCl (2 × 75 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified using flash column chromatography (silica; 8 × 18 cm, 10% to 25% ethyl acetate/hexanes as the eluent) to provide *endo* **Int-6c** (10.9 g, 9%) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 7.19 (m, 5H), 6.00 5.95 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 3H), 3.47 (s, 1H), 3.03 (s, 1H), 2.97 (q, *J* = 6.5 Hz, 1H), 2.41 (s, 1H), 1.86 (d, *J* = 8.2 Hz, 1H), 1.26 (t, *J* = 6.6 Hz, 3H), 1.17 (t, *J* = 6.6 Hz, 3H). *Exo* **Int-6c** (84.3 g, 74%) was also collected as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 7.19 (m, 5H), 6.36 6.33 (m, 1H), 6.22 6.18 (m, 1H), 4.37 (s, 1H), 3.87 (q, *J* = 6.8 Hz, 2H), 3.10 (q, *J* = 6.5 Hz, 1H), 2.96 (s, 1H), 2.27 (s, 1H), 2.20 (d, *J* = 8.4 Hz, 1H), 1.48 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 1.00 (m, 1H).

Step B– Representative Example for the Preparation of Compound **Int-*6d***

A mixture of *exo*-**Int-6c** (15.8 g, 0.582 mol) and 10% Pd/C (4.07 g, 50% wet) in a 1:2 mixture of EtOH/EtOAc (150 mL) was shaken for 23 hours in a Parr hydrogenation apparatus under an atmosphere of H_2 (50 psi). The reaction mixture was then filtered through Celite® and the filtrate was concentrated *in vacuo*. ^{1}H NMR analysis of the residue (10.8 g) showed some aromatic resonances present. Repetition of the hydrogenation procedure using 10% Pd/C (2.0 g) provided **Int-6d** (10.0 g, quant.) as

a brown oil, which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.2 Hz, 3H), 3.54 (s, 1H), 3.32 (s, 1H), 2.62 (s, 1H), 2.23 (s, 1H), 1.64 1.39 (m, 5H), 1.31 1.20 (m, 4H).

Step C – Preparation of Compound **Int-*6e***

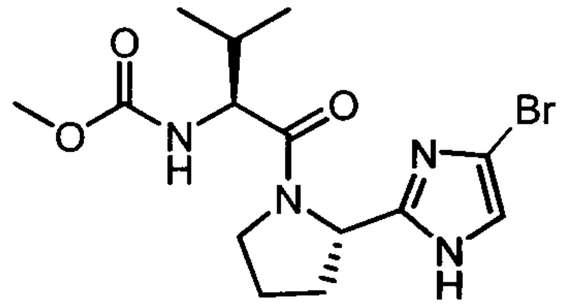
To a solution of **Int-6d** (36.6 g, 0.236 mol) and sat. aq. Na_2CO_3 (300 mL) in THF (600 mL) at 0 °C was added di-*tert*-butyl dicarbonate (59.0 g, 0.270 mol). The resulting reaction was allowed to slowly warm to room temperature with stirring over 6 hours, then was allowed to stir at room temperature for an additional 68 hours. The reaction mixture was diluted with EtOAc (250 mL) and water (250 mL) and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic extracts were washed with sat. aq. NaCl (2 × 75 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified using flash column chromatography (silica; 16 × 10 cm) using 10 20% ethyl acetate/hexanes as the eluent to provide Compound **Int-6e** (49.0 g, 84%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (s, 0.6H), 4.22 4.10 (m, 2.4H), 3.81 (s, 0.45H), 3.71 (s, 0.55H), 2.66 (s, 1H), 1.96 1.90 (m, 1H), 1.76 1.50 (m, 3H), 1.55 1.45 (m, 5H), 1.39 (s, 5H), 1.30 1.23 (m, 4H).

Step D– Preparation of Compound 2.2.1 Bicyclic Acid Intermediate **Int-*6f***

To a stirred mixture of **Int-6e** (49.0 g, 0.182 mmol) in 1:1 THF/water (600 mL) was added $LiOH•H_2O$ (15.3 g, 0.364 mol). The reaction mixture was heated to 60 °C and allowed to stir at this temperature for 47 hours. The reaction mixture was then cooled to room temperature, concentrated *in vacuo*, and the residue obtained was diluted with CH_2Cl_2 (200 mL) then acidified with 2N HCl to pH ~ 4. The acidic solution was extracted with CH_2Cl_2 (4 × 100 mL) and the combined organic extracts were washed with sat. aq. NaCl (25 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide Compound **Int-6f**, (1*R*, 3*S*, 4*S*)-*N*-Boc-2-azabicyclo[2.2.1]heptane-3-carboxylic acid (41.2 g, 93%) as an off white solid, which was used without further purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.44 (s, 1H), 4.13 (s, 0.56H), 4.06 (s, 0.47H), 3.61 (d, *J* = 4.0 Hz, 1H), 2.59 (s, 1H), 1.75 1.45 (m, 5H), 1.39 (s, 4H), 1.32 (s, 5H), 1.23 (t, *J* = 8.4 Hz, 1H); Optical Rotation: $[\alpha]^D_{25}$ –169.0° (c = 1.1, $CHCl_3$).

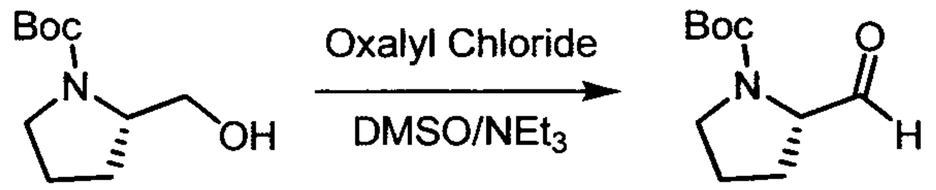
EXAMPLE 7

Preparation of Intermediate Compound **Int-7h**



Int-7h

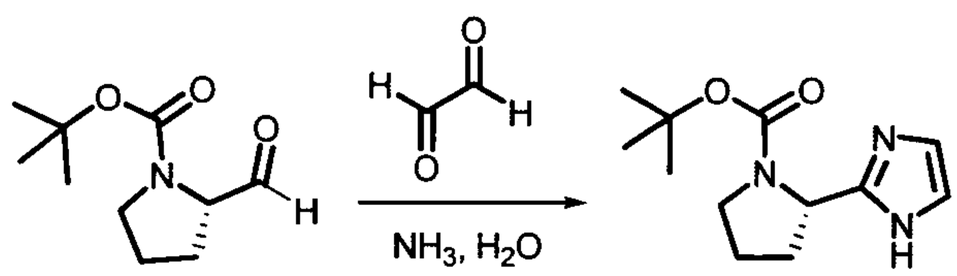
*Step A – Preparation of Compound **Int-7b***



Int-7a **Int-7b**

A 2 L, 3-necked round bottomed flask equipped with an overhead stirrer and a N_2 inlet was charged with a solution of oxalyl chloride (130 mL, 0.26 mol) in dichloromethane (250 mL). The solution was cooled to -78 °C, and a solution of DMSO (20 mL, 0.28 mol) in dichloromethane (30 mL) was added dropwise. After 30 minutes, a solution of (*S*)-*N*-Boc-prolinol, **Int-7a** (40 g, 0.20 mol) in dichloromethane (200 mL) was added dropwise. After 30 minutes, triethylamine (140 mL, 1.00 mol) was added to the solution, and the flask was transferred to an ice/water bath and allowed to stir for another 30 minutes. The reaction mixture was diluted with dichloromethane (200 mL) and washed successively with H_2O, 1M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide crude (*S*)-2-formyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester, **Int-7b** (40 g) as oil, which was used without further purification.

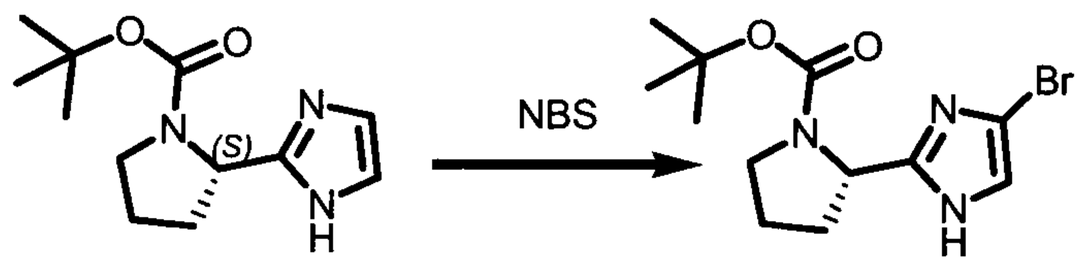
Step B – Preparation of Compound ***Int-7c***



Int-7b **Int-7c**

To (*S*)-Boc-prolinal, **Int-7b** (crude, 80g, 0.4 mol) was added a solution of ammonia in MeOH (prepared from 150 mL of 7 N ammonia/MeOH and 200 mL MeOH, 1.05 mol, 260 mol%). An exotherm was noted with the internal temperature rising to ~ 30 °C. The solution was allowed to stir for 0.5 hours at room temperature, then glyoxal (76 g, 0.52 mol, 130 mole%) was added over 5 minutes in portions, with the internal temperature rising to ~ 60 °C and then returning to room temperature after 1 hour. The reaction was allowed to stir for an additional 15 hours and the reaction mixture was concentrated *in vacuo*. The resulting residue was diluted with dichloromethane (1 L) and water (0.5 L) were added and the organic phase was washed with water (0.25 L), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue obtained was slurried with warm ethyl acetate (~ 100 mL) and Hexane (100 mL), then was cooled and filtered. The solid obtained was washed with 30%ethyl acetate/Hexane to provide Compound **Int-7c** (66.2g, 70% yield).

Step C – Preparation of Compound ***Int-7d***

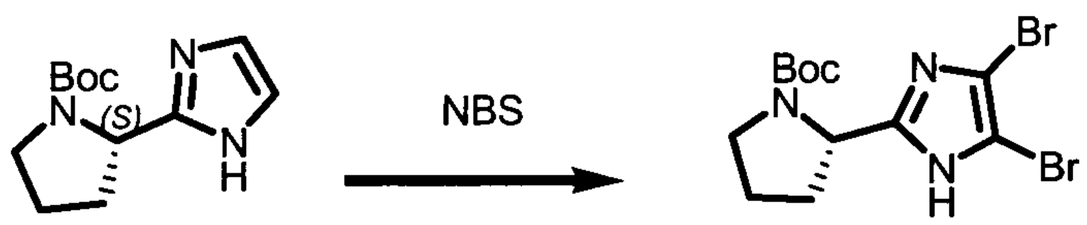


Int-7c **Int-7d**

N-Bromosuccinimide (838.4 mg, 4.71 mmol) was added in portions over 15 minutes to a cooled (ice/water) CH_2Cl_2 (20 mL) solution of imidazole **Int-7c** (1.06 g, 4.50 mmol). The reaction mixture was allowed to stir for 75 minutes and concentrated *in*

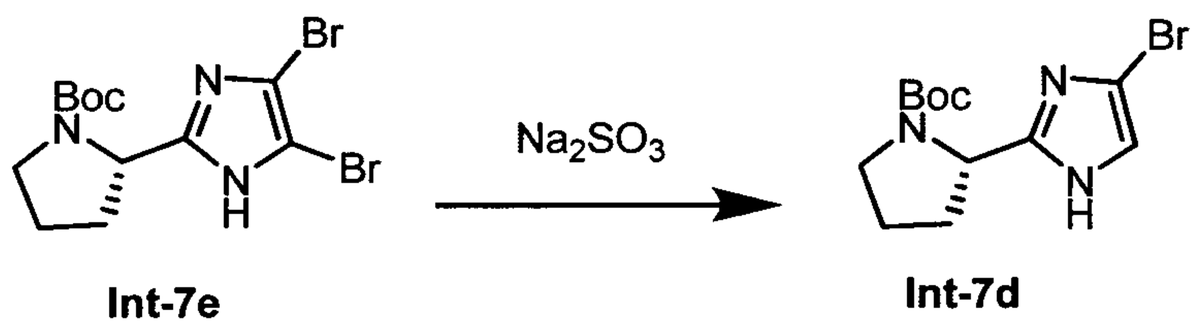
vacuo to oil. The residue obtained was purified using silica-gel RPLC (Acetonitrile/ water/ 0.1% TFA) to separate the mono bromide from its dibromo analog (over bromination) and the starting material. The RPLC elute was neutralized with excess NH_3/MeOH, and the volatile component was removed *in vacuo*. The residue obtained was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with water. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide Compound **Int-7d** as a white solid (374 mg). ^{1}H NMR (DMSO) δ: 12.12 (br s, 1H), 7.10 (m, 1H), 4.70 (m, 1H), 3.31 (m, 1H; overlapped with water signal), 2.25-1.73 (m, 4H), 1.39/1.17 (s, 3.8H + 5.2H).

*Step D - Alternative Synthesis of **Int-7d***



Int-7b **Int-7e**

To a suspension of **Int-7b** (140 g, 0.59 mol) in THF (2000 mL) was added N-bromosuccinimide (200 g, 1.1 mol). The mixture was allowed to stir at room temperature under N_2 gas for about 15 hours. The solvent was then removed *in vacuo*, and the residue obtained was purified using silica-gel chromatography (ethyl acetate eluent) to provide 230 g of the desired dibromo Compound Int-**7e**. MS (ESI) m/e ($M+H^+$): 396.

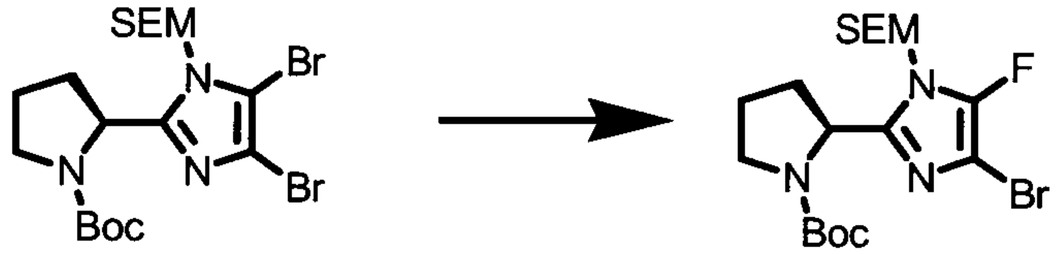


Int-7e **Int-7d**

To a suspension of **Int-7e** (230 g, 0.58 mol) in EtOH/H_2O (1:1 ratio, 3000 mL) was added Na_2SO_3 (733 g, 5.8 mol). The resulting mixture was allowed to stir at mild reflux for about 15 hours. After cooling to room temperature, the mixture was extracted with dichloromethane twice and the combined organic layer was concentrated

in vacuo to a semi-solid. The residue obtained was purified using chromatography on silica gel to provide the desired Compound Int-**7d**. MS (ESI) m/e ($M+H^+$): 317.

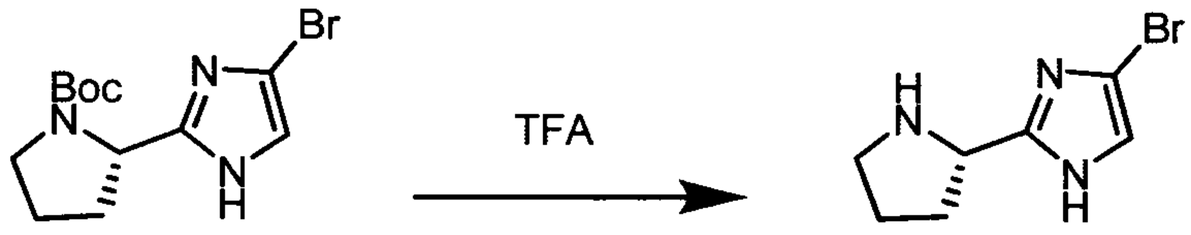
*Step E – Preparation of Compound **Int-7f***



Int-7e **Int-7f**

Compound **Int-7e** (2.63 g, 5.0 mmol) was dissolved in THF (30 mL) and cooled to – 78 °C, n-BuLi (1M in hexane, 2.2 mL, 5.5 mmol) was added and the reaction was allowed to stir for 20 minutes. N-fluorodibenzenesulfonamide (1.6 mL, 5.0 mmol) was added at -78 °C and the reaction mixture was allowed to warm slowly to room temperature again. The reaction was quenched with aq. NH_4Cl then partitioned between water and ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue obtained was purified using flash column chromatography (Gradient Ethyl acetate:petroleum ether from 0-20% Ethyl acetate) to provide Compound **Int-7f**. (63 % yield). MS (ESI) m/z $(M+H)^+$: 464, 466. ^{19} F NMR = -151.8 ppm .

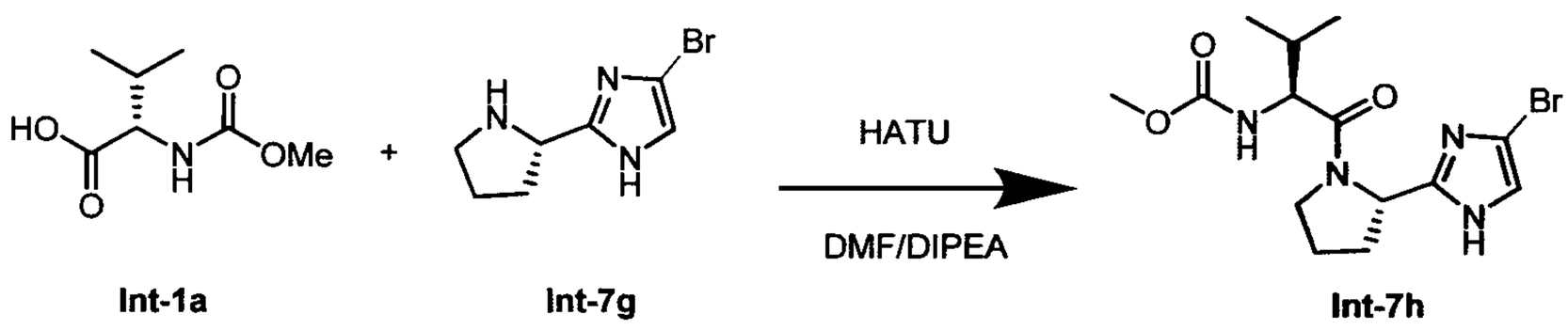
*Step F – Preparation of Compound **Int-7g***



Int-7d **Int-7g**

Intermediate **7d** (2.51 g, 7.94 mmol, 1.0 eq) was dissolved in 20 mL of CH_2Cl_2 and to the resulting solution was added trifluoroacetic acid (5 mL). The reaction mixture was allowed to stir for about 15 hours at room temperature under N_2, and the reaction was diluted with hexanes (15 mL) and concentrated *in vacuo* to provide a yellow oil. CH_2Cl_2 and toluene were added and the solution was re-concentrated *in vacuo*. This step was repeated until excess TFA was removed, giving a solid which was dried *in vacuo* for 1 hour to provide 3.5 g of solid **Int-7g**. MS (ESI) m/z $(M+H)^+$:217/ 218.1.

Step G – Preparation of Compound ***Int-7h***

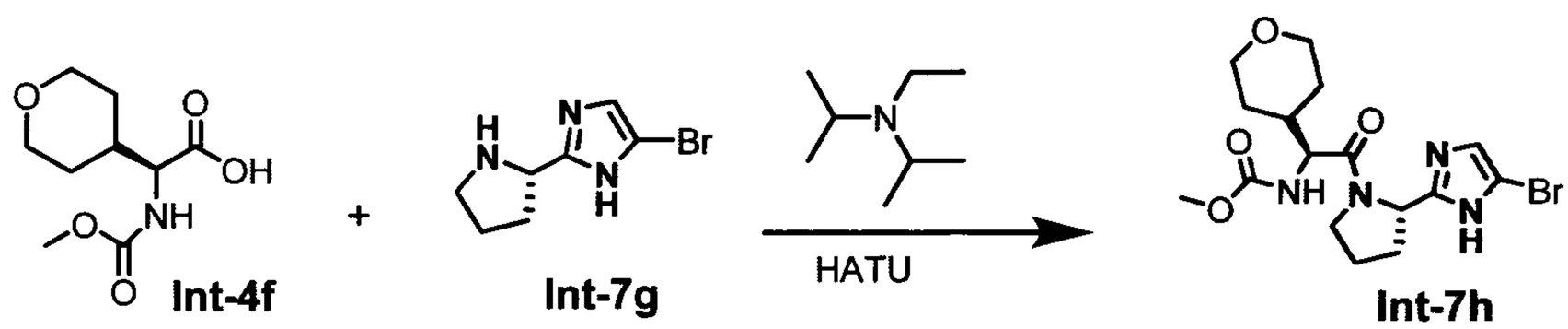


Int-1a **Int-7g** **Int-7h**

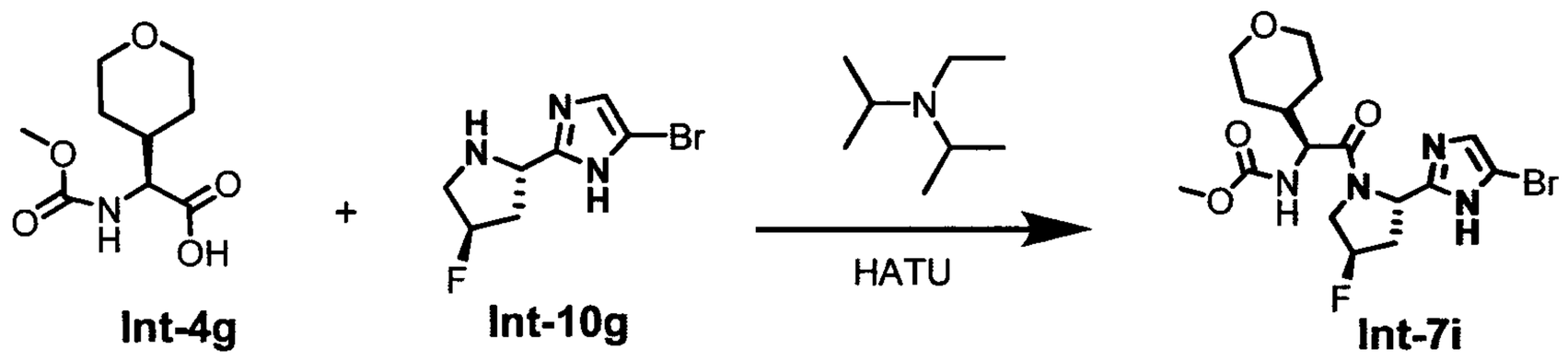
Int-7g (3.01g, 6.78 mmol, 1.0 eq) and **Int-1a** (1.202 g, 6.86 mmol, 1.01 eq) were added to a 250 mL round-bottomed flask equipped with a stir bar. DMF was added, and the flask was connected to a vacuum line. The flask was cycled between vacuum and N_2 twice, then cooled in an ice-methanol bath for 10 minutes. HATU (2.75 g, 7.23 mmol, 1.07 eq) was added, followed by diisopropylethyl amine (2.80 mL). The reaction mixture was allowed to stir at -15 °C for 20 minutes. Additional diisopropylethyl amine (2.0 mL) was added. The reaction mixture was allowed to stir for 40 minutes, then quenched with water (1.5 mL). The resulting solution was diluted with EtOAc (100 mL) and Et_2O (100 mL), then washed with water (6 x 15 mL) and brine (2 x 25 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* yielding 2.23 g of a clear oil. The residue obtained was purified via chromatography using an 80 g Isco Gold SiO_2 cartridge with a 0.5%-2.5% MeOH/ CH_2Cl_2 gradient as the mobile phase. The major peak was collected to provide 1.28 g **Int-7h** as a white foam. This material was further purified via sgc on an 80 g Isco Gold SiO_2 cartridge using a 45%-65% gradient of (5% methanol in EtOAc)/hexanes. Triethylamine 1% by volume was added to the MeOH/EtOAc solution. The fractions were assayed via TLC using Hanessian's stain. (See Example 13 below for more information on Hanessian's stain.) The major peak was collected as product to provide 1.18 g of **Int-7h** as a white foam. MS (ESI) m/z $(M+H)^+$:373.1.

EXAMPLE 7B

Preparation of Intermediate Compound **Int-7i**



N-Moc-(S)-tetrahydropyranyl glycine (**Int-4f)** (252 mg, 1.160 mmol), **Int-7g** (354 mg, 1.225 mmol), DMF (6 mL), and DIPEA (0.7 mL, 4.01 mmol) were added to a 40 mL screw cap vial equipped with a stir bar. The reaction mixture was placed under a blanket of N_2 and the vial was capped. The vial was cooled in an ice-methanol bath for 10 minutes. HATU (445 mg, 1.215 mmol) was added, and the reaction mixture was left stirring at -15 °C. After 3 hours, the bath temp was 10 °C. The reaction mixture was diluted with ethyl acetate and aqueous ammonium chloride. The layers were separated. The organic layer was washed with water and brine, gravity filtered, dried with $MgSO_4$, and filtered again. The solvent was evaporated under reduced pressure on the rotovap to provide a clear oil-(458 mg). The crude product was purified via flash silica gel column chromatography on an Isco 24 g SiO_2 Gold cartridge, using a $MeOH(NH_3)/CH_2Cl_2$ gradient (0-5%) as the mobile phase to provide **Int-7h** as a clear oil. Weight = 246 mg Took ^1H NMR and LC/MS. Obsd M+H = 415.1.



N-Moc (S)-tetrahydropyranyl glycine **Int-4f** (236 mg, 1.086 mmol) and **Int-10g** (333 mg, 1.085 mmol), DMF (5 mL), and DIPEA (0.6 mL, 3.44 mmol) were added to a 40 mL screw cap vial equipped with a stir bar. The reaction mixture was placed under a blanket of N_2 and the vial was capped. The vial was cooled in an ice-methanol bath for 15 minutes. HATU (418 mg, 1.141 mmol) was added, and the reaction mixture was left stirring at -15 °C. After 3h, the bath temp was 10 °C. The reaction mixture was diluted with ethyl acetate and water. The layers were separated. The organic

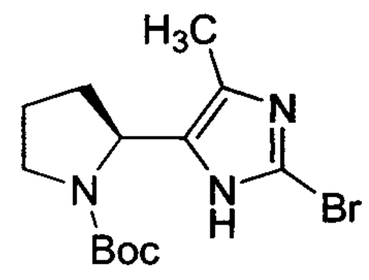
layer was washed with water and brine, gravity filtered, dried with $MgSO_4$, and filtered again. The solvent was evaporated under reduced pressure on the rotovap to provide a clear oil. The crude product was dissolved in methanol and left standing at room temperature over the weekend.

The reaction mixture was concentrated *in vacuo*. The crude product was purified via flash silica gel column chromatography on an Isco 40 g SiO_2 Gold cartridge. The column was initially eluted (mistakenly) with a 0%-50% EtOAc/hexanes gradient, then flushed with 5% (MeOH/(1%NH□(Aq.)))/CH_2Cl_2. The fractions were combined to provide 0.50 g of impure product as a clear oil.

The impure product was purified via flash silica gel column chromatography on an Isco 24 g SiO_2 Gold cartridge, using a 0%-5% MeOH/CH_2Cl_2 gradient as the mobile phase to provide **Int-7i** as a clear oil-(0.306g). When a sample was dissolved in deuterated methanol, a white solid formed in the flask. Took ^1H NMR and LC/MS. Obsd M+H = 433.1

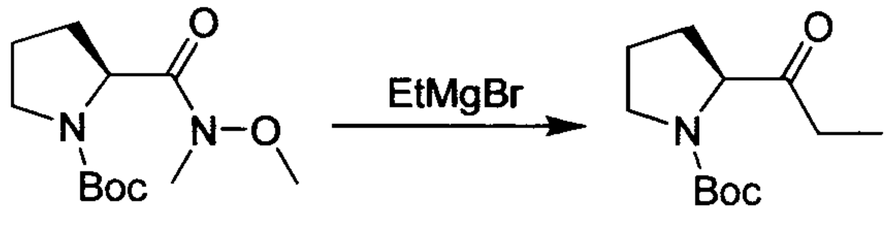
EXAMPLE 8

Preparation of Intermediate Compound **Int-8h**



Int-8h

*Step A – Preparation of Compound **Int-8b***

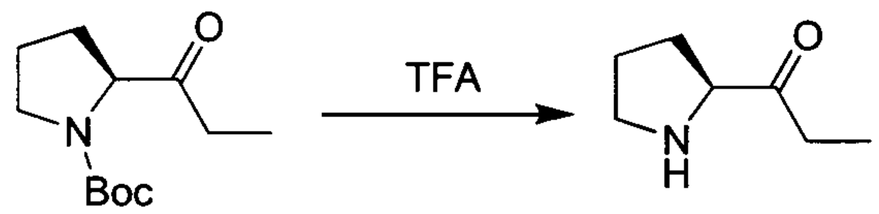


Int-8a **Int-8b**

A solution of **Int-8a** (11.0 g, 42.6 mmol) in THF (50 mL) was cooled to 0 °C and to the cooled solution was added EtMgBr (82 mmol). After addition was complete, the cooling bath was removed and the resulting reaction was allowed to stir at room temperature for 6 hours. 3 N HCl was then added and the reaction mixture was

extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water, brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue obtained was purified using flash column chromatography on silica gel to provide Compound **Int-8b** (7.5 g, 50% yield).

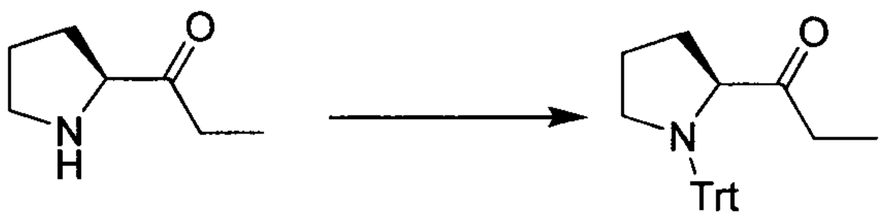
*Step B – Preparation of Compound **Int-8c***



Int-8b **Int-8c**

Int-8b (7.5 g, 21.3 mmol) was dissolved in 100 mL of dichloromethane and cooled to 0 °C. TFA (100 mL) was added and the reaction was allowed to stir to room temperature over 2h. The solvent was removed and the residue obtained was redissolved in EtOAc then washed with saturated bicarbonate solution then brine. The extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide Compound **Int-8c** as an oil, which was used without further purification.

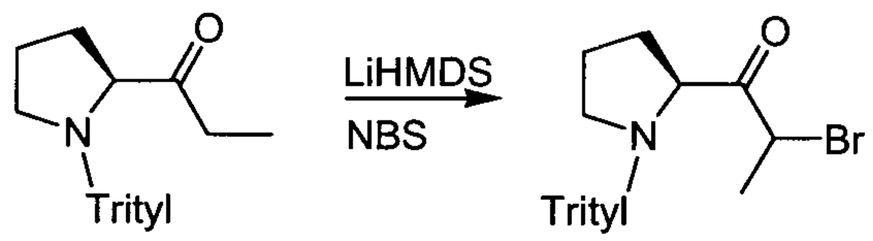
*Step C – Preparation of Compound **Int-8d***



Int-8c **Int-8d**

To a solution of Compound **Int-8c**(4.2 g, 33 mmol) in THF (30 mL) was added Et_3N (4.1 g, 49 mmol) and then trityl chloride (8.7 g, 40 mmol). The mixture was allowed to stir at room temperature for 2 hours, then concentrated *in vacuo*. The residue obtained was purified using flash chromatography on silica gel to provide Compound **Int-8d** (8.7 g, 71% yield). MS (ESI) m/z $(M+H)^+$: 370.

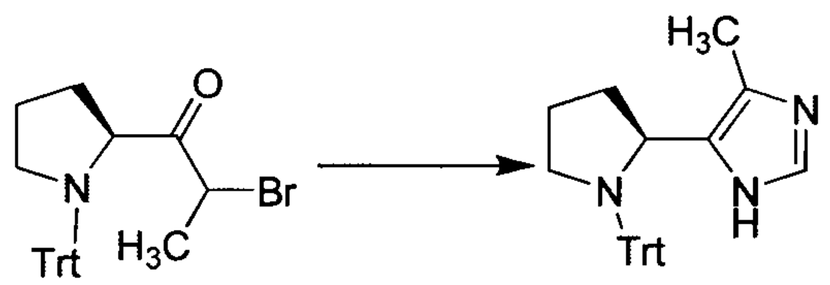
*Step D – Preparation of Compound **Int-8e***



Int-8d **Int-8e**

To a solution of Compound **Int-8d** (3.6 g, 10.0 mmol) in THF (30 mL) was added LiHMDS (11.0 mmol) and then NBS (1.8 g, 10 mmol) at 0 °C. The mixture was allowed to stir at room temperature for 2 hours and then 3 N HCl was added to the mixture and the resulting solution was extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were concentrated *in vacuo* and the residue obtained was purified using chromatography to provide Compound **Int-8e** (1.98 g, 44% yield). MS (ESI) m/z $(M+H)^+$: 478, 480.

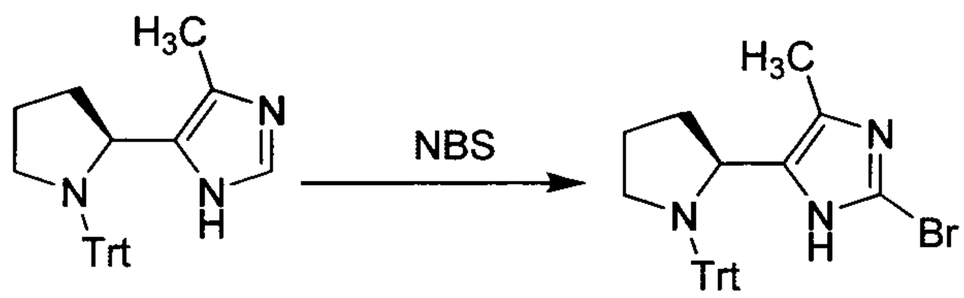
*Step E – Preparation of Compound **Int-8f***



Int-8e **Int-8f**

To a solution of Compound **Int-8e** (3.6 g, 10.0 mmol) in THF (30 mL) was added LiHMDS (11.0 mmol) and then NBS (1.8 g, 10 mmol). The mixture was allowed to stir at room temperature for 2 hours and then 3 N HCl was added to the mixture and extracted with ethyl acetate twice. The organic layer was concentrated *in vacuo*. The residue obtained was purified using chromatography to provide the **Int-8f** (1.98 g, 44% yield). MS (ESI) m/z $(M+H)^+$: 478, 480.

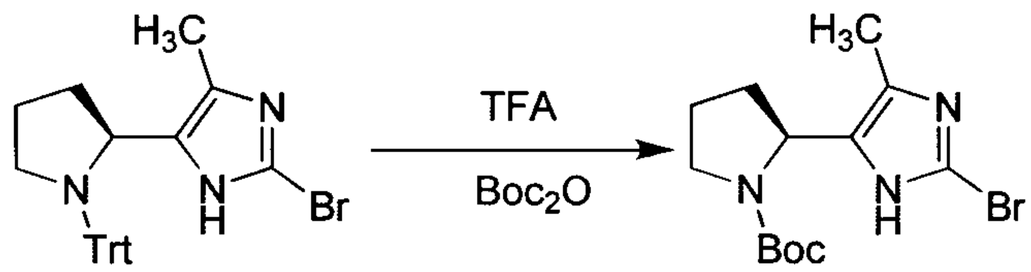
*Step F – Preparation of Compound **Int-8g***



Int-8f **Int-8g**

To a solution of Compound **Int-8f** (3.9 g, 10 mmol) in chloroform (30 mL) was added NBS (1.76 g, 10 mmol) and the mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was then concentrated *in vacuo* and the residue obtained was purified using flash chromatography to provide Compound **Int-8g** (2.2 g, 47% yield).

Step G – Preparation of Compound ***Int-8h***

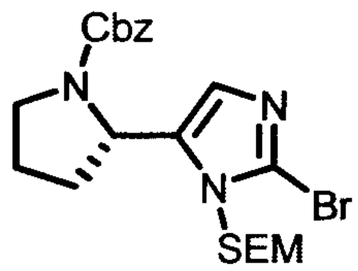


Int-8g **Int-8h**

To a solution of Compound **Int-8g** (1.28 g, 2.7 mmol) in dichloromethane (10 mL) was added TFA (10 mL) and the mixture was allowed to stir at room temperature for 2 hours. Then the mixture was concentrated *in vacuo* and used in the next reaction directly. The residue obtained was dissolved in THF (20 mL) and Et_3N (5 mL) and to the resulting solution was added BOC anhydride (590 mg, 2.7 mmol). The mixture was allowed to stir at room temperature for 2 hours and concentrated *in vacuo*. The residue obtained was purified using chromatography to provide Compound **Int-8h** (600 mg, 67% yield). MS (ESI) m/z $(M+H)^+$: 331.

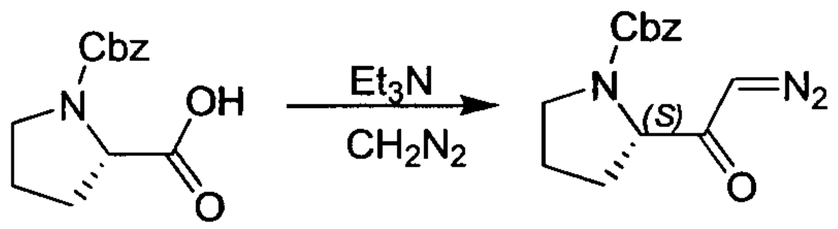
EXAMPLE 9

Preparation of Intermediate Compound **Int-9g**



Int-9g

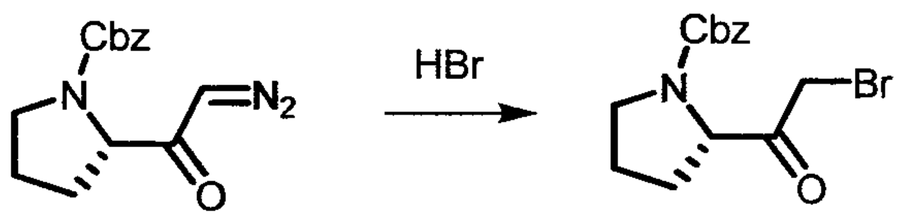
*Step A – Preparation of Compound **Int- 9b***



Int-9a **Int-9b**

To a solution of Compound **Int-9a** (50 g, 0.2 mol) in THF (500 mL) and Et_3N (20 mL) was added dropwise isopropyl chloroformate (25 g, 0.22 mol) at ice water bath. Then the resulting solution was allowed to warm to room temperature and allowed to stir for 1h. Then a solution of CH_2N_2 (0.22 mol) in ether was added slowly until no N_2 gas evolution was noted. Acetic acid (4 mL) was added and the reaction mixture was allowed to stir for 10 minutes. $NaHCO_3$ solution was then added and the reaction mixture extracted three times with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to provide crude product. The crude product was then purified using column chromatography on silica gel (Pet Ether: Ethyl.Acetate = 3:1) to provide Compound **Int-9b** (38 g, 70% yield)

*Step B – Preparation of Compound **Int-9c***

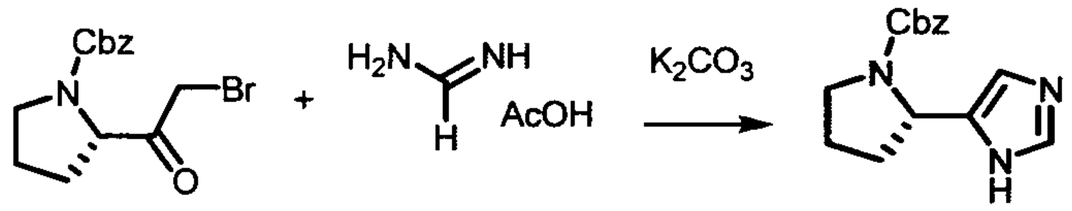


Int-9b **Int-9c**

To a solution of **Int-9b** (38 g, 0.14 mol) in HOAc (20 mL) was added dropwise an aqueous HBr solution (11.2 g, 0.14 mol). After 10 minutes, the mixture was

poured into an aqueous $NaHCO_3$ solution and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, water, dried over Na_2SO_4 and concentrated *in vacuo* to provide the product **Int-9c** (30 g, **68%** yield).

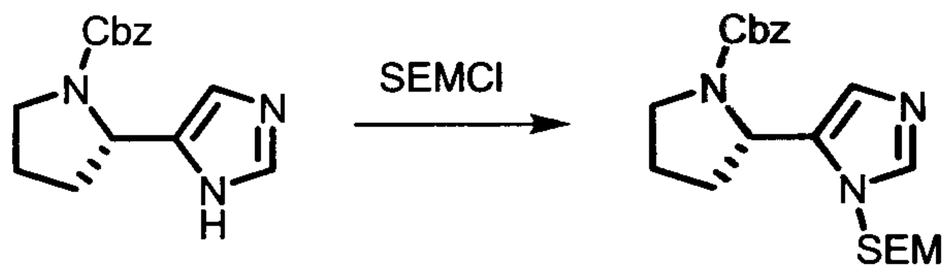
Step C – Preparation of Compound ***Int-9e***



Int-9c **9d** **Int-9e**

To a solution of **Int-9c** (10 g, 32 mmol) and Compound **9d** (8.4 g, 64 mmol) in DMF (70 mL) was added K_2CO_3 (18 g, 126 mmol). The mixture was allowed to stir at 100 °C in a sealed tube for about 15 hours. The solvent was removed and the residue obtained was purified using column chromatography on silica gel (dichloromethane: MeOH = 20:1) to provide the product **Int-9e**. (6 g, 59% yield).

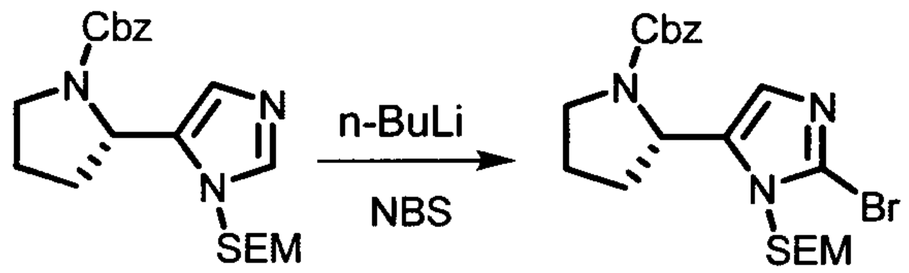
Step D – Preparation of Compound ***Int-9f***



Int-9e **Int-9f**

To a solution **Int-9e** (4 g, 14.7 mmol) in THF (40 mL) was added NaH (6.6 g, 60 % content, 16.17 mmol) at 0 °C. The mixture was allowed to stir at room temperature for 30 minutes. and then cooled to 0 °C, and SEM-Cl (2.4 g, 14.7 mmol) added dropwise. The resulting mixture was allowed to stir at 0 °C for 2 hours. The solvent was removed *in vacuo* and the residue obtained was purified using column chromatography on silica gel (dichloromethane: MeOH =20:1) to provide the product **Int-9f**. (2 g, 34 % yield).

Step E – Preparation of Compound ***Int-9g***

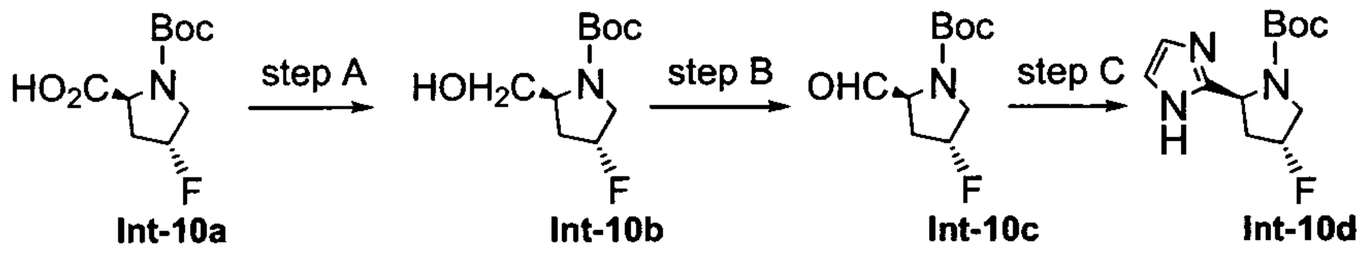


Int-9f **Int-9g**

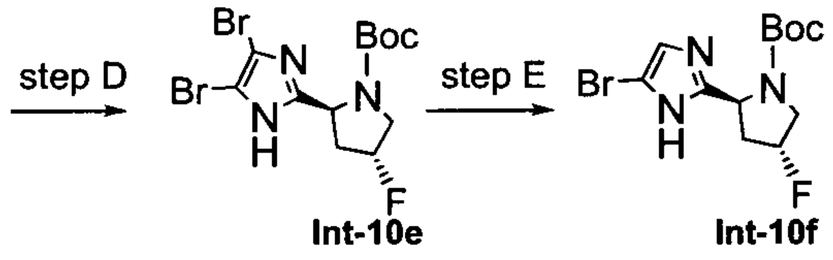
To a solution of **Int-9f** (2 g, 5 mmol) in THF (20 mL) was added dropwise n-BuLi (2.5 mL, 6.3 mmol) at -78 °C (bath) under N_2 protection. The resulting solution was allowed to stir at this temperature for 30 minutes. Then a solution of NBS (0.89 g, 5 mmol) in THF (10 mL) was added dropwise at -78 °C. The mixture was allowed to stir at -78 °C for 1 hour and then aqueous NH_4Cl solution was added. The organic layer was separated and concentrated off to provide a crude residue, which was purified using column chromatography on silica gel (petroleum ether :EA=3:1 as the eluent) to provide Compound **Int-9g** (400 mg, 16.5% yield).

EXAMPLE 10

Preparation of Intermediate Compound **Int-10f**



Int-10a **Int-10b** **Int-10c** **Int-10d**



Int-10e **Int-10f**

*Step A – Preparation of Compound **Int-10b***

(2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (**Int-10a**, 20 g, 85.75 mmol) was dissolved in anhydrous THF and cooled to 0 °C. BH_3·THF (1M in THF, 171 mL, 171 mmol) was added via an addition funnel. The

solution was gradually warmed up to room temperature and allowed to stir at room temperature for about 15 hours. MeOH was added until no bubbles came out. The solution was concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (330g, 0% to 60% of EtOAc in Hexane) to provide Compound **Int-10b** (15.1 g, 80.3%)

*Step B – Preparation of Compound **Int-10c***

To a dry 1000 mL round bottom flask was added oxalyl chloride (7.50 mL, 88.9 mmol) and dry dichloromethane (250 mL). After the solution was cooled to -78 °C, DMSO (6.80 mL, 95.8 mmol) in dichloromethane (20 mL) was added dropwise. The solution was allowed to stir at -78 °C for 30 minutes. **Int**-10b (15.0 g, 68.4 mmol) in dichloromethane (50 mL) was added via syringe. After the solution was allowed to stir at – 78 °C for 30 minutes, TEA (38.1 mL, 273.6 mmol) was added. The solution was allowed to stir at -78 °C for 30 minutes and at 0 °C for one hour. The solution was diluted with dichloromethane (300 mL) and washed with water, 1N HCl, sat $NaHCO_3$, and brine. It was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was dried *in vacuo* for 1 hour to provide Compound **Int-10c** which was used without further purification.

*Step C – Preparation of Compound **Int-10d***

To a 1000 mL round bottom flask was added **Int-10c** and NH_3 (7N in MeOH, 150 mL). Glyoxal (15 mL, 40% in water, 131 mmol) was added slowly. The solution was allowed to stir at room temperature for about 15 hours. Additional glyoxal (5 mL, 44 mmol) was added and the reaction was allowed to stir at room temperature for another 24 hours. The solution was concentrated *in vacuo* and the residue obtained was purified using flash column chromatography on silica gel (240g, 0% to 5% of MeOH in dichloromethane, with 0.1% $NH_3 \cdot H_2O$) to provide Compound **Int-10d** (8.5 g, 48.7% from **2**)

*Step D – Preparation of Compound **Int-10e***

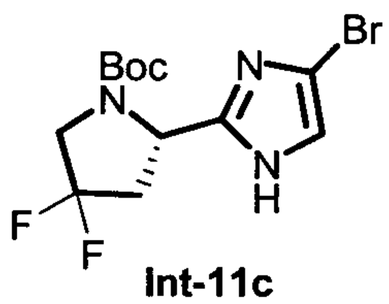
To a 100 mL round bottom flask was added **Int-10d** (8.5 g, 33.3 mmol) and CH3CN (250 mL). More CH_3CN was added to form a clear solution. NBS (11.3 g, 63.3 mmol) was added in one portion and the solution was allowed to stir at room temperature for about 15 hours. CH_3CN was removed *in vacuo* and dichloromethane (50 mL) was added with stirring. The solid was filtered and washed with dichloromethane twice. The filtrate was concentrated *in vacuo* to about 30 mL and filtered again. The filtrate was purified using flash column chromatography on silica gel (120g, 20% to 80% of EtOAc in Hexane) to provide Compound **Int-10e** (11.88 g, 86.4%).

*Step E – Preparation of Compound **Int-10f***

To a 1000 mL round bottom flask was added **Int-10d** (11.88 g, 28.76 mmol), sodium sulfite (Na_2SO_3, 36.0 g, 288 mmol), EtOH (270 mL) and water (130 mL). The solution was allowed to stir at reflux for about 15 hours. More Na_2SO_3 (10 g, 79 mmol) was added and the solution was allowed to stir at reflux for another 24 hours. After cooling down, the solid was filtered and washed with EtOAc three times. The filtrate was concentrated *in vacuo* and the residue obtained was dissolved in a mixture of EtOAc (300 mL) and water (200 mL). The organic layer was separated and washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue obtained was purified using flash column chromatography on silica gel (240g, 0% to 33% of EtOAc in Hexane) to provide Compound **Int-10f** (5.12 g, 53.3%).

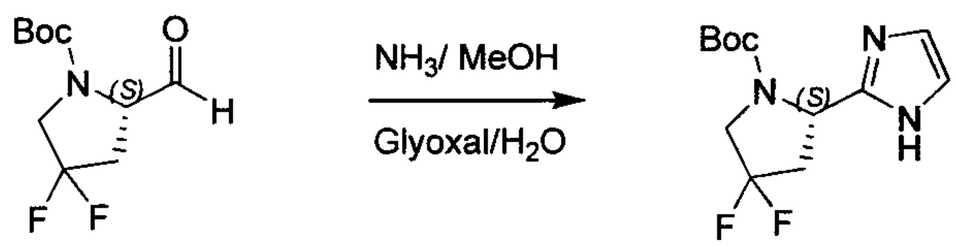
EXAMPLE 11

Preparation of Intermediate Compound **Int-11c**



Int-11c

*Step A – Preparation of Compound **Int-11b***

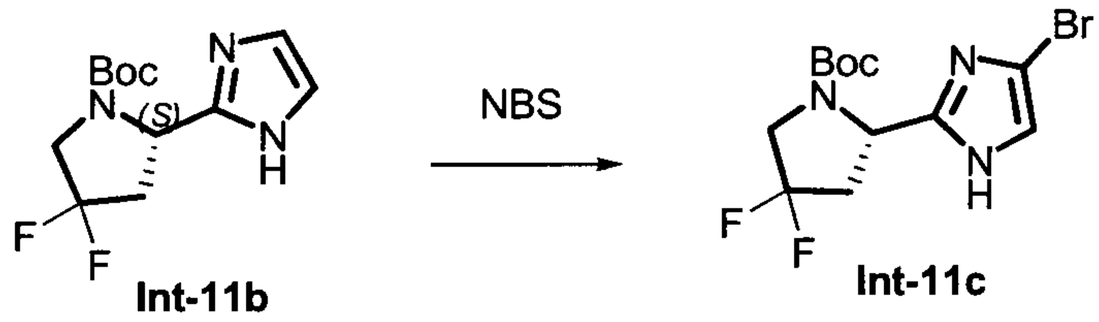


Int-11a **Int-11b**

The aldehyde **Int-11a** was prepared from the commercially available alcohol using the method described in Example 10.

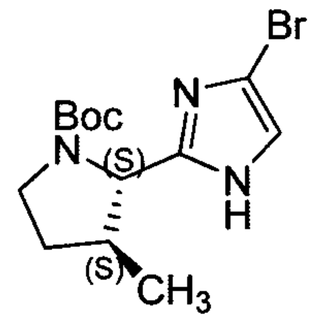
A flask was charged with aldehyde **Int-11a** (82g, 0.35 mol) and a 2.33 N ammonia/MeOH solution was added with good stirring (600 mL, 4.0 eq., prepared from 200ml 7N ammonia/MeOH diluted with 400 mL MeOH). The reaction was then heated to 35 °C and allowed to stir at this temperature for 2 hours, after which time a solution of 40 wt% glyoxal in water (80 mL, 2.0 eq.) was added dropwise over about 15 minutes. After stirring for an additional 2 hours, a solution of 7N ammonia/MeOH (100 mL, 2.0 eq.) was added and the reaction was allowed to stir at 35 °C for 1 hour. Additional glyoxal (40 mL, 1.0 eq.) was then added dropwise over 5 minutes and the resulting reaction was allowed to stir at 35 °C for 1 hour. The reaction mixture was then allowed to cool room temperature and stir for about 15 hours. Additional 7N ammonia/MeOH (50 mL, 1.0 eq.) was then added and the reaction reheated to 35 °C and allowed to stir at this temperature for 1 hour. An additional amount of glyoxal (20 mL, 0.5 eq.) was then added and the resulting reaction was allowed to stir at 35 °C for 1 hour, then the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* and the residue obtained was diluted with dichloromethane and water (2 L, 1:1). The organic layer was separated, washed with 1L of water, then brine and dried ($MgSO_4$), filtered and concentrated *in vacuo*. The brown foam residue obtained was further purified using being passed through a short silica gel column to provide Compound **Int-11b** (60g, 62%).

Step B – Preparation of Compound ***Int-11c***

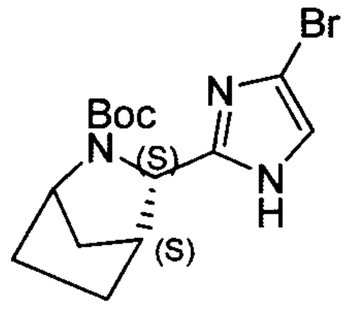


Int-11c was prepared from **Int-11b** using the method described in Example 10.

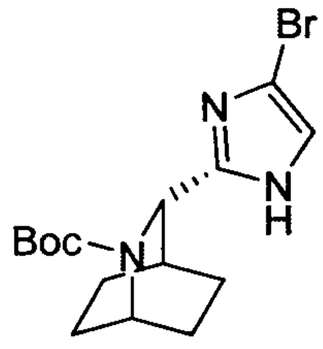
Intermediate Compounds **Int-11d**, **Int-11e** and **Int-11f** can be prepared using the methods described in Example 10 and Example 11.



Int-11d



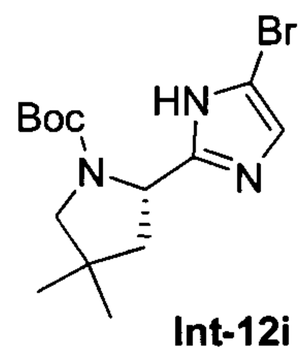
Int-11e



Int-11f

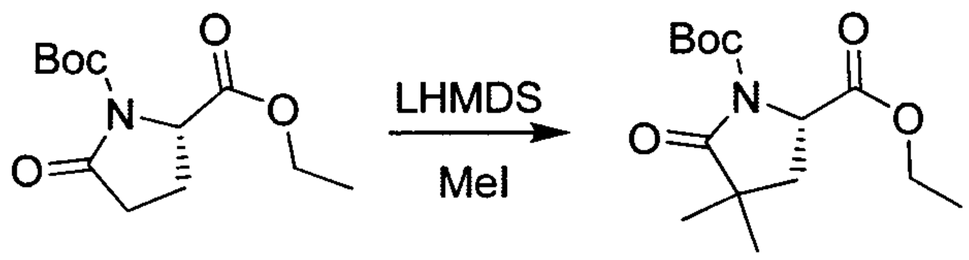
EXAMPLE 12

Preparation of Intermediate Compound **Int-12i**



Int-12i

*Step A – Preparation of Compound **Int-12b***

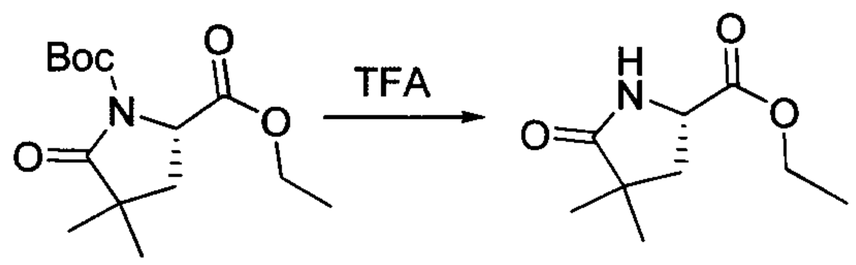


Int-12a **Int-12b**

To a solution of Compound **Int-12a** (60 g, 0.24 mol) in dry THF (1 L) allowed to stir at -78 °C was added lithium hexamethyldisilazide (82 g, 0.49 mol, 1 M in THF). After the reaction mixture had been allowed to stir at -78 °C for 1 hour, the iodomethane (66 g, 0.46 mol) dissolved in dry THF (100 mL) was added at -78 °C and the

mixture was allowed to stir for 15 minutes at this temperature and 2 hours at 25 °C. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with dichloromethane (3 x 300 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The products were purified using flash column chromatography on silica gel to provide Compound **Int-12b** (18.3 g, 27% yield). ^1H NMR δ: 4.38-4.34 (m, 1 H), 4.08-4.05 (m, 2 H), 2.09-2.03 (m, 1 H), 1.77-1.73 (m, 1 H), 1.35 (s, 9 H), 1.12 (t, J = 8 Hz, 3 H), 1.06 (s, 6 H).

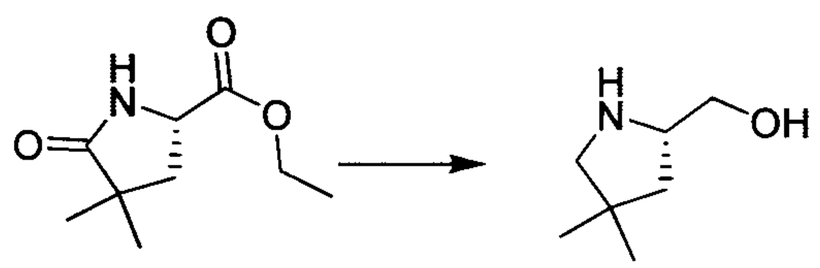
*Step B – Preparation of Compound **Int-12c***



Int-12b **Int-12c**

To a solution of Compound **Int-12b** (18.3 g, 60 mmol) in dichloromethane (150 mL) was added TFA (15 mL) and the mixture allowed to stir at room temperature for 30 minutes. The solvent was removed to provide Compound **Int-12c** (11.2 g, 100% yield).

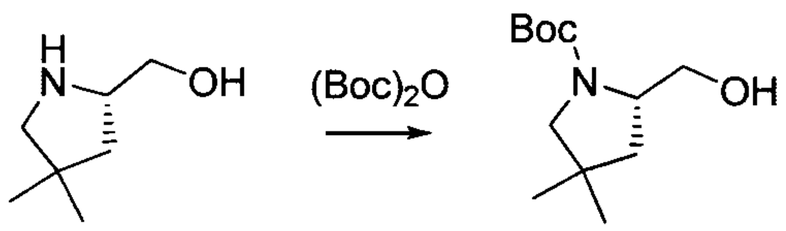
*Step C – Preparation of Compound **Int-12d***



Int-12c **Int-12d**

A suspension of $LiAlH_4$ (16.2 g, 0.44 mol) and Compound **Int-12c** (11.2 g, 54.8 mmol) in THF (200 mL) was allowed to stir under reflux for 8 hours. After successive addition of 17 mL of water, 17 mL of 10% aq NaOH, and 51 mL of water, and filtration, the filtrate was concentrated *in vacuo* to provide Compound **Int-12d** (6.7 g, 94% yield).

*Step D – Preparation of Compound **Int-12e***



Int-12d **Int-12e**

Compound **Int-12D** was dissolved in THF and Et_3N, $(Boc)_2O$ were added. The mixture was allowed to stir at room temperature for 2 hours and concentrated *in vacuo*. The residue obtained was purified using chromatography to provide Compound **Int-12e** (14 g, 100% yield).

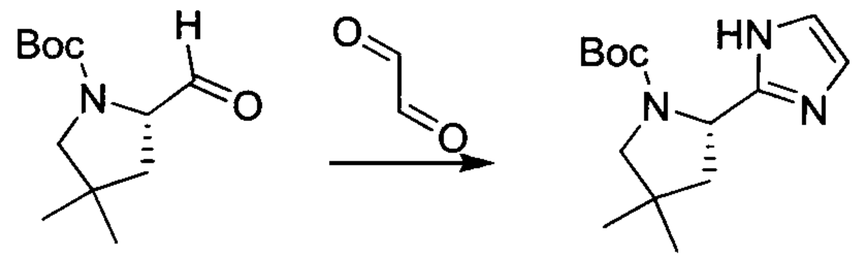
Step E – Preparation of Compound ***Int-12f***



Int-12e **Int-12f**

To a solution of Compound **Int-12e** (14g, 65.4 mmol) in dichloromethane was added Dess-Martin reagent (41.6 g, 98.1 mol). After stirring at room temperature for about 15 hours, the solvent was removed and the residue obtained was purified using flash column chromatography on silica gel to provide Compound **Int-12f** (7 g, 47% yield). ^1H NMR δ: 9.40 (s, 1 H), 4.05-4.03 (m, 1 H), 3.14-3.11 (m, 2 H), 1.83-1.79 (m, 1 H), 1.66-1.63 (m, 1 H), 1.36 (s, 9 H), 1.02 (s, 6 H).

Step F – Preparation of Compound ***Int-12g***

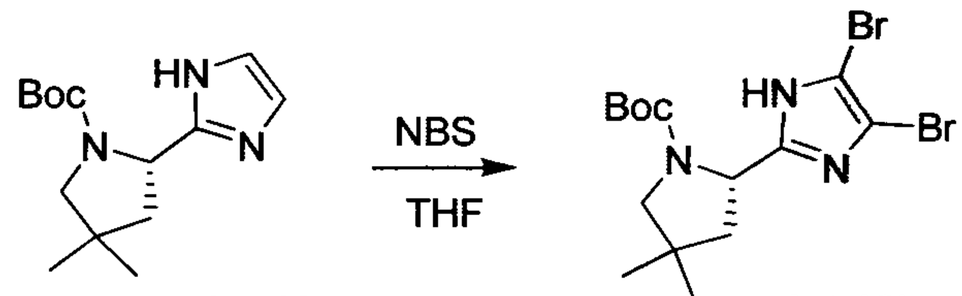


Int-12f **Int-12g**

Glyoxal (1.75 mL of 40% in water) was added dropwise over 11 minutes to a solution of NH_4OH (26 mL) and Compound **Int-12f** (6.1 g, 28.8 mmol) in methanol

and allowed to stir at room temperature for 19 hours. The volatile component was removed *in vacuo* and the residue obtained was purified using a flash chromatography on silica gel to provide Compound **Int-12g** (3 g, 39% yield).
MS (ESI) m/z $(M+H)^+$: 266.

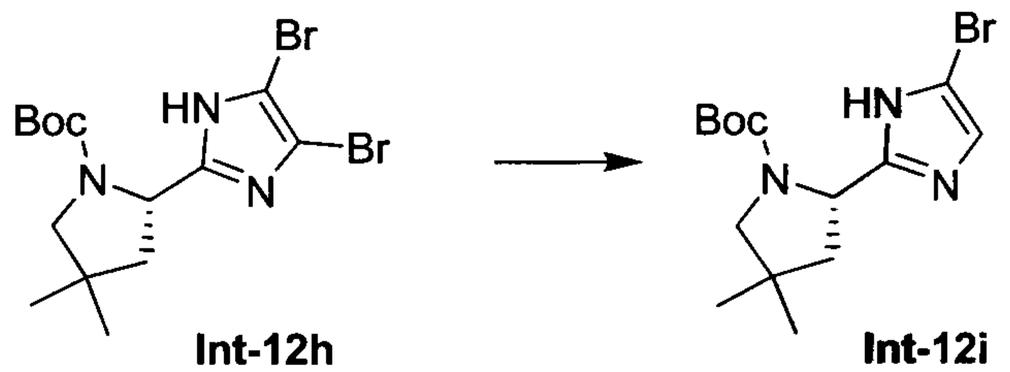
Step G – Preparation of Compound ***Int-12h***



Int-12g **Int-12h**

A mixture of Compound **Int-12g** (2.2 g, 8.3 mmol), N-bromosuccinimide (2.66 g, 14.9 mmol) in anhydrous THF (80 mL) was heated at reflux for about 15 hours. After cooling to room temperature, the solids are removed by filtration and the filtrate was concentrated *in vacuo* and the residue obtained was purified using chromatography to provide Compound **Int-12h** (2.0 g, 57% yield). ^{1}H NMR (**J000120117 H10170-003-1** $CDCl_3$ varian 400 MHz) δ: 11.03 (s, 1 H), 4.79 (t, J = 8 Hz, 1 H), 3.25 (t, J = 12 Hz, 1 H), 2.96 (t, J = 12 Hz, 1 H), 2.58-2.53 (m, 1 H), 2.95-1.90 (m, 1 H), 1.34 (s, 9 H), 1.05 (s, 3 H), 0.99 (s, 3 H). **MS (ESI)** m/z $(M+H)^+$: 422.

Step H – Preparation of Compound ***Int-12i***



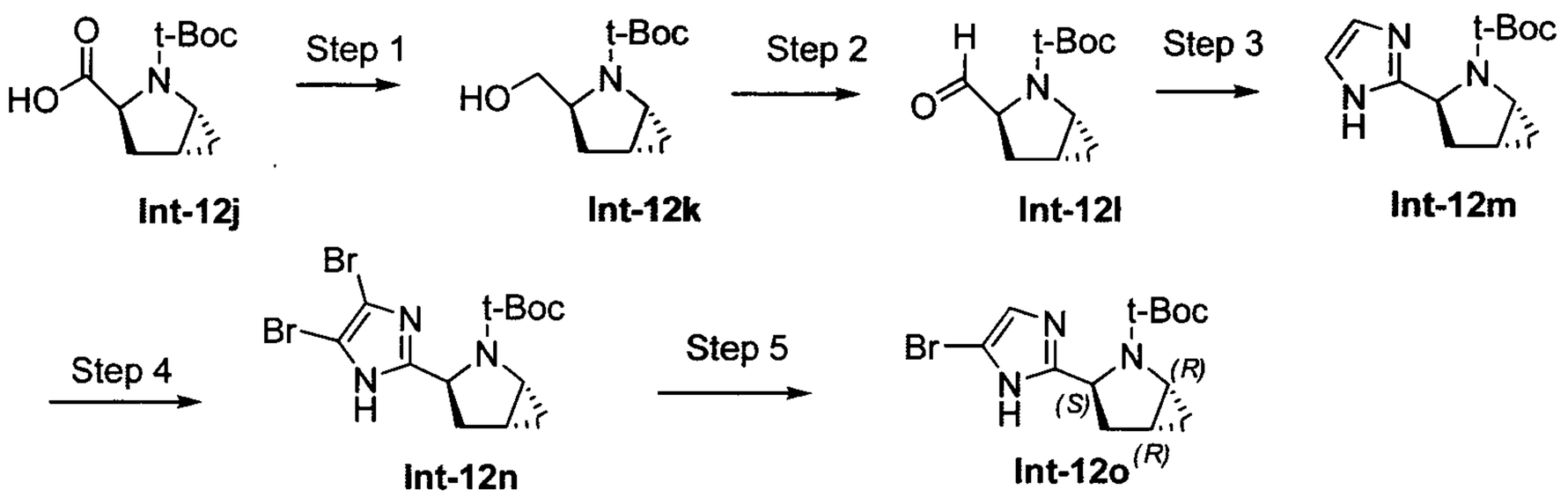
Int-12h **Int-12i**

To a solution of Compound **Int-12h** (1.9 g, 4.5 mmol) in H_2O/EtOH (40 mL /20 mL) was added Na_2SO_3 (5.6 g, 4.5 mmol) and the mixture was allowed to stir at room temperature for about 15 hours. The reaction mixture was concentrated *in vacuo* and the residue obtained was dissolved in ethyl acetate, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue obtained was purified using

chromatography on silica gel to provide Compound **Int-12i** (0.75 g, **48% yield**). ^{1}H NMR δ: 6.92 (s, 1 H), 4.71-4.67 (m, 1 H), 3.26-3.21 (m, 2 H), 2.01-1.96 (m, 1 H), 1.78-1.72 (m, 1 H), 1.13 (s, 9 H), 1.00 (s, 3 H).

EXAMPLE 12A

Preparation of Intermediate Compound **Int-12o**



Step A

Acid **Int-12j** (22.7 g, 100 mmol) was dissolved in dry THF (400 ml) in a 1000 mL flask, and cooled with an ice-water bath. Borane tetrahydrofuran complex (1.0 M in THF, 200 ml, 200 mmol) was added via an additional funnel dropwise over a period of 80 minutes. After 1 hour at 0 °C the reaction was allowed to warm to room temperature and stir for about 15 hours. Methanol was then added dropwise via an additional funnel (~100 ml) and then the reaction was then concentrated *in vacuo*. The residue was purified on a 300 g ISCO silica column/ Combi-Flash Rf system using a gradient of 0-70% ethyl acetate in hexanes to provide alcohol **Int-12k** as a colorless oil (18.2 g, 85%).

Step B

Oxalyl chloride (14.08 g, 111 mmol) was dissolved in methylene chloride (340 ml) in a 1000 mL flask and cooled to -78 °C under nitrogen atmosphere. DMSO (9.33 g, 119 mmol) was added slowly via syringe over a period of 10 minutes. The resulting solution was allowed to stir at -78 °C for 45 minutes prior to the slow addition of the alcohol **Int-12k** (15.2 g, 85 mmol) in methylene chloride (50 ml) and stirred at -

78 °C under nitrogen for 45 minutes before addition of triethylamine (34.5 g, 341 mmol). After 40 minutes at -78 °C, then reaction was warmed to 0 °C and stirred at 0 °C for an additional 1 hour. After addition of 500 mL of methylene chloride, the organic solution was washed with water, 1N HCl solution (300 ml), and water. The organic layer was dried over sodium sulfate, concentrated *in vacuo* to provide aldehyde **Int-12l** as a colorless oil (18.14 g, ~100%). This crude product was used for the next reaction without purification.

Step C

The aldehyde **Int-12l** (18.14 g, 86 mmol) was dissolved in methanol (37 ml) and the resulting solution was cooled with a RT water bath. A 7N ammonia solution in methanol (31.9 ml, 223 mmol) was then added dropwise via an additional funnel over a period of 15 minutes. The reaction mixture was allowed to stir at room temperature for 20 minutes before a 40% aqueous solution of glyoxal (16.2 g, 112 mmol) was added. The reaction mixture was allowed to stir at room temperature for about 15 hours and then concentrated *in vacuo*. The residue was purified using a 220 g ISCO silica column/Combi-Flash Rf system (0-7% methanol in dichloromethane eluent) to provide Compound **Int-12m** as a slightly yellow solid (10.8 g, 51.5%).

Step D

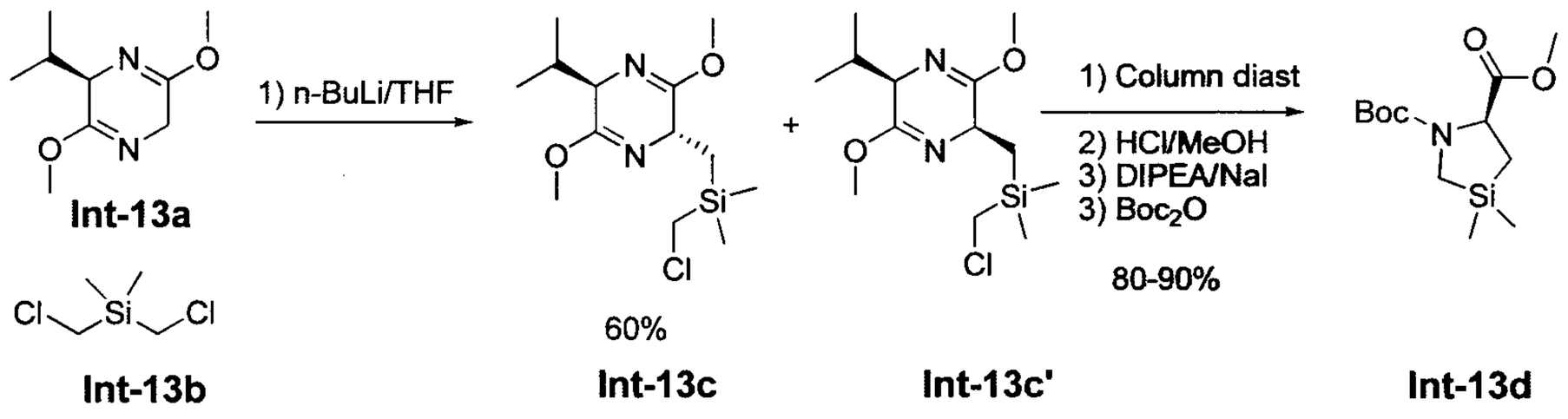
Intermediate **Int-12m** (10.81 g, 43.4 mmol) was dissolved in THF (200 ml) in a 250 mL flask and NBS (15.43 g, 87 mmol) was added slowly at room temperature. The resulting solution was allowed to stir at room temperature for 4.5 hours and concentrated to semi-solid. The residue was dissolved in ethyl acetate (300 ml), washed with brine (3X100 ml), dried over sodium sulfate, and concentrated *in vacuo*. The crude material was purified using crystallization from dichloromethane to provide Compound **Int-12n** as a white solid (7.68 g, 43.5%). The mixture from mother liquid was purified using a 220 g ISCO silica column/Combi-Flash Rf system using 0-70% ethyl acetate in hexanes as the eluent to provide a second batch of **Int-12n** as a pale solid (7.73g, 43.8).

Step E

Intermediate **Int-12n** (14.4 g, 35.4 mmol) was dissolved in methanol (45 ml) and water (16 ml) and placed in a water bath. EDTA (10.34 g, 35.3 mmol) followed by 7N ammonia in methanol (20.21 ml, 141 mmol) were then added. Zinc powder (2.314 g, 45.4 mmol) was then added and the resulting solution was allowed to stir at room temperature. After 6 hours the reaction was then concentrated and the residue was redissolved with ethyl acetate (100 ml), washed with water (2x50 ml), dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified on a 80 g silica column with a Combi-Flash Rf system using a gradient of 0-70% ethyl acetate in hexanes to provide **Int-12o** as a white solid (7.56 g, 65%).

EXAMPLE 13

Preparation of Intermediate Compounds **Int-13d and Int-13e**



Step A – Preparation of Compound ***Int – 13c***

A 5 L- 3 necked round bottomed flask, equipped with a mechanical stirrer, temperature probe, addition funnel and N_2 inlet, was charged with the Schollkopf chiral auxiliary-(**Int-13a**, 200 g, 1.09 mol, 1.0 eq), bis(chloromethyl) dimethylsilane (**Int-13b**, 256 g, 1.63 mol, 1.5 eq), and THF (2 L, Aldrich anhydrous). The flask was cooled in a dry ice/ 2-propanol bath until the internal temperature reached -75 °C. n-Butyllithium (Aldrich 2.5 M in hexanes , 478 mL, 1.19 mol, 1.09 eq) was added via a dropping funnel over 1 hour while maintaining the internal reaction temperature between -67 °C and -76 °C. The resulting orange-red solution was allowed to gradually warm to room temperature for about 15 hours. The reaction mixture was then re-cooled to 0 °C and quenched with 500 mL of water. Diethyl ether (2L) was added and the layers were

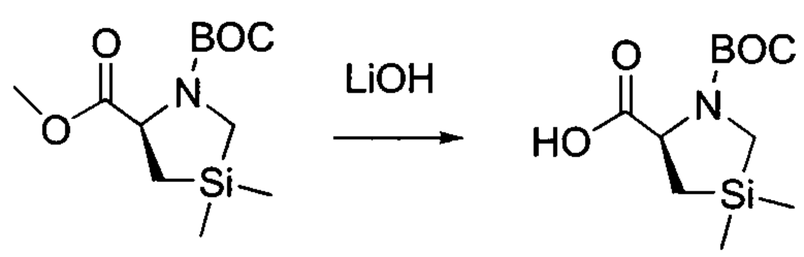
separated. The aqueous layer was extracted with 1 L of diethyl ether. The combined organic extracts was washed with water and brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*, giving 480 g of orange oil. This material was left *in vacuo* for about 15 hours to provide 420 g of oil. The crude product was split into two batches and purified via silica gel chromatography on a 1.6 kg flash column. The column was eluted with gradient of 0-4% Et_2O in hexanes. The product fractions were concentrated *in vacuo* at a bath temperature at or below 40 °C giving 190 grams of **Int-13c**-(60%yield).

*Step B – Preparation of Compound **Int-13d***

A 5 L, 3-necked round bottomed flask equipped with a mechanical stirrer, addition funnel, temperature probe, external water bath and N_2 inlet was charged with Compound **Int-13c** (196 g, 0.643 mol, 1.0 eq) and methanol (1.5 L). Aqueous HCl (500 mL of 10% by volume) was added at room temperature over 30 minutes, with a mild exotherm observed. The temperature increased to 37 °C then dropped back down. The reaction mixture was allowed to stir at room temperature for 3 hours and was monitored by TLC and LC/MS. The reaction mixture was then concentrated *in vacuo* to an oil. Additional methanol (3 x 200 mL) was added and the reaction mixture was concentrated *in vacuo* again. The resulting crude product was dried under house vacuum for about 15 hours. The crude product was then dissolved in CH_2Cl_2 (750 mL) and Et_2O (1250 mL) and sodium iodide (96.4 g, 0.643 mol, 1.0 eq) was added. Diisopropylethylamine (336 mL, 1.929 mol, 3.0 eq) was added slowly over 25 minutes with stirring, causing the temperature to increase to 35 °C then decrease to room temperature again. The reaction mixture was allowed to stir at room temperature for 2 hours, after which time the MS of an aliquot indicated consumption of the starting material. The reaction mixture was allowed to stir for an additional 2 hours and then Boc-anhydride (281 g, 1.286 mol, 2.0 eq) was added. The reaction mixture was then allowed to stir at room temperature. After two days, the reaction mixture was diluted with EtOAc (2 L) and water (1 L), and he layers were separated. The aqueous phase was extracted with 500 mL of EtOAc. The combined organic extracts were washed with water (500 mL) and brine (500 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo* to a yellow oil (380 g). The crude product was split into two 180 g portions for convenience and each portion was purified

via flash silica gel chromatography. Column conditions for a 180 g portion of crude product are as follows. The 180 gram sample of crude product was loaded onto a 191 g SiO_2 cartridge and purified on a 1.5 kg SiO_2 column. The column was eluted using a 0%-20% EtOAc/hexanes gradient as the mobile phase to provide 52 grams of pure **Int-13d** and additional fractions of **Int-13d** that contained a small amount of a Boc-valine impurity. The impure fractions from the two columns were recombined and re-purified. After chromatography, Compound **Int-13d** was obtained as an oil which solidified to a white solid on standing (128 g, 65 % yield over the three steps.)

Step C – Preparation of Compound ***Int-13e***



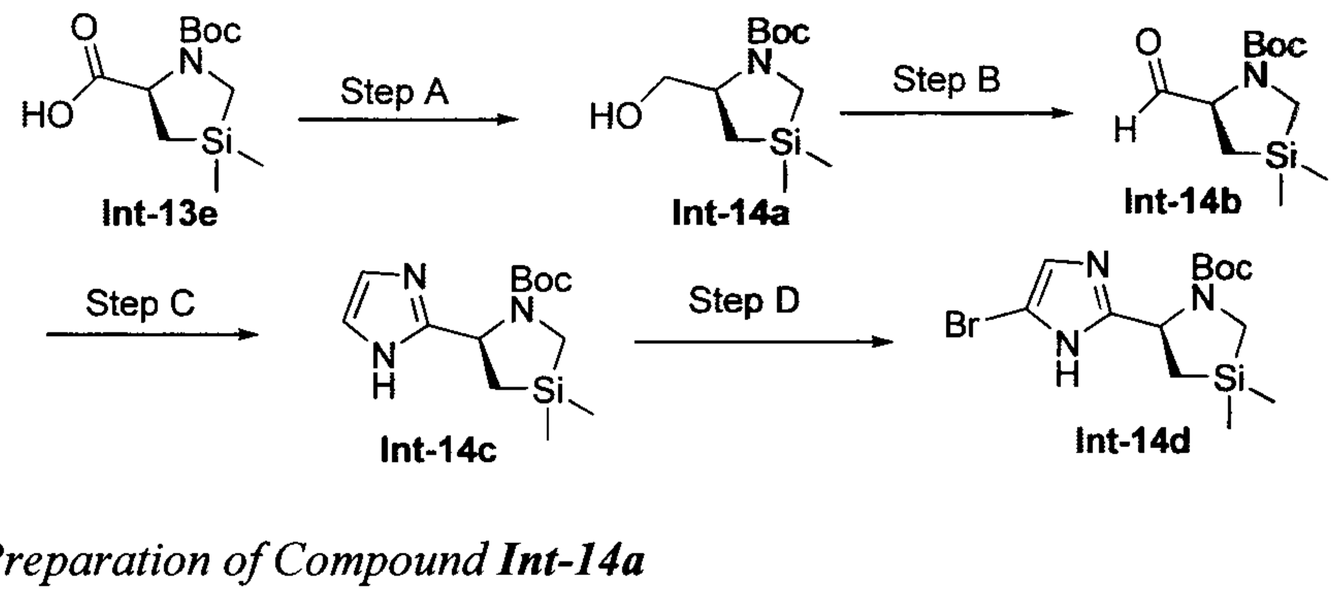
Int-13d **Int-13e**

A solution of **Int-13d** (8.5 g, 31.1 mmol) in methanol (100 mL) and 1.0 M aqueous KOH solution (48 mL, 48 mmol) was allowed to stir at room temperature for about 15 hours. The reaction was then neutralized with 48 mL of 1.0 M aqueous HCl solution to pH ~5, and partially concentrated *in vacuo*. The aqueous layer was then extracted twice with dichloromethane (2 x 100 mL). The combined organic solutions were concentrated *in vacuo* to provide Compound **Int-13e** as a gel (7.74 g, 96%).

Note: The above reactions were monitored by TLC using Hanessian's stain. To prepare the visualization stain, combine 450 mL of H_20, 25 g ammonium molybdate, 5 g of ceric sulfate, and 50 mL of conc. HCl or conc. H_2SO_4.

EXAMPLE 14

Preparation of Intermediate Compound **Int-14d**



*Step A – Preparation of Compound **Int-14a***

To a mixture of carboxylic acid **Int-13e** (20 g, 77 mmol) in THF (400 mL) at 0 °C was added 1M BH_3 in THF (0.17 L) via addition funnel at 0 °C. The mixture was allowed to warm to room temperature and stir for about 15 hours. The reaction was carefully quenched by addition of MeOH (~ 75 mL) until bubbling ceased. The reaction mixture was concentrated *in vacuo* whereupon the residue obtained was partitioned between EtOAc and H_2O. The layers were separated and the aqueous layer was extracted with EtOAc (2x). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to provide Compound **Int-14d** (18 g, 99%) as a clear oil, which was used without further purification. MS (ESI) m/e $(M+H+Na)^+$: 268.

*Step B – Preparation of Compound **Int-14b***

To a dry 2-necked flask equipped with a stir bar was added oxalyl chloride (8.2 mL, 96 mmol) and CH_2Cl_2 (280 mL). The solution was cooled to -78 °C whereupon a solution of DMSO (7.4 mL, 0.10 mol) in CH_2Cl_2 (22 mL) was added and the mixture was allowed to stir for 30 minutes at -78 °C. A solution of alcohol **Int-14a** (18 g, 74 mmol) from Step A in CH_2Cl_2 (60 mL) was added dropwise via addition funnel over 30 minutes. The resulting solution was allowed to stir for an additional 30 minutes at -78 °C whereupon Et_3N (42 mL, 0.30 mol) was added dropwise. The mixture was allowed to stir for 30 minutes at -78 °C, warmed to 0 °C, and allowed to stir for an additional 1.5 hours. The mixture was diluted with CH_2Cl_2 (400 mL) and was transferred to a separatory funnel. The organic layer was washed with sat. aq NH_4Cl (2 x 100 mL) and brine (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide Compound **Int-14b,**18 g (99%) as a clear oil, which was used without further purification.

Step C – Preparation of Compound ***Int-14c***

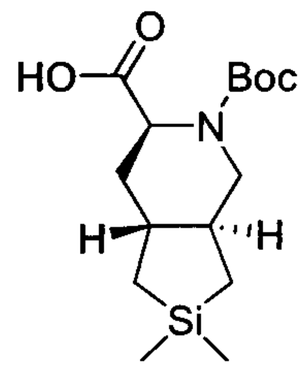
To a round bottom flask charged with aldehyde **Int-14b** (18 g, 74 mmol) from Step B was added a 7N NH_3 in MeOH solution (28 mL, 0.19 mol) in MeOH (37 mL) at room temperature. The mixture was allowed to stir for 30 minutes at room temperature whereupon a solution of glyoxal (14 g, 96 mmol) was added over 5 minutes. The resulting solution was allowed to stir for 12 hours at room temperature and was concentrated *in vacuo*. The residue obtained was purified using column chromatography using a gradient of 100% CH_2Cl_2 to 97.5% CH_2Cl_2/2.5% MeOH to provide Compound **Int-14c**, 9.9 g (48%) as yellow oil. MS (ESI) m/e $(M+H)^+$: 282.

Step D – Preparation of Compound ***Int-14d***

To a solution of imidazole **Int-14c** (1.0 g, 3.6 mmol) from Step C in CH_2Cl_2 (5 mL) at 0 °C, was added NBS (0.44 g, 2.5 mmol) in CH_2Cl_2 (10 mL) dropwise via addition funnel. The resulting mixture was allowed to stir for 90 minutes at 0 °C whereupon the mixture was concentrated *in vacuo*. The crude residue obtained was partitioned between $CHCl_3$ (10 mL) and water (3 mL) and the layers were separated. The organic layer was washed with water (3 x 3 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue obtained was purified using column chromatography (80g) using a gradient of 100% hexanes to 65% hexanes/35% EtOAc to provide Compound **Int-14d**, (0.35 g, 27%) as a white solid. MS (ESI) m/e $(M+H)^+$: 360/362.

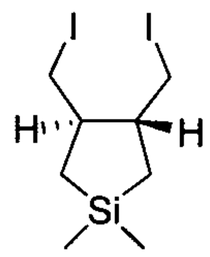
EXAMPLE 15

Preparation of Intermediate Compound **Int-15c**



Int-15c

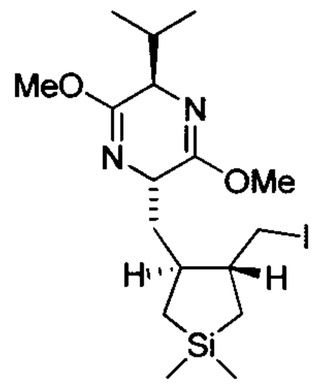
Step A – Preparation of Compound ***Int-15a***



Int-15a

To a solution of dichlorozirconocene (Cp_2ZrCl_2) (4.2 g, 14.2 mmol) in 40 mL THF at -78 °C was added n-BuLi (1.6 M in hexane, 18 mL, 28.4 mmol). The resulting reaction was allowed to stir for 1 hour, then diphenyldiallylsilane (2 g, 14.2 mmol) in 17 mL of THF was added at -78 °C . The reaction was allowed to stir for 1 hour at -78 °C and for 18 hours at 25 °C. Iodine (9 g, 35.5 mmol) in 20 mL THF was then added at -78 °C and the mixture was allowed to stir for 1 hour. The reaction was quenched with 10% aqueous H_2SO_4 and the organic phase was extracted by ether. The organic solution was washed with saturated aqueous $NaHCO_3$ solution, brine solution, and dried (Na_2SO_4). After filtration, the filtrate was concentrated *in vacuo* and the residue obtained was purified using an ISCO 120 g column (hexane) to provide Compound **Int-15a**, 2.75 g (49%). ^{1}H NMR ($CDCl_3$) δ 3.44 (dd, J = 2.2, 10.0 Hz, 2H), 3.33 (dd, J = 4.7, 10.0 Hz, 2H), 1.20 (m, 2H), 0.93 (dd, J = 5.9, 14.7 Hz, 2H), 0.63 (dd, J = 11.1, 14.2 Hz, 2H), 0.19 (s, 6H).

*Step B – Preparation of Compound **Int-15b***



Int-15b

To a solution of (2R)-(–)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (0.61 g, 4.36 mmol) in THF (8 mL) was added n-BuLi (2.5 M in hexane, 1.8 mL, 4.58 mmol) at -78 °C. After allowed to stir for 0.3 hours, Compound **Int-15a** (2.75 g, 6.98 mmol) in 2 mL of THF was added and the mixture was allowed to stir at the temperature for 4 hours. The reaction was quenched by saturated aqueous NH_4Cl solution and the

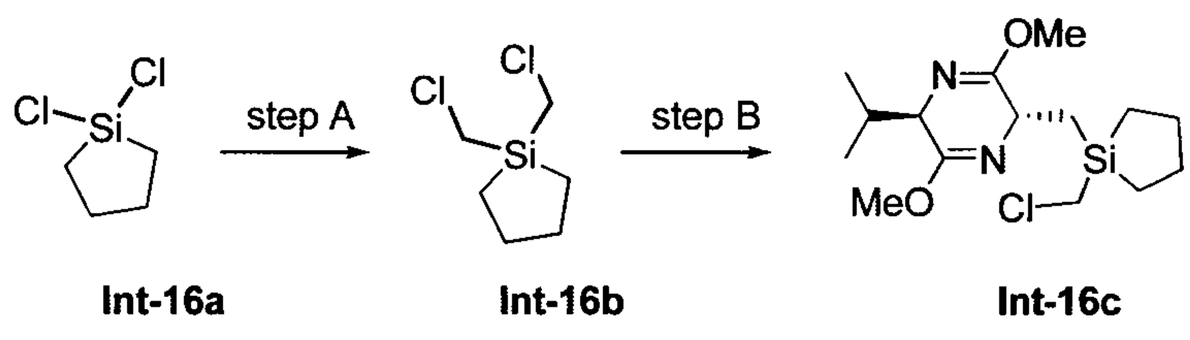
organic layers were extracted with EtOAc. The combined organic solution was washed with brine solution, dried (Na_2SO_4), and concentrated *in vacuo*. The residue obtained was purified using an ISCO 40 g column (gradient from 0% to 2.5% ether in hexane) to provide Compound **Int-15b**, 783 mg (44%). ^{1}H NMR ($CDCl_3$) δ 4.05 (m, 1H), 3.96 (t, *J* = 3.4 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.49 (dd, *J* = 2,8, 0.4 Hz, 1H), 3.26 (dd, *J* = 6, 9.4 Hz, 1H), 2.30 (m, 1H), 1.96 (m, 1H), 1.60 (m, 2H), 1.37 1.17 (m, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.99 0.86 (m, 2H), 0.72 (d, *J* = 6.6 Hz, 3H), 0.49 (dd, *J* = 11.0, 14.4 Hz, 1H), 0.35 (dd, *J* = 11.0, 14.2 Hz, 1H), 0.16 (s, 6H).

*Step C – Preparation of Compound **Int-15c***

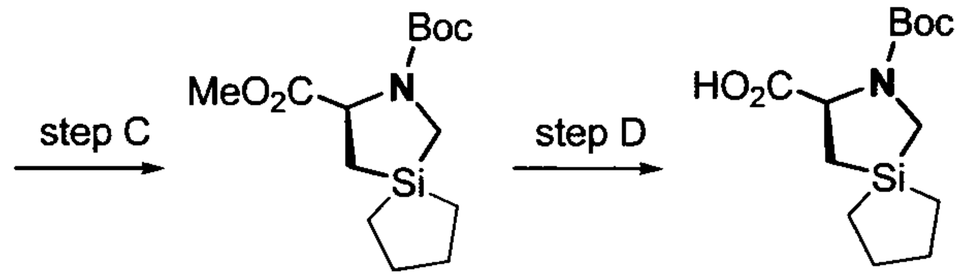
To a solution of Compound **Int-15b** (780 mg, 1.92 mmol) in MeOH (9 mL) was added 10% aqueous HCl (3 mL) at 0 °C and the mixture was allowed to stir at 25 °C for 18 hours. The mixture was concentrated *in vacuo* and the residue obtained was reconcentrated *in vacuo* with MeOH twice. The resulting white foam was dissolved in ether (6 mL) and CH_2Cl_2 (9 mL), and diisopropylethylamine (1 mL, 5.7 mmol) was added. After allowed to stir at 25 °C for 18 hours, di-t-butyl dicarbonate (922 mg, 4.22 mmol) was added and the resulting mixture was allowed to stir at 25 °C for 2 days. The mixture was added to cold water and the organic layers were extracted with EtOAc. The combined organic solution was washed with brine solution, dried (Na_2SO_4), and concentrated *in vacuo*. Then the residue obtained was dissolved in MeOH (8 mL) and treated with aqueous 1 M KOH solution (3.3 mL, 3.3 mmol). After allowed to stir at 0 °C to 25 °C, the reaction mixture was acidified with 10% aqueous HCl and the organic layers were extracted with CH_2Cl_2. The combined organic solution was washed with brine solution, dried (Na_2SO_4), and concentrated *in vacuo* to provide Compound **Int-15c**, which was used without further purification.

EXAMPLE 16

Preparation of Intermediate Compound **Int-16e**



Int-16a **Int-16b** **Int-16c**



Int-16d **Int-16e**

*Step A – Preparation of Compound **Int-16b***

To a 1000 mL flame dried flask was added 1, 1-dichlorosilolane (**Int-16a**, 28.09 g, 181.1 mmol), bromochloromethane (23.5 mL, 362.2 mmol), and anhydrous THF (400 mL). The solution was cooled to -70 °C, then *n*-BuLi (2.5M in hexane, 145 mL, 362 mmol) was added slowly over a period of 1 hour. The resulting reaction was allowed to stir at -70 to -60 °C for 20 minutes, then was allowed to warm to room temperature over 1 hour. Saturated NH_4Cl solution (200 mL) and Et_2O (200 mL) were then added and the organic layer was separated and the aqueous layer was extracted with Et_2O (100 mL) twice. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified using SiO_2 chromatography (240 g, eluted with hexane) to provide Compound **Int-16b** (17.2 g, 51.9%).

*Step B – Preparation of Compound **Int-16c***

To a 500 mL flame dried flask was added (*R*)-2-isopropyl-3, 6-dimethoxy-2,5-dihydropyrazine (10.0 g, 54.3 mmol) and anhydrous THF (200 mL). The solution was cooled to -78 °C. *n*-BuLi (2.5M in hexane, 24.0 mL, 59.7 mmol) was added dropwise. After the solution was allowed to stir at -78 °C for 30 minutes, Compound **Int-16b** (in 5 mL anhydrous THF) was added dropwise. After the solution was allowed to stir at -78 °C for 1 hour, it was allowed to warm up to room temperature in two hours. Water (100 mL) and Et_2O (150 mL) were added. The organic layer was

separated and the aqueous layer was extracted with Et_2O (100 mL) twice. The organic layers were combined, washed with brine, dried over Na_2SO4, filtered and concentrated *in vacuo*. The residue obtained was purified using SiO_2 chromatography (40 g, eluted with Et_2O in Hexane: 0% to 3%) to provide Compound **Int-16c** (10.43 g, 58.0%).

*Step C – Preparation of Compound **Int-16d***

To a 500 mL flask was added Compound **Int-16c** (11.5 g, 34.8 mmol) and MeOH (80 mL). 10% HCl (20 mL) was added. The solution was allowed to stir at room temperature for 5 hours and concentrated *in vacuo*. The residue obtained was dissolved in 20 mL MeOH and concentrated again to remove water and HCl. This process was repeated three times. The residue obtained was dissolved in dichloromethane (50 mL) and Et_2O (70 mL). DIPEA (15.4 mL, 86.9 mmol) and NaI (5.2 g, 34.75 mmol) were added. The solution was allowed to stir at room temperature for about 15 hours. Di-tert-butyl dicarbonate (18.9 g, 86.9 mmol) was added. The solution was allowed to stir at room temperature for 4 hours. Water (100 mL) and EtOAc (100 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (100 mL) twice. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue obtained was purified using SiO_2 chromatography (220g, Hexane/EtOAC: 0% to 20%) to provide Compound **Int-16d** (7.9 g, 75.9%).

*Step D – Preparation of Compound **Int-16e***

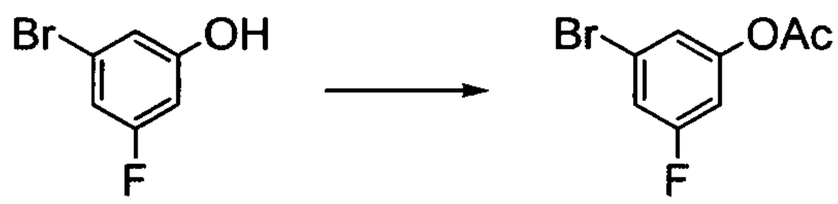
Compound **Int-16d** (7.9 g, 26.4 mmol) was dissolved in MeOH (100 mL) and cooled to 0 °C. KOH (1M in water, 39.6 mL, 39.6 mmol) was added. The solution was allowed to stir at 0 °C for 2 hours, and then at room temperature for 3 hours. HCl (2 N, 20 mL) was added, then additional HCl was added slowly to adjust the solution to pH 4. The acidified solution was concentrated *in vacuo* and to the residue obtained was added water (150 mL) and EtOAc (200 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in*

vacuo. The residue obtained was dried *in vacuo* for 48 hours to provide Compound **Int-16e** (7.45 g, 99%), which was used without further purification.

EXAMPLE 17

Preparation of Intermediate Compounds **Int-17c** and **Int-17d**

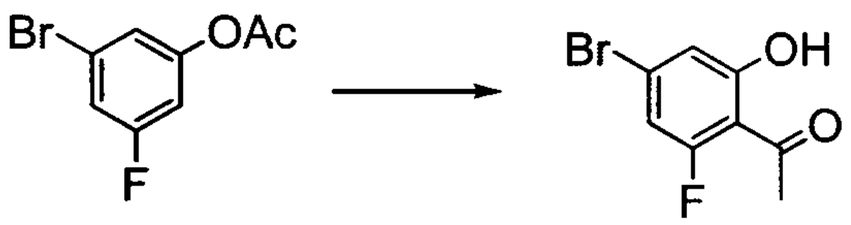
*Step A – Preparation of Compound **Int-17b***



Int-17a **Int-17b**

To a 500 mL flask was added **Int-17a** (25.0 g, 130 mmol), dry dichloromethane (250 mL) and DIPEA (25.37 g, 195 mmol). The solution was cooled to 0 °C and acetyl chloride (13.27g, 169 mmol, in 30 mL dry dichloromethane) was added dropwise. The resulting reaction was allowed to stir at 0 °C for one hour and then at room temperature for about 15 hours. The solution was diluted with EtOAc and washed with water. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue obtained was purified using flash column chromatography on silica gel (330g, 0% to 50% of EtOAc in Hexane) to provide Compound **Int-17b** (22.58 g, 74.5%)

*Step B – Preparation of Compound **Int-17c***

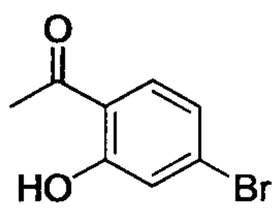


Int-17b **Int-17c**

To a 500 mL flask was added **Int-17b** (21.45 g, 92.05 mmol) and dry dichloromethane (200 mL). It was cooled to 0 °C and aluminum trichloride ($AlCl_3$, 36.82 g, 276.2 mmol) was added in portions. After the solution was allowed to stir at 0 °C for 30 minutes, it was concentrated *in vacuo*. The semi-solid residue obtained was heated at 140 °C for three hours. After it was cooled to 80 °C, water (10 mL) was added dropwise.

It was then cooled to 0 °C and EtOAc (300 mL) and water (200 mL) were added. The suspension was allowed to stir at 0 °C until the entire solid dissolved. More EtOAc was added and the organic layer was separated. The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue obtained was purified using flash column chromatography on silica gel (330g, 0% to 10% of EtOAc in Hexane)to provide Compound **Int-17c** (18.76 g, 87%).

*Step C - Preparation of Compound **Int-17d***

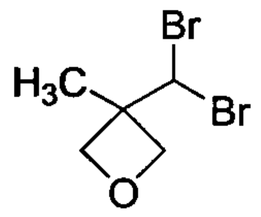


Int-17d

Compound **Int-17d** was prepared using the method described above for the synthesis of Compound **Int-17c** and substituting 2-bromophenol for Compound **Int-17a** in Step A

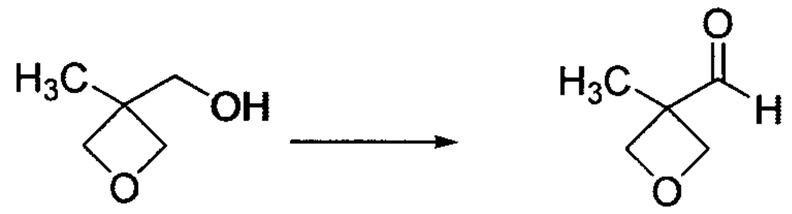
EXAMPLE 18

Preparation of Intermediate Compound **Int-18c**



Int-18c

*Step A – Preparation of Compound **Int-18b***



Int-18a **Int-18b**

To a stirred solution of (3-methyloxetan-3-yl)methanol (**Int-18a**,10.0 g, 97.9 mmol) in methylene chloride (400 mL) at 0 °C, under inert atmosphere, was added silica gel (20 g). PCC (29.5 g, 137 mmol) was then added in portions over a 2 minutesute

period. The solution was allowed to slowly warm to room temperature and stirred for 6.5 hours. The reaction mixture was then filtered through a mixture of Celite:silica gel (1:1, 400 g total) and the Celite:Silica gel was washed with methylene chloride (4 L). The filtrate and washing were combined and concentrated *in vacuo* to provide 4.98 g (51%) of **Int-18b** as a clear solution (48.5 wt%) in methylene chloride. ^{1}H NMR ($CDCl_3$ 500 MHz): δ 9.94 (s, 1H), 4.89 4.83 (m, 2H), 4.52 4.46 (m, 2H), 1.48 (s, 3H).

*Step B – Preparation of Compound **Int-18c***

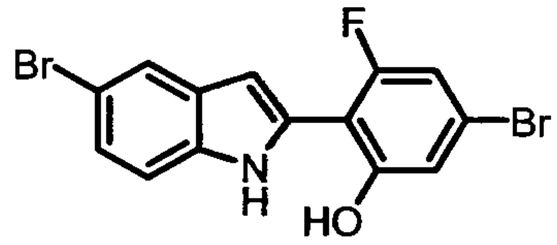


Int-18b **Int-18c**

To a stirred solution of triphenylphosphite (5.10 mL, 19.5 mmol) in methylene chloride (9 mL) at 0 °C, under inert atmosphere, was added bromine (1.00 mL, 19.5 mmol) dropwise at 0 °C. A solution of Compound **Int-18b** (1.00 g, 9.99 mmol) in methylene chloride (1 mL) was then added and the resulting reaction was allowed to stir for 40 minutes at 0 °C. The reaction mixture was diluted with hexanes (10 mL) and the solution was passed through a plug of silica gel (4 g). The solids were washed with MTBE (20 mL). The filtrate and washing was combined and concentrated *in vacuo* to ~10 mL and purified using flash column chromatography on silica gel (methylene chloride/pentane) to provide 1.06 g (44%) of Compound **Int-18c** as clear colorless oil. ^{1}H NMR ($CDCl_3$,500 MHz): δ 5.98 (s, 1H), 3.76 (d, J = 10.5 Hz, 2H), 3.65 (d, J = 10.5 Hz, 2H), 1.44 (s, 3H).

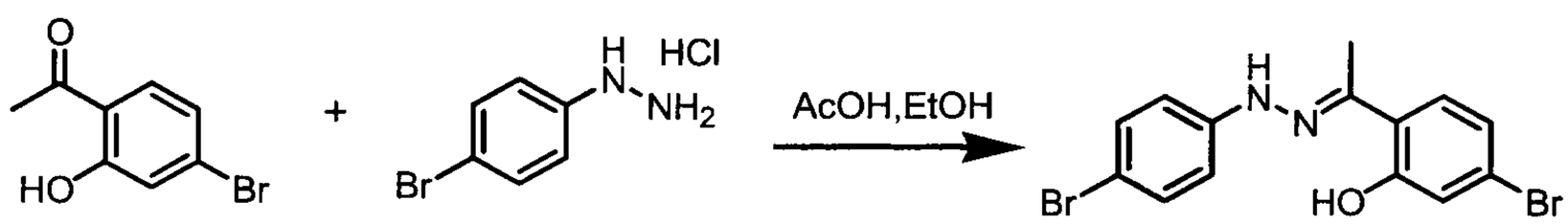
EXAMPLE 19

Preparation of Intermediate Compound **Int-19e**



Int-19e

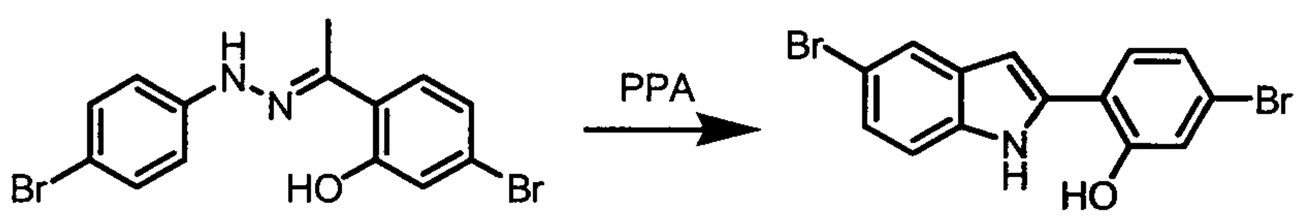
Step A – Preparation of Compound ***Int-19a***



Int-17d **Int-19a**

A mixture of **Int-17d** (4.2 g, 20 mmol) and 4-bromophenyl hydrazine hydrochloride (4.4 g, 20 mmol) in AcOH and EtOH (1:10, 100 mL) was heated to reflux and allowed to stir at this temperature for 6 hours. The reaction mixture was cooled to room temperature and concentrate *in vacuo* to provide Compound **Int-19a** as a solid, which was used without further purification (9.2 g). MS (ESI) **m / e** ($M+H^+$): 383.

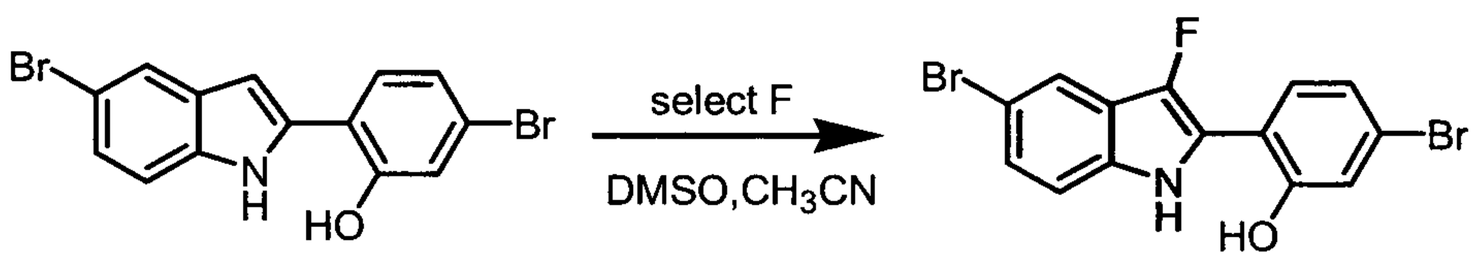
Step B – Preparation of Compound ***Int-19b***



Int-19a **Int-19b**

A mixture of **Int-19a** (9.2 g) in PPA was heated to **80** °C and allowed to stir at this temperature for 2 hours. After cooling to room temperature, the reaction mixture was poured into ice water. The resulting solution was extracted with dichloromethane and the organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified using column chromatography to provide Compound **Int-19b** (4.8 g). MS (ESI) **m** / e ($M+H^+$): 368.

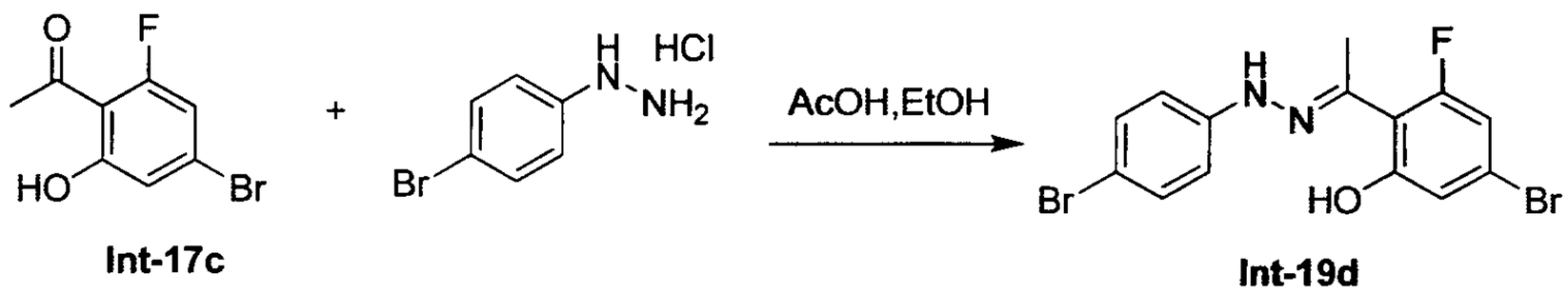
Step C – Preparation of Compound ***Int-19c***



Int-19b **Int-19c**

To a solution of **Int-19b** (6 g, 16.3 mmol) in DMSO/CH_3CN (1:1, 24 mL) was added Select-F (5.8 g, 16.3 mmol) in portions. The reaction was allowed to stir for 1 hour at room temperature, then the reaction mixture was concentrated *in vacuo* and the residue obtained was purified using HPLC to provide Compound **Int-19c** as a solid (1.0 g). MS (ESI) m / e ($M+H^+$): 386.

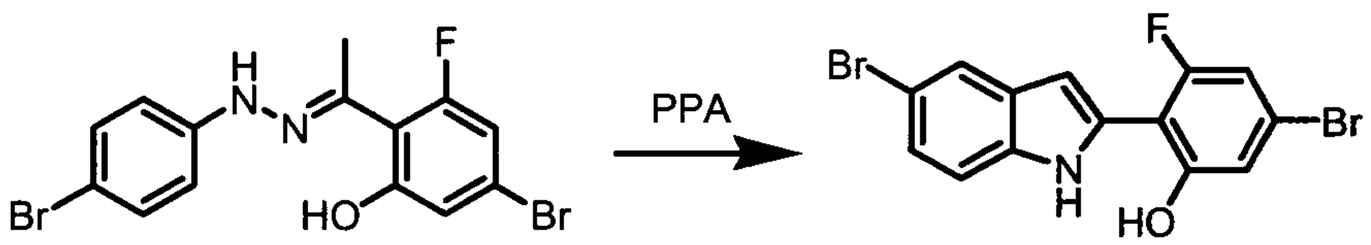
*Step D – Preparation of Compound **Int-19d***



Int-17c **Int-19d**

A suspension of **Int-17c** (51.6 g, 221 mmol, 1.0 eq) in 910 mL of absolute ethanol and 100 mL of glacial acetic acid was heated to 40 °C and 4-chlorophenyl hydrazine hydrochloride (41.66 g/232 mmol/1.05 eq) was added in portions, with stirring, followed by 3 Angstrom molecular sieves (23 g) and additional acetic acid (350 mL). The reaction mixture was placed under a N_2 atmosphere, heated to 70 °C and allowed to stir at this temperature for 4 hours. The reaction mixture was allowed to cool to room temperature and was allowed to stand for about 15 hours, without stirring, under N_2. The reaction mixture was filtered, the filtrate was concentrated *in vacuo* and the residue obtained was taken up in toluene (230 mL) and absolute ethanol (100 mL). The resulting solution was then concentrated *in vacuo*. The residue obtained was diluted with absolute ethanol (400 mL) and the resulting solution was allowed to stand in a 54 °C water bath for 45 minutes, then was allowed to cool to room temperature with stirring. The resulting precipitate was filtered and the collected solid was washed with 30 mL of absolute ethanol and 75 mL of hexanes, then dried *in vacuo* to provide Compound **Int-19d** as an off white solid (50.2 grams (63%)). This material was used without further purification. MS (ESI) m / e ($M+H^+$): 357.0, 359.0.

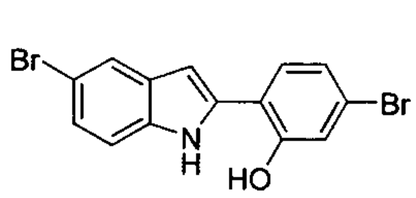
*Step E – Preparation of Compound **Int-19e***



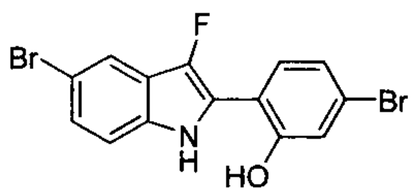
Int-19d **Int-19e**

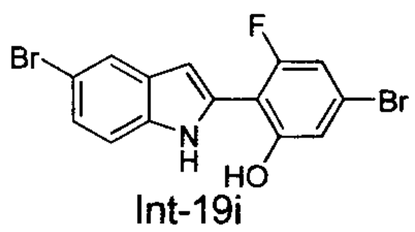
Polyphosphoric acid (111.8 g) and xylenes (260 mL) were added to a 1 liter 3-necked flask. The flask was placed in a 100 °C oil bath, connected to a N_2 inlet, and equipped with a mechanical stirrer. The PPA/xylenes mixture was allowed to stir for 30 minutes to bring the internal temperature up to 100 °C. Compound **Int-19d** was then added in portions over 10 minutes. The reaction was placed under N_2 atmosphere, capped, stirred for 30 minutes at 100 °C, and then stirred for 2.5 hours at 110 °C. The flask was lifted out of the oil bath and allowed to cool for 15 minutes. Ice (750 mL) was added in portions to the reaction mixture with stirring. After about 15 minutes, the reaction mixture was suction filtered through fiberglass filter paper in a Buchner funnel and an orange solid was collected. The collected solid was dissolved in EtOAc, and the resulting purple solution was washed with water and brine, then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue obtained was purified using flash chromatography on a 345 g SiO_2 column using 5%-25% EtOAc/hexanes gradient, to provide Compound **Int-19e** (11.22 g) as a yellow solid (47%).

The following 2-aryl indole intermediates can be made using the method described above and substituting the appropriate reactants:

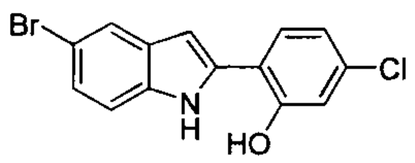


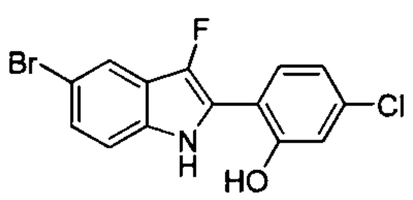
Int-19b

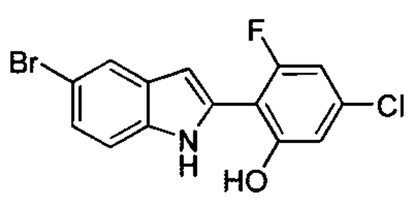


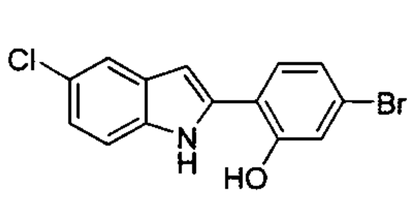


Int-19i

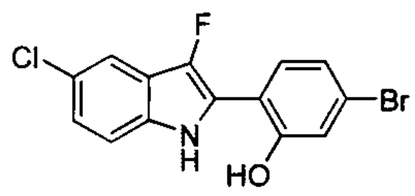




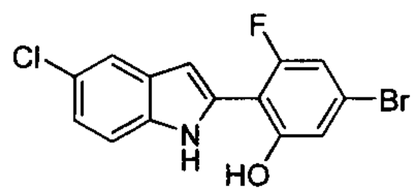




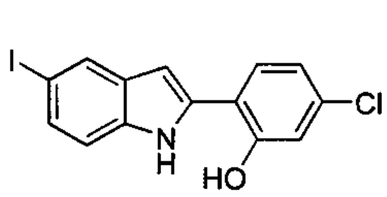
Int-19g

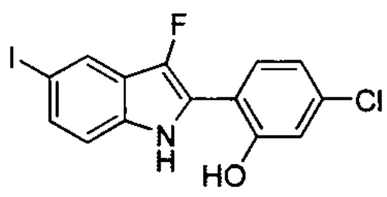


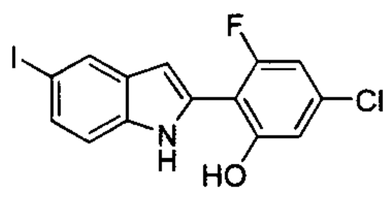
Int-19h

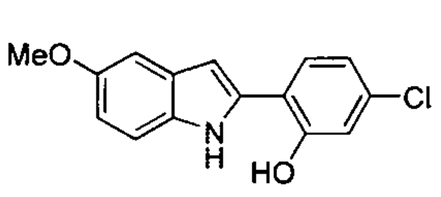


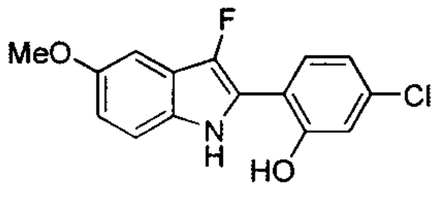
Int-19j

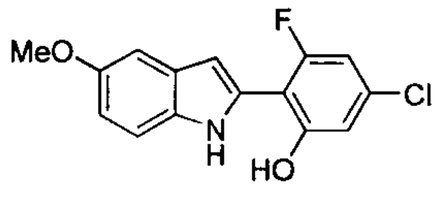


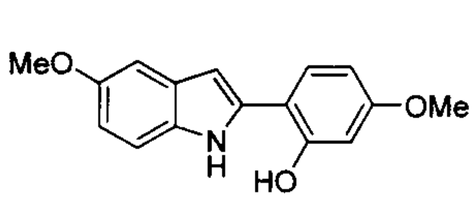


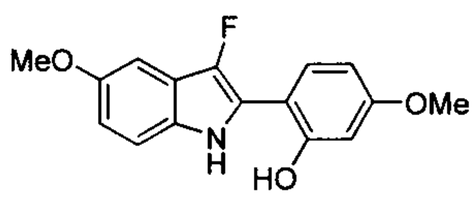


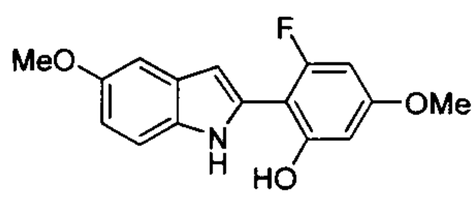






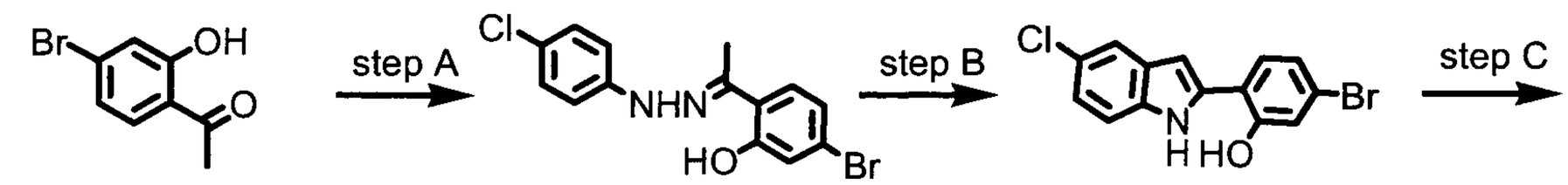




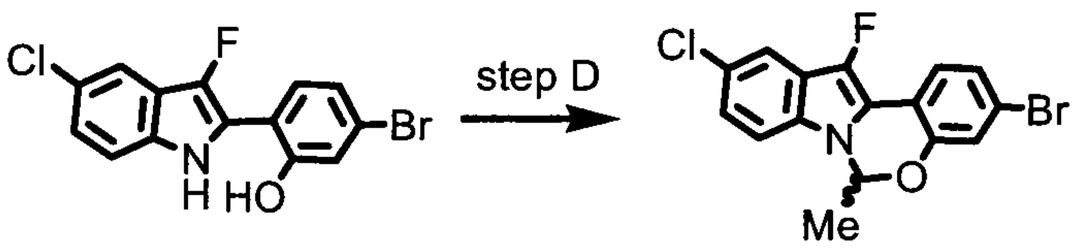


EXAMPLE 19a

Preparation of Intermediate Compound **Int-19i**



Int-17d **Int-19f** **Int-19g**



Int-19h **Int-19i**

*Step A – Preparation of Compound **Int-19f***

To a solution of **Int-17d** (14.0 g, 65.1 mmol), (4-chlorophenyl)hydrazine (23.3g, 130 mmol) in EtOH (400 mL) was added glacial acetic acid (40 mL). The reaction was heated to 90 °C and allowed to stir at this temperature for about 15 hours. The reaction mixture was cooled to room temperature, filtered, and the filtrate was concentrated *in vacuo* and dried *in vacuo* for 15 minutes. The resulting residue was diluted with dichloromethane (600 mL) and the resulting suspension was allowed to stir at room temperature for 30 minutes. The solid was removed by filtration and washed with dichloromethane five times. The filtrate was concentrated *in vacuo* and MeOH (100 mL) was added. The suspension was allowed to stir at room temperature for 15 minutes and filtered. The solid was dried *in vacuo* for two hours to provide Compound **Int-19f** (17.9 g, 81.0%).

*Step B – Preparation of Compound **Int-19g***

To a 250 mL three-neck flask with a mechanic stirrer was added polyphosphoric acid (PPA, 100g). PPA was heated to 110 °C and **Int-19f** (10.3 g, 30.3 mmol) was added in small portions. The reaction mixture gradually became dark green. The reaction mixture was allowed to stir at 110 °C for two hours. After cooling down, crushed ice was added slowly with stirring until the dark green color disappeared. Water was added and the suspension was transferred into a 1000 mL beak. The suspension was allowed to stir for 10 minutes and filtered. The solid was washed with water (100 mL)

three times and dried *in vacuo* at 60 °C for about 15 hours to provide Compound **Int-19g** (9.72 g, 99.4%).

*Step C – Preparation of Compound **Int-19h***

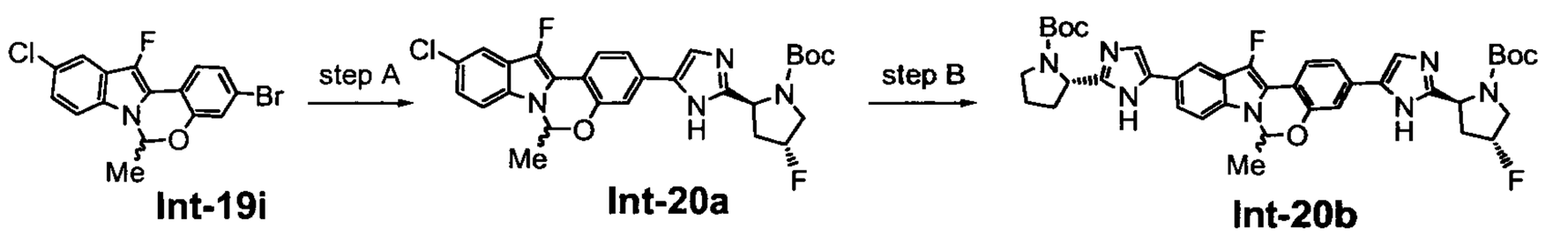
To a 100 mL round bottom flask was added **Int-19g** (2.62 g, 8.12 mmol), DMSO (15 mL), and MeCN (15 mL). The solution was cooled to 0 °C and Select-F (2.3 g, 6.5 mmol) was added in three portions. The reaction was allowed to stir at 0 °C for 1.5 hours, then gradually warmed up to room temperature in one hour. The reaction mixture was then diluted with 20 mL MeOH and filtered. The filtrate was concentrated *in vacuo* to about 20 mL and purified using C18 chromatography (150g, 50% to 100% of MeCN in water, with 0.05% TFA) to provide Compound **Int-19h** (964 mg, 35%).

*Step D – Preparation of Compound **Int-19i***

A solution of **Int-19h** (2.05 g, 6.02 mmol), DMF (120 mL), Cs_2CO_3 (10.0 g, 31.0 mmol), and dibromoethane (5.2 mL, 60.2 mmol) was heated to 100 °C and allowed to stir at this temperature for about 15 hours. Additional dibromoethane (4.0 ml, 46 mmol) and Cs_2CO_3 (3.0 g, 9.2 mmol) were added and the reaction was allowed to stir at 100 °C for 8 hours. The reaction mixture was cooled to room temperature and water (200 mL) and EtOAc (250 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (100 mL). The organic layers were combined, washed with water (2 x 100 mL) and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (0% to 50% of EtOAc in Hexane) to provide Compound **Int-19i** (1.24 g, 56.2%).

EXAMPLE 20

Preparation of Compound **37**



Int-19i **Int-20a** **Int-20b**

Int-20c **Compound 37**

*Step A – Preparation of Compound **Int-20a***

To a 40 mL vial was added **Int-19i** (329 mg, 0.898 mmol), bis(pinacolato)diboron (228 mg, 0.898 mmol), $Pd(dppf)_2Cl_2$·dichloromethane (146 mg, 0.18 mmol), and KOAc (264 mg, 2.7 mmol). The vial was degassed, refilled with N_2, and capped. Dioxane was added via a syringe and the solution was allowed to stir at 90 °C for 2 hours. (2*S*,4*R*)-*tert*-butyl-2-(5-bromo-1*H*-imidazol-2-*yl*)-4-fluoropyrrolidine-1-carboxylate praline (300 mg, 0.90 mmol), $Pd(dppf)_2Cl_2$·dichloromethane (83 mg, 0.1 mmol), and K_2CO_3 (1M, 3.3 mL, 3.3 mmol) were added and the reaction was allowed to stir at 90 °C for 2 hours. The reaction mixture was cooled to room temperature, diluted with 5 mL EtOAc, and the aqueous layer was separated and extracted with 3 mL EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified using flash column chromatography on silica gel (24 g, 15% to 70% of EtOAc in Hexane) to provide Compound **Int-20a** (387 mg, 79.7%).

*Step B – Preparation of Compound **Int-20b***

To a 40 mL vial was added **Int-20a** (182 mg, 0.336 mmol), bis(pinacolato)diboron (89.7 mg, 0.353 mmol), $Pd_2(dba)_3$·$CHCl_3$ (35 mg, 0.034 mmol), X-phos (32 mg, 0.067 mmol), and KOAc (98 mg, 1.0 mmol). The vial was degassed, refilled with N_2, and capped. Dioxane was added via a syringe and the solution was allowed to stir at 120 °C for 2 hours. (*S*)-*tert*-butyl-2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (116.9 mg, 0.37 mmol), $Pd(dppf)_2Cl_2$·dichloromethane (28 mg, 0.034 mmol), and K_2CO_3 (1M, 1.0 mL, 1.0 mmol) were added. The reaction was

allowed to stir at 80 °C for about 15 hours, then was cooled to room temperature. The aqueous layer were separated and extracted with 5 mL EtOAc. The organic extracts were combined and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified using flash column chromatography on silica gel (43 g, A: dichloromethane; B: 10% MeOH in EtOAc: A/B: 0% to 80%) to provide Compound **Int-20b** (191 mg, 89.9%).

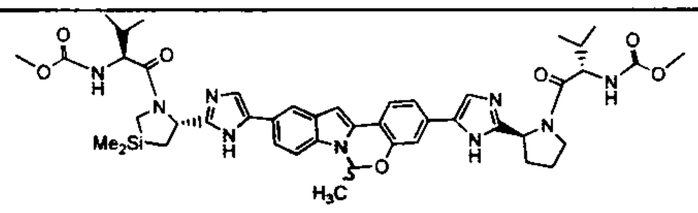
*Step C – Preparation of Compound **Int-20c***

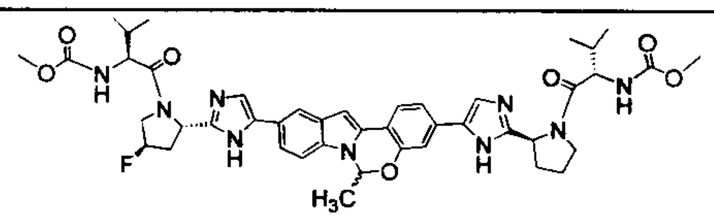
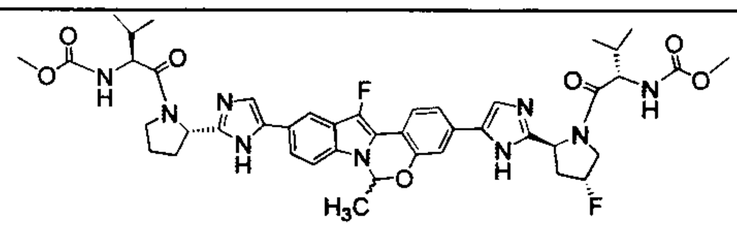
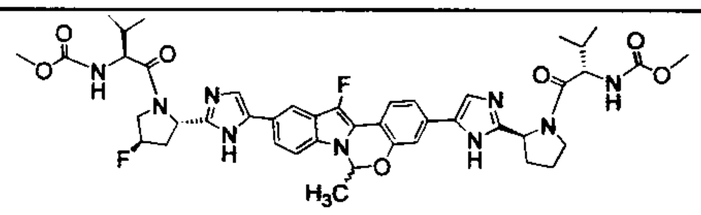
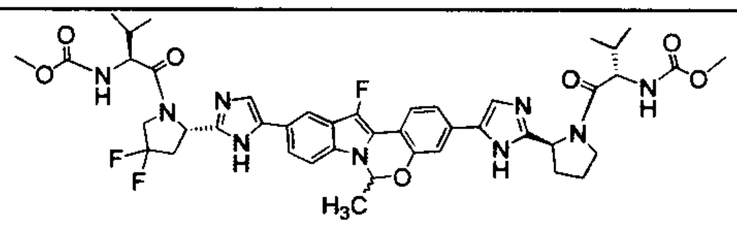
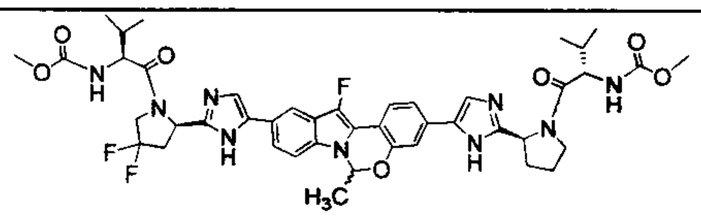
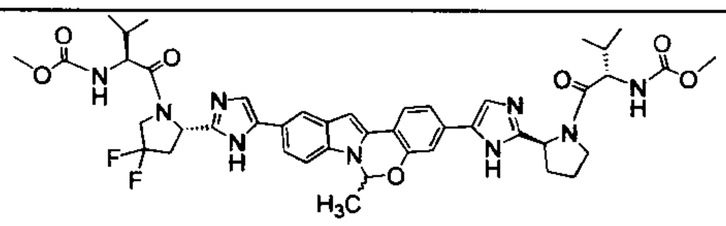
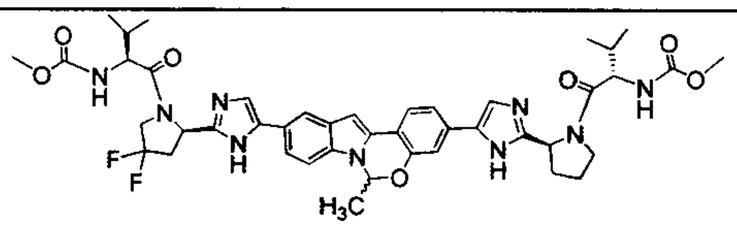
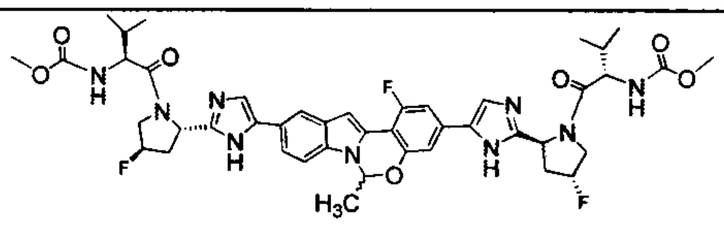
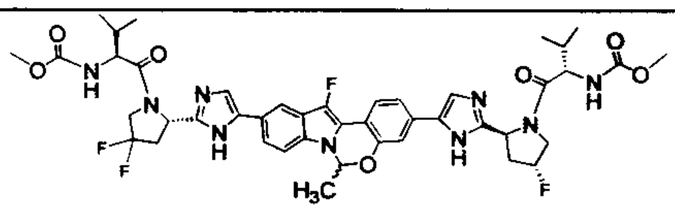
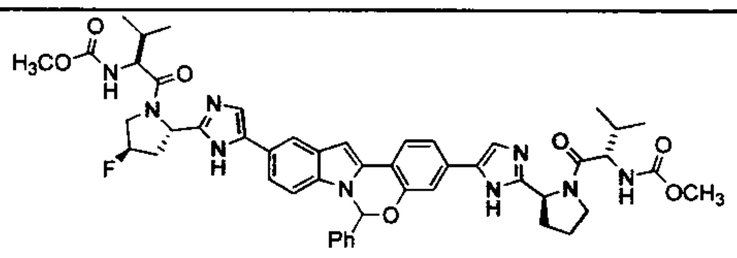
To a 40 mL vial was added **Int-20a** (190 mg, 0.256 mmol), MeOH (2 mL), and HCl (4M in dioxane, 6 mL, 24 mmol). The solution was allowed to stir at room temperature for two hours, then was concentrated *in vacuo* and the residue obtained was dried *in vacuo* for 30 minutes to provide Compound **Int-20c**, which was used without further purification.

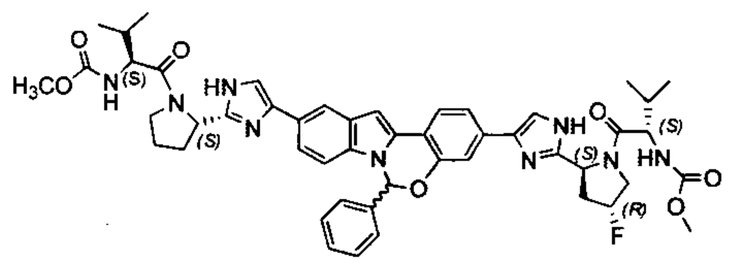
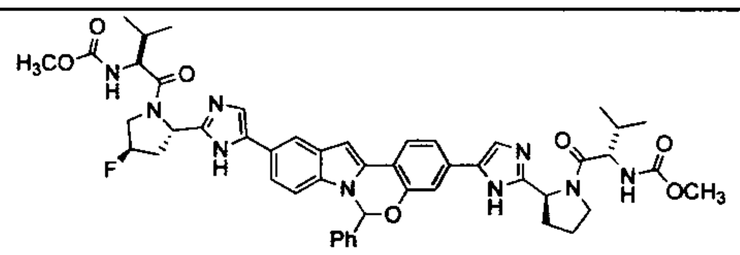
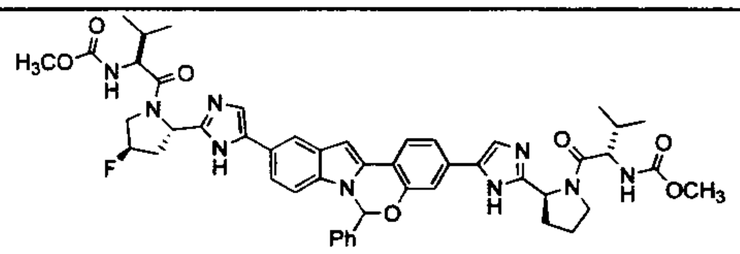
Step D – Preparation of Compound 37

To a 40 mL vial was added **Int-20c** (~ 0.256 mmol), (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (90.0 mg, 0.512 mmol), HATU (214 mg, 0.56 mmol), and DMF (3 mL). The resulting solution was cooled to 0 °C and DIPEA (0.32 ml, 1.79 mmol) was added. The reaction was allowed to stir at 0 °C for 2 hours, then was diluted with water (0.2 mL) and the resulting solution was purified using a C18 column (43g, 10% to 60%, of CH_3CN in water with 0.05% TFA) to provide Compound **37** (46 mg, 21.4% from **Int-20b**). MS 874.4 $[M+H]^+$

The following Compounds of the present invention were made using the method described in Example 20.

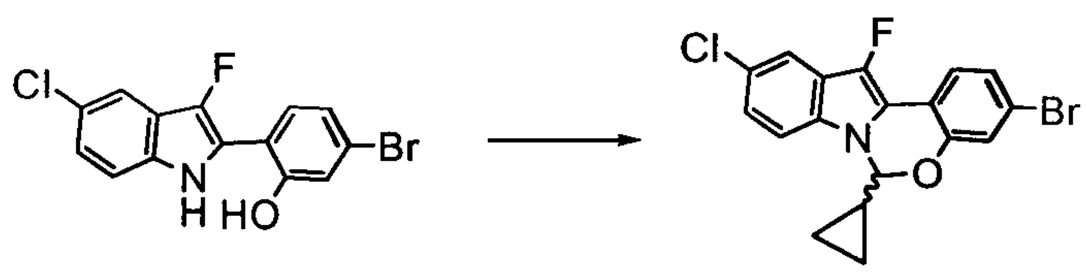
Compound	**Structure**	**MS**
61		864.3 $[M+H]^+$

62		838.4 $[M+H]^+$
63		856.3 $[M+H]^+$
64		856.4 $[M+H]^+$
66		874.3 $[M+H]^+$
67		874.4 $[M+H]^+$
31		856.4 $[M+H]^+$
32		856.4 $[M+H]^+$
68		873.5 $[M]^+$
69		891.4 $[M]^+$
87		900.5 $[M+H]^+$

92		900.5 $[M+H]^+$
93		900.5 $[M+H]^+$
94		900.5 $[M+H]^+$

EXAMPLE 21

Preparation of Intermediate Compound **Int-21a**

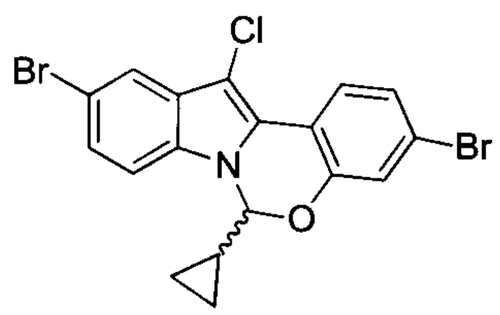


Int-19h **Int-21a**

To a 20 mL microwave vial was added **Int-19h** (1.16 g, 3.41 mmol), anhydrous toluene (15 mL), cyclopropane-carboxaldehyde (1.28 mL, 17.1 mmol), and p-toluenesulfonyl chloride (65 mg, 0.34 mmol). The vial was capped and sealed, then placed in a microwave reactor and heated to 170 °C for three hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue obtained was dissolved in dichloromethane (40 mL) and filtered through a short pad of Celite. The filtrate was concentrated *in vacuo* and purified using flash column chromatography on silica gel (80 g, hexane) to provide Compound **Int-21a** (778 mg, 58.1%).

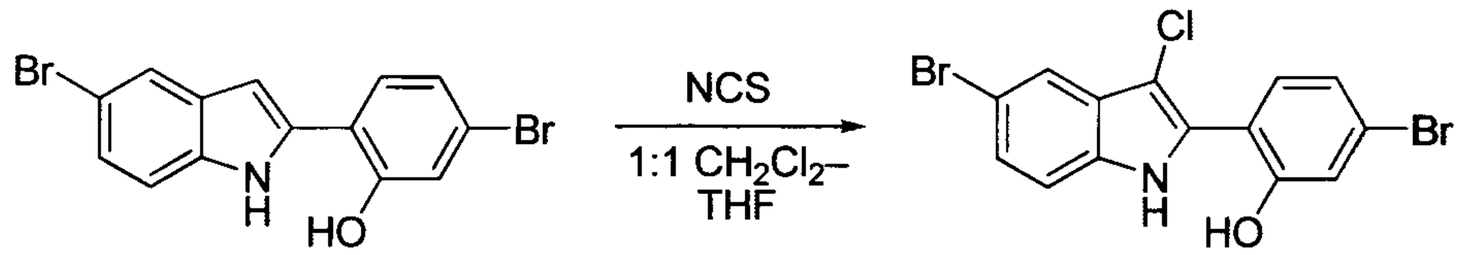
EXAMPLE 22

Preparation of Intermediate Compound **Int-22c**



Int-22c

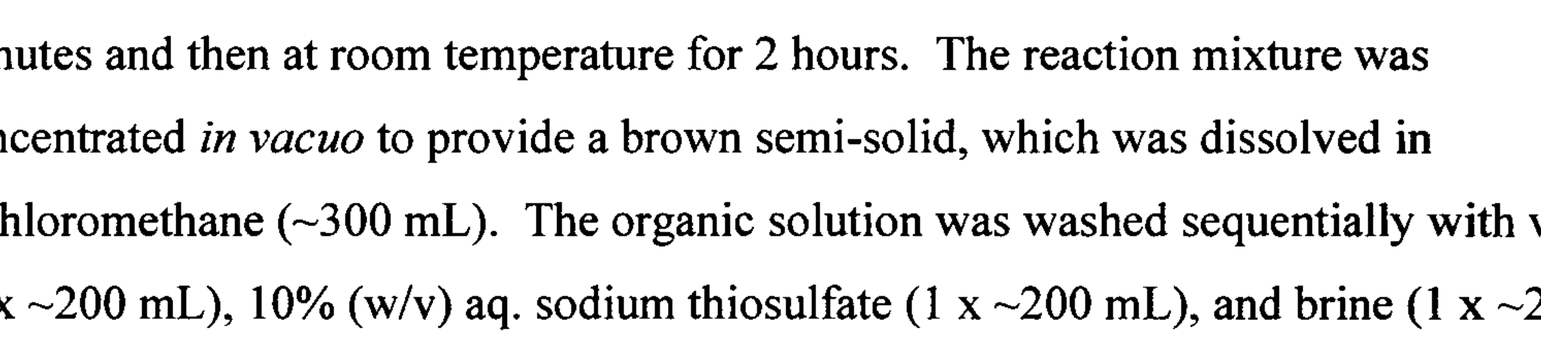
Step A – Preparation of Compound ***Int-22a***



Int-19b **Int-22a**

Int-19b (5.82 g, 0.016 mmol) was dissolved in dichloromethane (50 mL) and THF (50 mL) and the mixture was allowed to stir at room temperature until all solids dissolved. The resulting solution was cooled in an ice-water bath for 30 minutes, after which NCS (2.13 g, 0.016 mmol) was added to the stirred reaction mixture in portions over ~10 minutes. The reaction mixture was allowed to stir at 0 °C for 30 minutes and then at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to provide a brown semi-solid, which was dissolved in dichloromethane (~300 mL). The organic solution was washed sequentially with water (1 x ~200 mL), 10% (w/v) aq. sodium thiosulfate (1 x ~200 mL), and brine (1 x ~200 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting solid residue was purified using column chromatography (330 g Teledyne-Isco RediSep® silica column, 0-30% EtOAc/hexanes over 12 column volumes at 200 mL/min) to provide 2.97 g of **Int-22a** (47% yield) as a brown solid. MS (ESI) m / e ($M+H^+$): 400.

Step B – Preparation of Compound ***Int-22b***

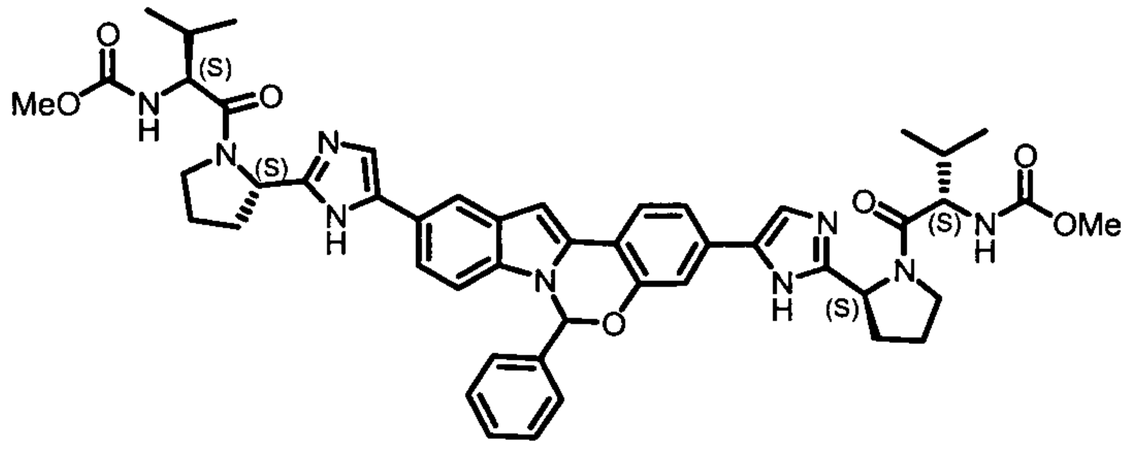


Int-22a **Int-22b**

In a 20-mL microwave tube, **Int-22a** (1.075 g, 2.68 mmol) was dissolved in dry toluene (13 mL). Cyclopropanecarboxaldehyde (1.0 mL, 0.94 g, 13.4 mmol), *p*-toluenesulfonyl chloride (51 mg, 0.27 mmol), and a magnetic stir bar were added. The tube was sealed and the reaction mixture was heated at 170 °C (microwave) with stirring for 3 hours. The reaction mixture was cooled to room temperature, the tube opened, and further aliquots of each of cyclopropanecarboxaldehyde (1.0 mL, 0.94 g, 13.4 mmol) and *p*-toluenesulfonyl chloride (51 mg, 0.27 mmol) were added. The tube was re-sealed and the reaction was again subjected to microwave heating at 170 °C for 4 hours, then cooled to room temperature and concentrated *in vacuo* to provide a brown solid residue. The brown solid residue was adsorbed onto silica gel (19 g) using EtOAc (~100 mL), followed by evaporation of the solvent, and then loaded onto a 100 g Biotage® KP-Sil SNAP cartridge. Elution with 100% hexanes over 13 column volumes at 85 mL/min provided 600 mg of **Int-22b** (50% yield) as a light brown solid. MS (ESI) m / e ($M+H^+$): 452.

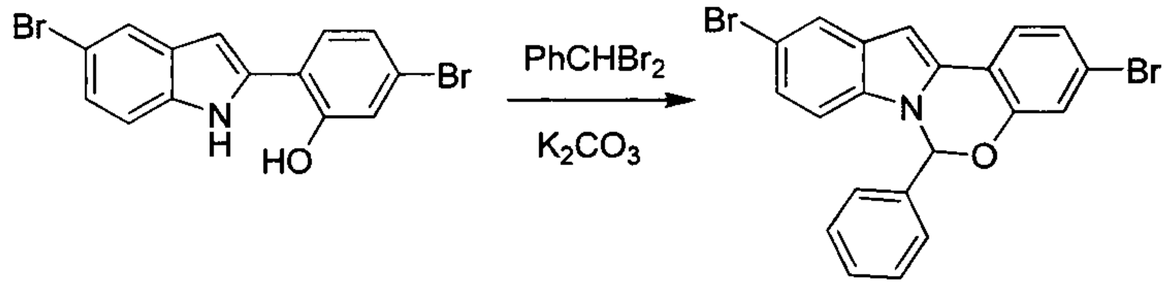
EXAMPLE 23

Preparation of Compound **23A**



23A

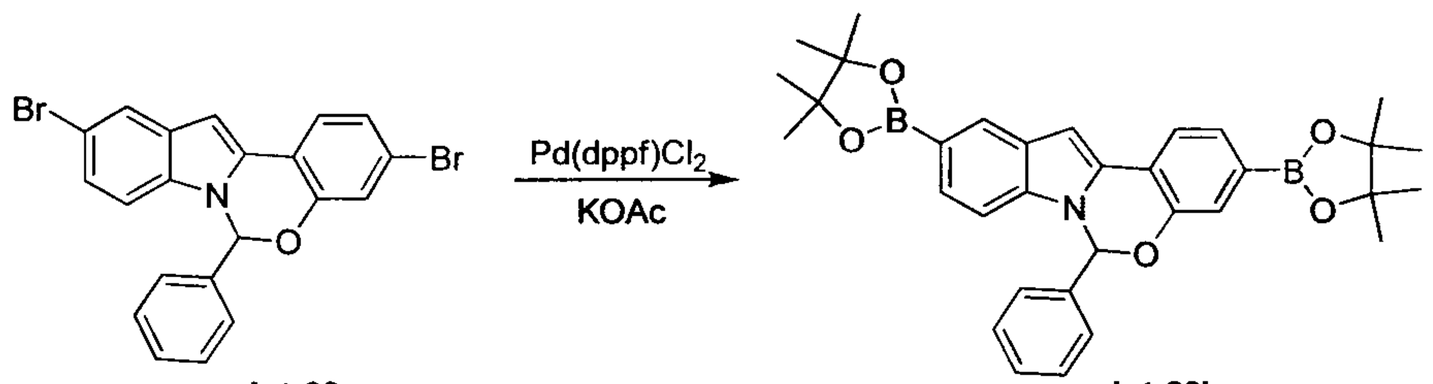
Step A – Preparation of Compound ***Int-23a***



Int-19b **Int-23a**

A mixture of Compound **Int-19b** (1.1 g, 3 mmol), (dibromomethyl)benzene (2.25 g, 9 mmol) and K_2CO_3 (1.2 g, 9 mmol) in 15 mL of DMF was heated to 100 °C and allowed to stir at this temperature for 3 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue obtained was dissolved with dichloromethane and water. The aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel to provide Compound **Int-23a** (380 mg, 28 %) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.72 (bs, 1 H), 7.44 - 7.46 (d, J = 8.4 Hz, 1 H), 7.21 - 7.28 (m, 3 H), 7.09 - 7.12 (m, 3 H), 7.04 (s, 1 H), 6.99 - 7.01 (bs, J = 6.8 Hz, 2 H), 6.78 (s, 1 H), 6.63 - 6.65 (d, J = 8.4 Hz, 1 H). MS (ESI) m/e ($M+H^+$): 456.

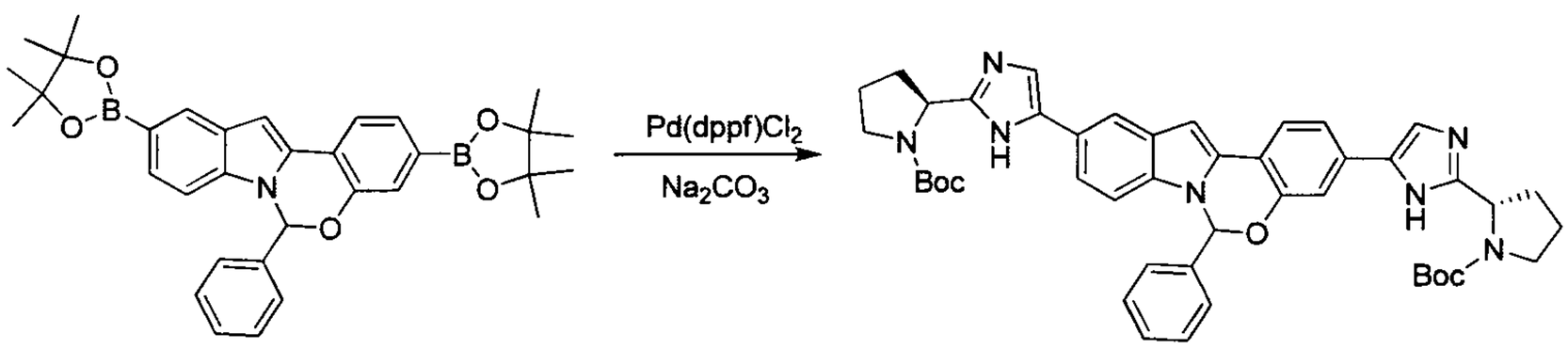
Step B – Preparation of Compound ***Int-23b***



Int-23a **Int-23b**

To a solution of **Int-23a** (456 mg, 1.0 mmol) in 1,4-dioxane was added bis pinacol borate (2.2 mmol) , $Pd(dppf)Cl_2$ (0.04 mmol) and KOAc (4 mmol). The reaction mixture was put under N_2, heated to 110°C and allowed to stir at this temperature for 3 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the residue obtained was purified using column chromatography on silica gel to provide Compound **Int-23b** (590 mg, 87 % yield). ^{1}H NMR ($CDCl_3$): δ 8.13 (s, 1 H), 7.60 (d, J = 7.6 Hz, 1 H), 7.52 (d, J = 8.0 Hz, 1H), 7.36 - 7.39 (m, 1 H), 7.14 -7.19 (m, 4 H), 6.93 - 6.95 (m, 3 H), 6.90 (s, 1 H), 1.26 - 1.29 (s, 24 H). MS (ESI) m / e (M+H+): 550.

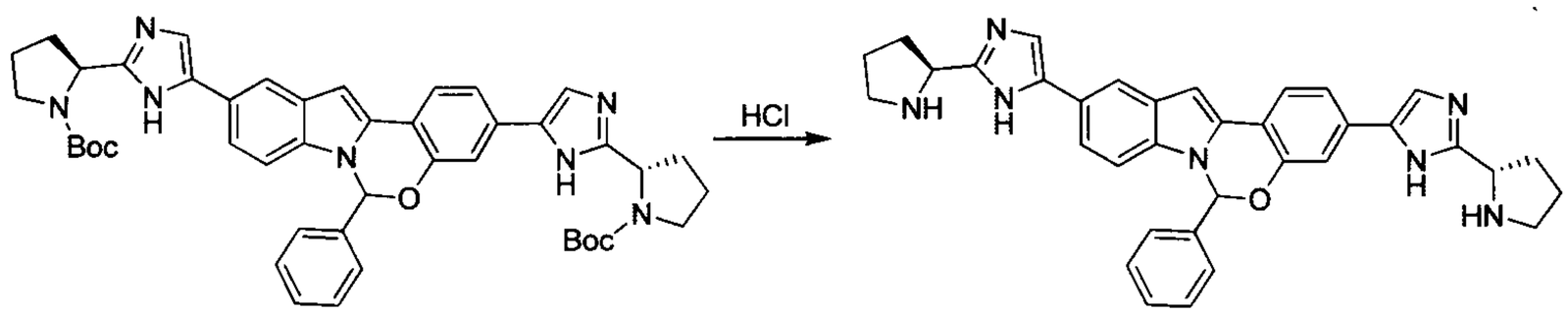
Step C – Preparation of Compound ***Int-23c***



Int-23b **Int-23c**

A suspension of **Int-23b** (550 mg, 1.0 mmol), *tert*-butyl 2-(2-bromo-1*H*-imidazol-5-yl) pyrrolidine-1-carboxylate (2.4 mmol), Pd(dppf) Cl_2 (200 mg), Na_2CO_3 (3 mmol) and in THF/H_2O (10:1, 33 mL) was allowed to stir at reflux for about 15 hours under N_2. The reaction mixture was cooled to room temperature and filtered, and the filtrate was washed with water (50 mL) and extracted with EtOAc (100 mL). The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified using column chromatography on silica gel to provide Compound **Int-23c** (160 mg). **MS (ESI)** m / e ($M+H^+$): 768.

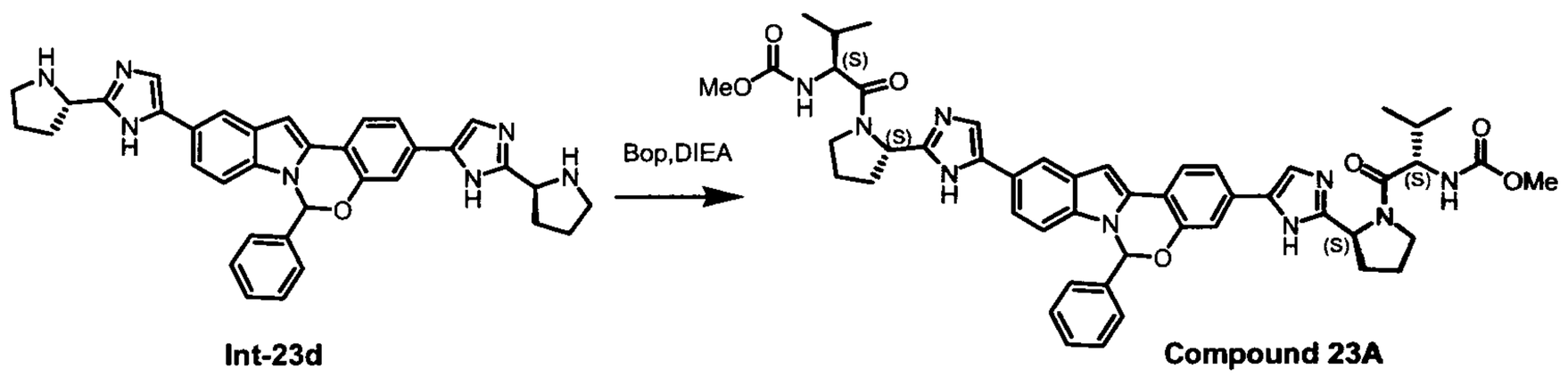
Step D – Preparation of Compound ***Int-23d***



Int-23c **Int-23d**

Int-23c (0.10 g, 0.13 mmol) was added to HCl/CH_3OH (5 mL, 3M) and the resulting reaction was allowed to stir at room temperature for about 3 hours. The reaction mixture was then concentrated *in vacuo* to provide Compound **Int-23d**, which was used without further purification. **MS (ESI)** m / e ($M+H^+$): 568.

*Step E – Preparation of Compound **23A***



Int-23d **Compound 23A**

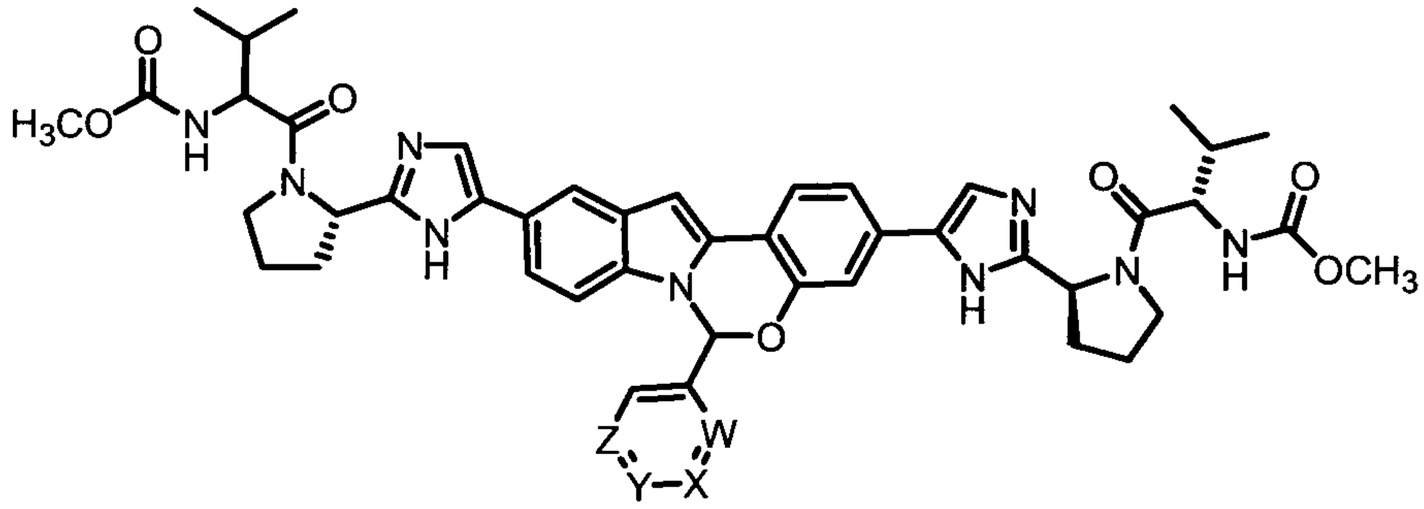
To a solution of **Int-23d** (56.8 mg, 0.10 mmol), (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (35.0 mg, 0.20 mmol) and DIPEA (0.8 mmol) in CH_3CN (1 mL) was added BOP (98 mg, 0.22 mmol). The resulting reaction was allowed to stir at room temperature and monitored using LC/MS. After LC/MS showed the starting material to be consumed, the reaction mixture was filtered, and the filtrate was purified using HPLC to provide Compound **A** as a white solid. ^{1}H NMR (MeOD): δ 7.94 (s, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.74 (s, 1 H), 7.63 (s, 1 H), 7.48 (s, 1 H), 7.35 - 7.37 (m, 2 H), 7.31 (s, 1 H), 7.17 - 7.18 (m, 4 H), 7.11 (s, 1 H), 6.96 - 6.98 (d, *J* = 7.6 Hz, 2 H), 5.09 - 5.17 (m, 2 H), 4.13 (t, *J* = 8.0 Hz, 2 H), 3.99 (bs, 2 H), 3.78 (bs, 2 H), 3.56 (s, 6 H), 2.44 - 2.47 (m, 2 H), 1.92 - 2.19 (m, 8 H), 0.77 - 0.85 (m, 12 H). MS (ESI) m / e ($M+H^+$): 882.

The diastereomers were separated on a chiral SFC column:

Isomer A: ^{1}H NMR (MeOD): δ 8.08 (s, 1H), 7.91 - 7.93 (m, 1 H), 7.72 (s, 1 H), 7.56 (s, 1 H), 7.24 - 7.43 (m, 7 H), 7.19 (s, 1 H), 7.03 - 7.05 (m, 2 H), 5.16 - 5.24 (m, 2 H), 3.81 - 4.21 (m, 6 H), 3.62 (s, 6 H), 2.52 - 2.54 (m, 2 H), 2.00 - 2.25 (m, 8 H), 0.84 - 0.91 (m, 12 H). MS (ESI) m/z $(M+H)^+$: 882.

Isomer B: ^{1}H NMR (MeOD): δ 7.90 (s, 1 H), 7.81 - 7.83 (m, 1 H), 7.72 (s, 1 H), 7.62 (s, 1 H), 7.45 (s, 1 H), 7.14 - 7.33 (m, 6 H), 7.09 (s, 1 H), 6.93 - 6.95 (m, 2 H), 5.06 - 5.14 (m, 2 H), 3.71 - 4.11 (m, 6 H), 3.52 (s, 6 H), 2.41 - 2.44 (m, 2 H), 1.90 - 2.15 (m, 8 H), 0.74 - 0.86 (m, 12 H). MS (ESI) m/z $(M+H)^+$: 882.

The Compounds of the present invention depicted in the table below were made using the method described in Example 23 and substituting the appropriate dibromotoluene derivative in Step A

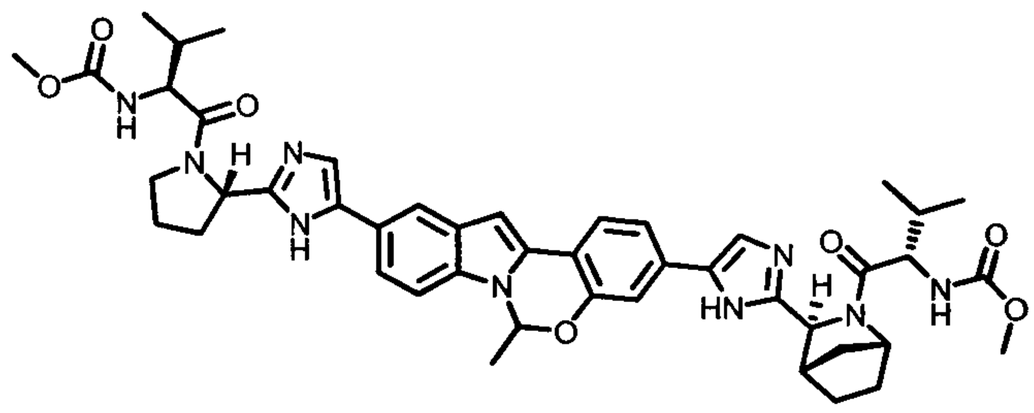


Cpd	W	X	Y	Z	MS
95	CH	CH	$C(OCH_3)$	CH	912
99	CH	CH	CF	CH	900
103	CH	CH	CCl	CH	916, 918
104	CH	CH	$C(CF_3)$	CH	950
108	CH	N	CH	CH	883
109	N	CH	CH	CH	883
110	CH	CF	CH	CH	900
117	CH	CCl	CH	CH	916, 918
121	CH	CH	N	CH	883
125	CH	CH	$C(OCF_3)$	CH	966
126	CH	CF	CF	CH	918
129	CH	CH	$C(CH_3)$	CH	896
130	CCl	CH	CH	CH	916, 918
133	CF	CF	CH	CH	918
136	CH	CH	CCN	CH	907

143	CH	CF	CH	CF	918
145	CH	$C(OCH_3)$	CH	CH	912
149	CF	CH	CH	CH	900
150	CH	$C(CF_3)$	CH	CH	950
153	CF	CH	CH	$C(OCH_3)$	930

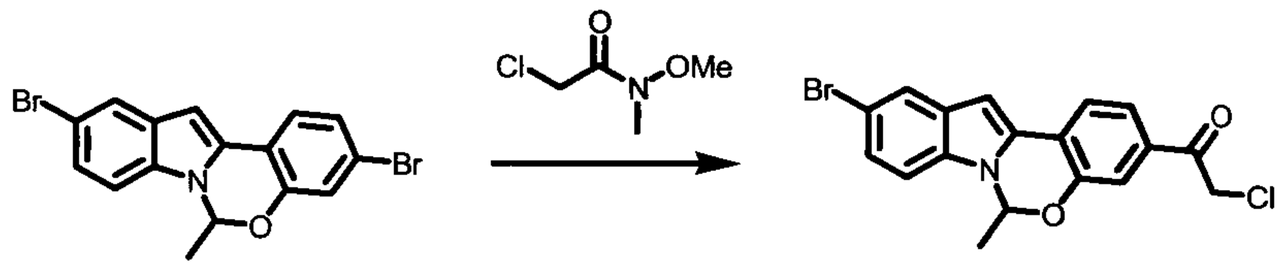
EXAMPLE 24

Preparation of Compound **16**



16

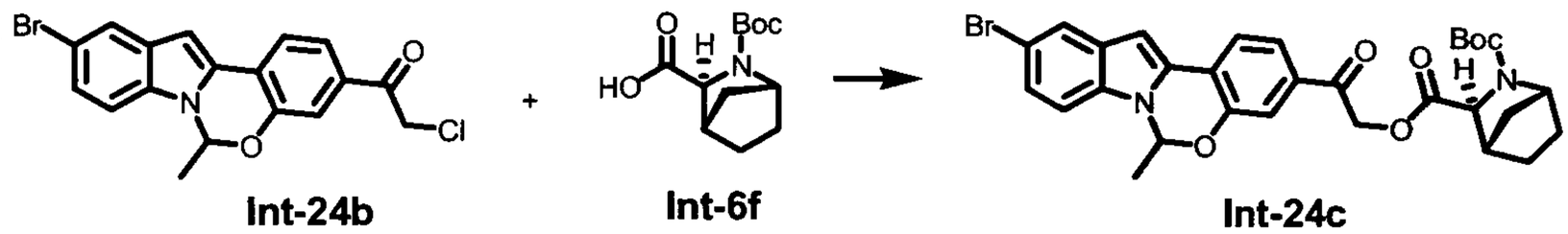
*Step A – Preparation of Compound **Int-24b***



Int-24a **Int-24b**

To a solution of Compound **Int-24a**(1.48 g, 3.76 mmol) in 11 mL THF at -78 °C was added n-BuLi (2.5 M in hexane, 1.66 mL, 4.14 mmol). The reaction was allowed to stir at -78 °C for 30 minutes, then 2-chloro-N-methoxy-N-methylacetamide(1.1 g, 7.52 mmol) in 2 mL of THF was added at -78 °C . The reaction was allowed to stir for 1 hour at -78 °C, then was quenched with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc and the organic extract was washed with brine solution, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting residue was purified using an ISCO 80 g column (hexane to 50% EtOAc-hexane, gradient) to provide Compound **Int-24b**, 503 mg (35%). LRMS: $(M+H)^+ = 390$.

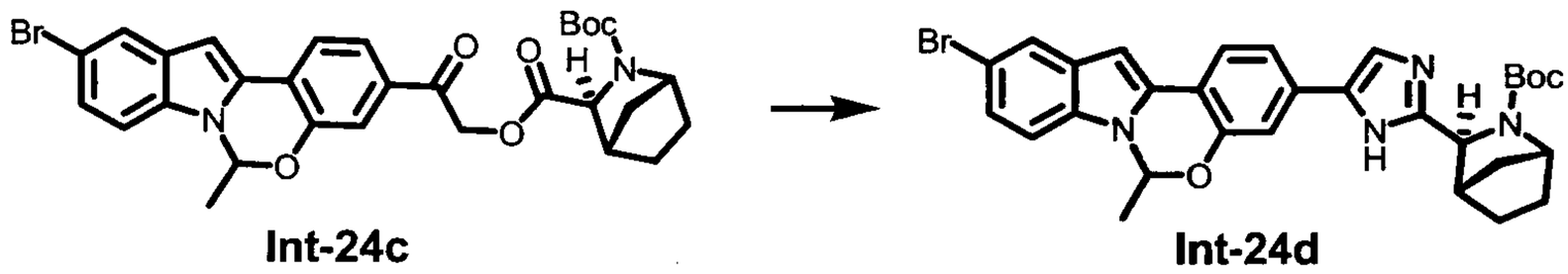
Step B – Preparation of Compound ***Int-24d***



Int-24b **Int-6f** **Int-24c**

To a solution of Compound **Int-24b** (97 mg, 0.25 mmol) and **Int-6f** (91 mg, 0.38 mmol) in DMF (2 mL) was added Cs_2CO_3 (163 mg, 0.50 mmol). The resulting reaction was heated to 40 °C, allowed to stir at this temperature for 1 hour, then cooled to 25 °C. The reaction mixture was poured into ice-water and the organic phase was extracted with EtOAc. The organic extract was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue obtained was purified using an ISCO 24 g column (gradient from hexane to 40% EtOAc in hexane) to provide Compound **Int-24c**, 135 mg (91%).

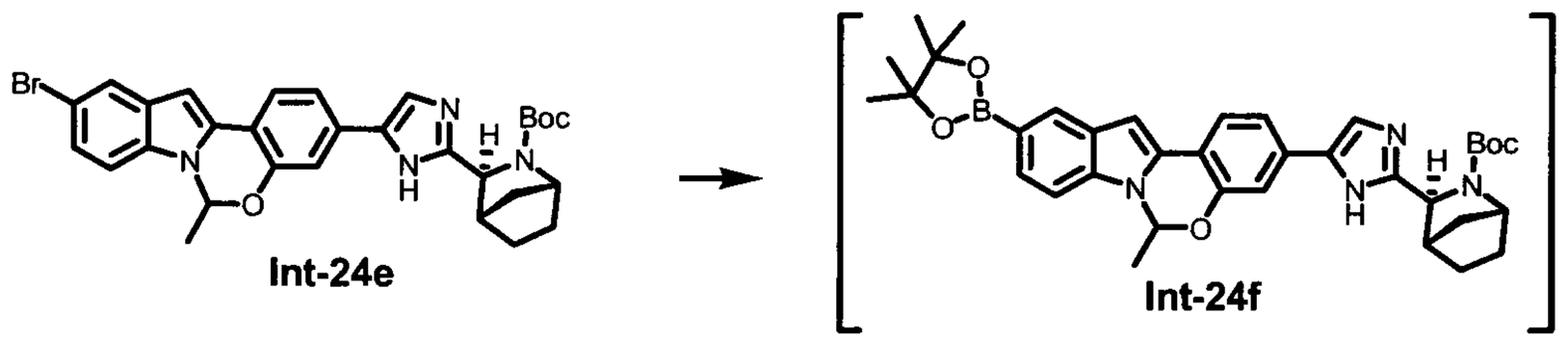
Step C – Preparation of Compound ***Int-24d***

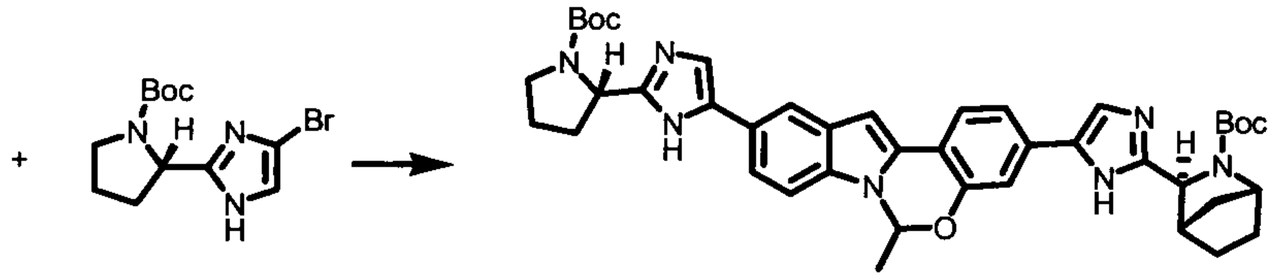


Int-24c **Int-24d**

To a solution of Compound **Int-24c** (135 mg, 0.23 mmol) in *o*-xylene (2 mL) was added ammonium acetate (107 mg, 1.38 mmol) and the resulting reaction was allowed to stir at 140 °C for 3 hours. After being cooled to 25 °C, the reaction mixture was added to aqueous $NaHCO_3$ solution and the organic layer were extracted with EtOAc. The combined organic solutions was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue obtained was purified using an ISCO 24 g column (gradient from hexane to 50% EtOAc in hexane) to provide Compound **Int-24d**, 84 mg (64%). LRMS: $(M+H)^+ = 575$

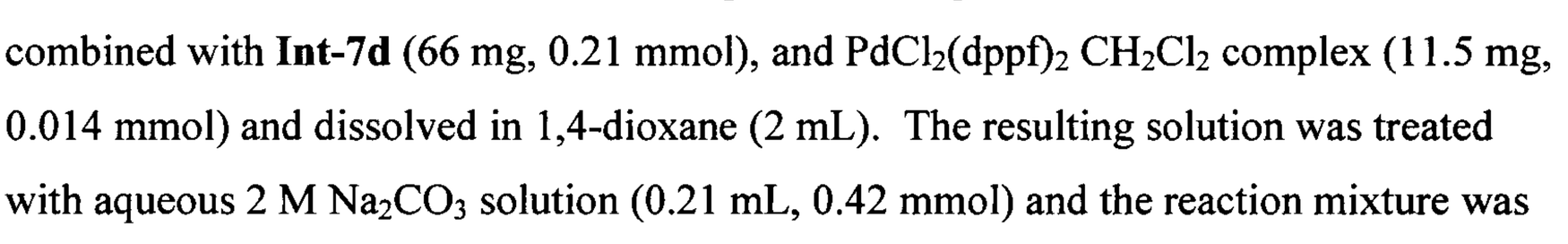
Step D – Preparation of Compound ***Int-24g***





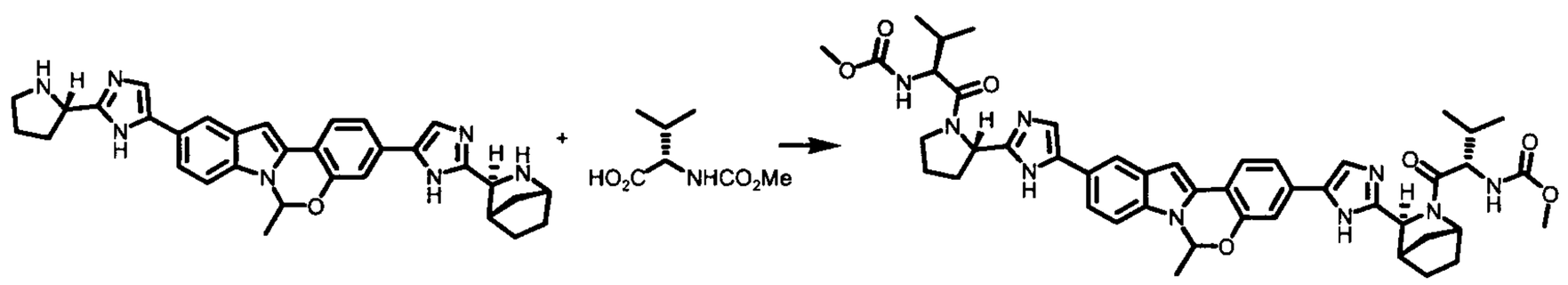
To a solution of Compound **Int-24d** (81 mg, 0.14 mmol), bis-pinacolatodiborane (53 mg, 0.21 mmol), $PdCl_2(dppf)_2$ CH_2Cl_2 complex (11.5 mg, 0.014 mmol) in 1,4-dioxane (2 mL) was added potassium acetate (41 mg, 0.42 mmol). The reaction was degassed and allowed to stir at 100 °C for 2 hours. After being cooled to 25 °C, the reaction mixture was diluted with EtOAc and filtered through a Celite pad. The filtrate was concentrated *in vacuo* to provide Compound **Int-24f**, which was combined with **Int-7d** (66 mg, 0.21 mmol), and $PdCl_2(dppf)_2$ CH_2Cl_2 complex (11.5 mg, 0.014 mmol) and dissolved in 1,4-dioxane (2 mL). The resulting solution was treated with aqueous 2 M Na_2CO_3 solution (0.21 mL, 0.42 mmol) and the reaction mixture was degassed and allowed to stir at 100 °C for 2 hours. After being cooled to 25 °C, the reaction mixture was diluted with EtOAc and filtered through a Celite pad. The filtrate was concentrated *in vacuo* and the residue obtained was purified using an ISCO 24 g column (gradient from 0% to 100% EtOAc in hexane) to provide Compound **Int-24g** (40 mg, 39%). LRMS: $(M+H)^+ = 732$.

Step E – Preparation of Compound ***Int-24h***



To a 0 °C solution of Compound **Int-24g** (40 mg, 0.054 mmol) in dichloromethane (2 mL) was added TFA (0.4 mL). The reaction was allowed to stir at 0 °C for 0.5 hours and then was warmed to 25 °C and allowed to stir for 2 additional hours. The reaction mixture was concentrated *in vacuo* and the residue obtained was dissolved in MeOH (2 mL) followed by addition of 4N HCl in dioxane (0.3 mL). The solution was concentrated *in vacuo* to provide Compound **Int-24h** as its HCl salt (40 mg), which was used without further purification. LRMS: $(M+H)^+ = 532$.

Step F – Preparation of Compound 16



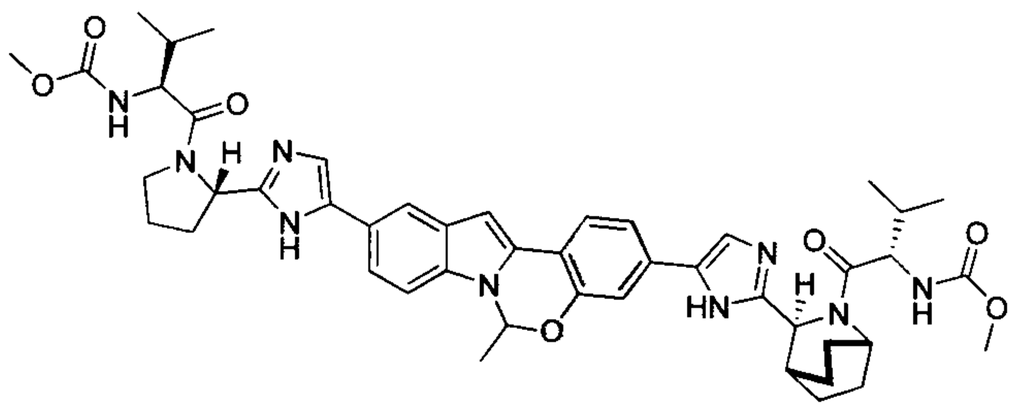
Int-24h **Int-1a** **16**

To a -30 °C solution of Compound **Int-24h** (41 mg, 0.068 mmol), Compound **Int-1a** (36 mg, 0.20 mmol), and diisopropylethylamine (83 µL, 0.48 mmol) in DMF (1.5 mL) was added HATU (103 mg, 0.27mmol). The mixture was allowed to stir at -30 °C to 0 °C for 1 hour and for an additional 2 hours at 0 °C. The reaction was then quenched by addition of cold water and the resulting mixture was purified using Gilson HPLC (CH_3CN–H_2O, 0.1% TFA) to provide Compound **16**. Compound **16** was dissolved in MeOH (10 mL) and treated with 4N HCl in dioxane (0.3 mL) followed by concentration *in vacuo* to provide the HCl salt of Compound **16** as a ~1:1 mixture of diastereomers, 16 mg (28%).

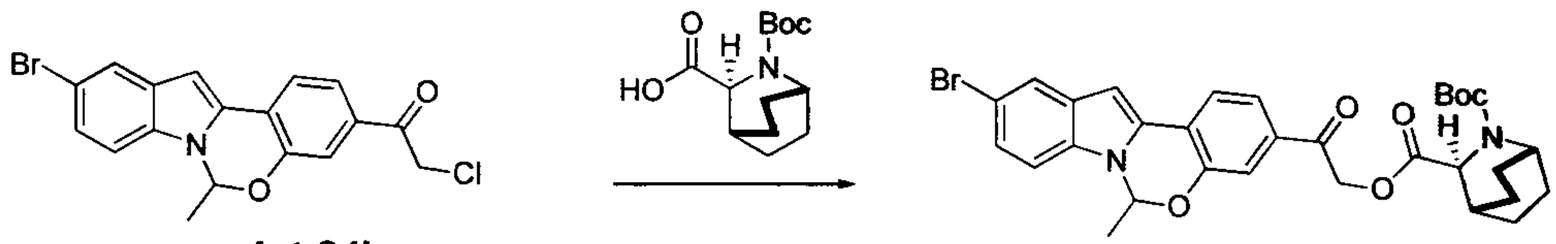
The diastereomers were separated by chiral HPLC using Chiral OD (Lux Cellulose-1) Semi-prep column (20% EtOH-hexane, 0.1% DEA) to provide Compound **16A** (retention time: 44 minutes), 6 mg, and Compound 37B (retention time : 66 minutes), 3 mg.

EXAMPLE 25

Preparation of Compound **17**



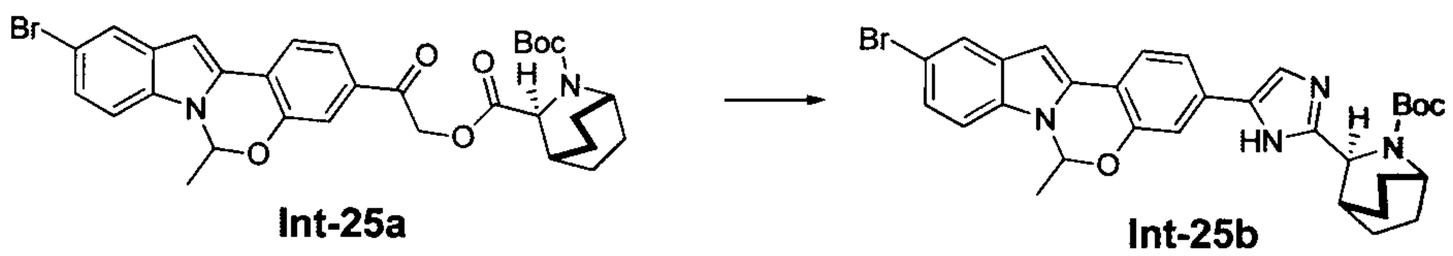
*Step A – Preparation of Compound **Int-25a***



Int-24b **Int-25a**

Compound **Int-25a** was prepared from Compound **Int-24b** using the method described in Example **24**, Step B (**100%**).

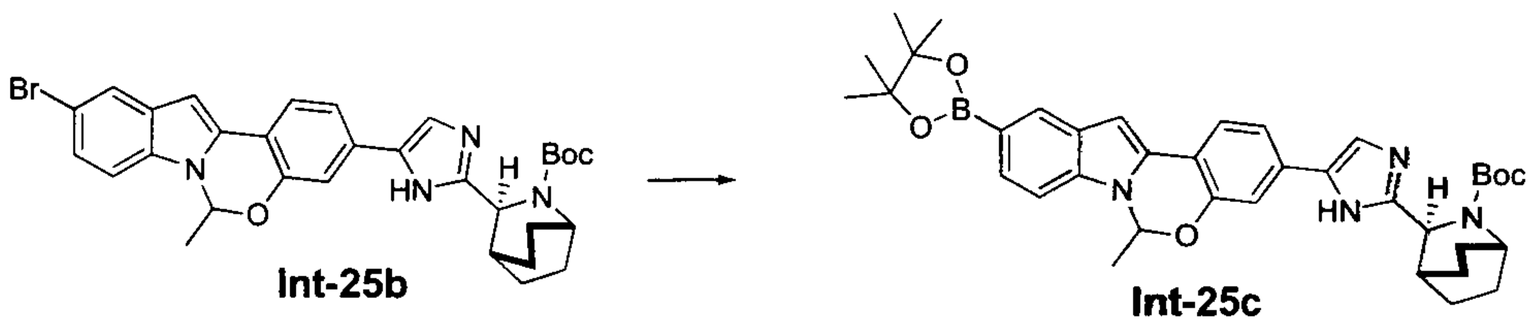
*Step B – Preparation of Compound **Int-25b***

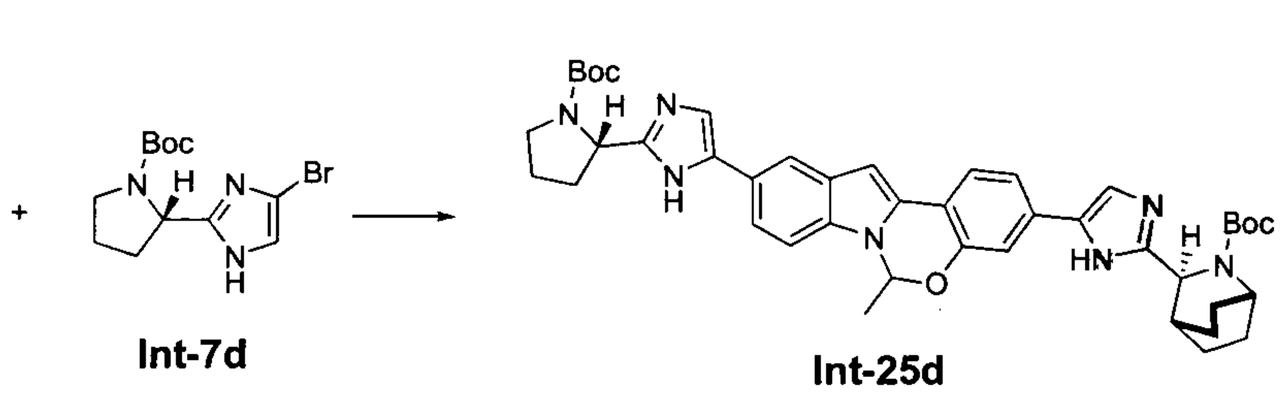


Int-25a **Int-25b**

Compound **Int-25b** was prepared from Compound **Int-25a** using the method described in Example **24**, Step C yield **(45%)**. LRMS $(M+H)^+$ = 589.

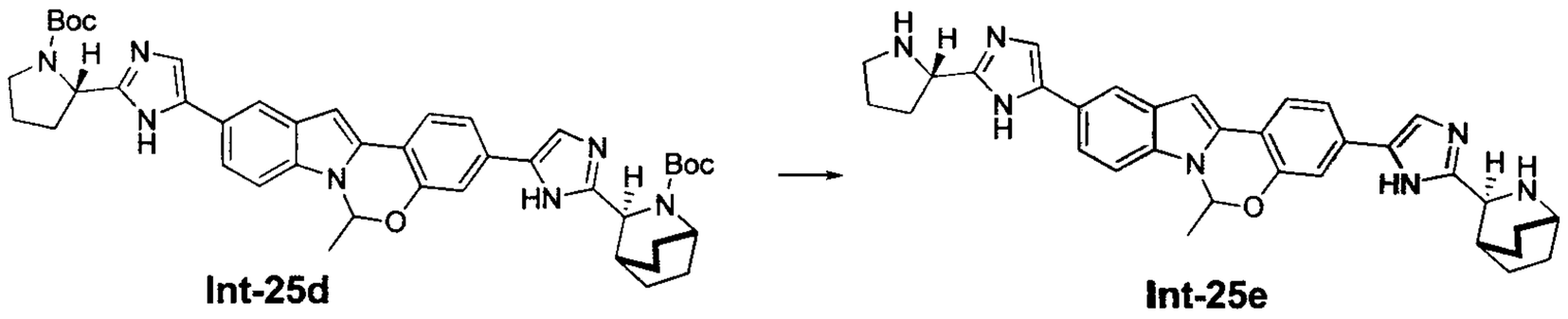
*Step C – Preparation of Compound **Int-25d***





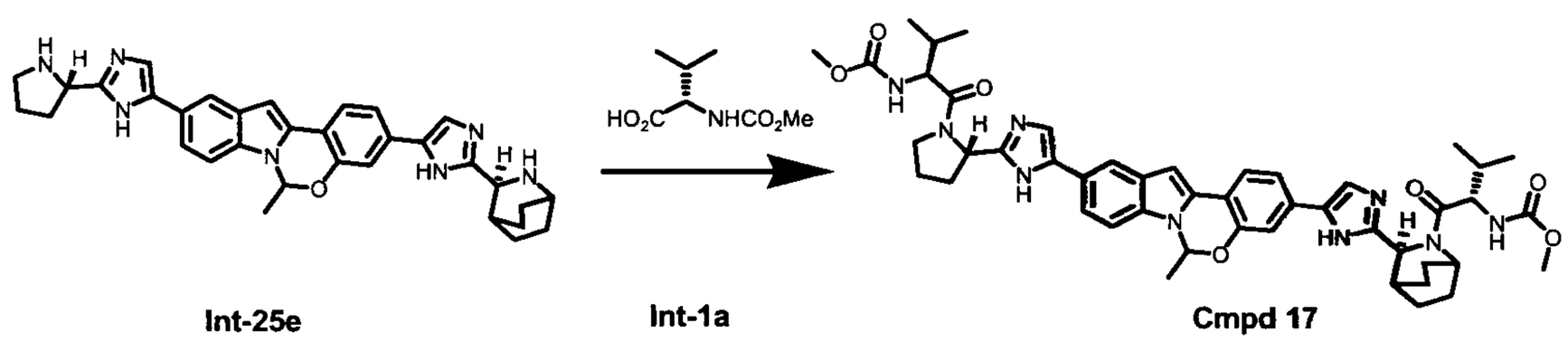
Compound **Int-25d** was prepared from Compound **Int-25b** using the method described in Example **24**, Step D yield (44%). LRMS: $(M+H)^+ = 746$.

Step D – Preparation of Compound ***Int-25e***



Compound **Int-25e** was prepared from Compound **Int-25d** using the method described in Example **24**, Step Eyield (100%).

Step E – Preparation of Compound ***17***

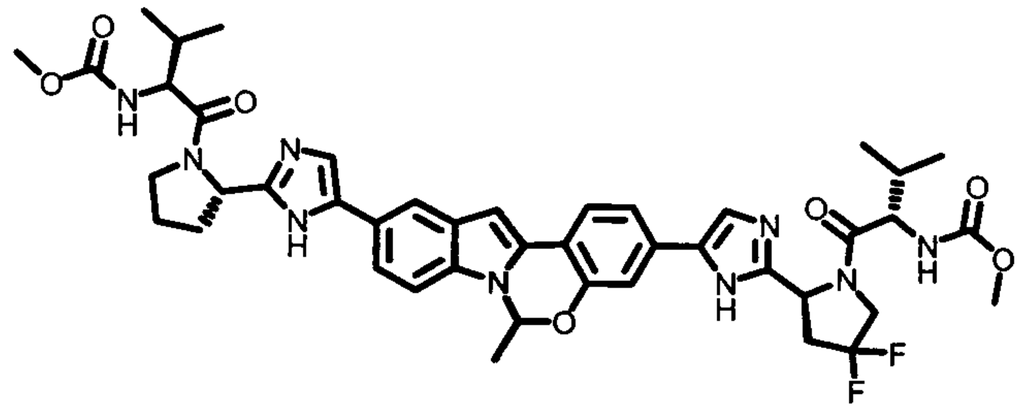


Compound **17** (HCl salt) was prepared from Compound **Int-25e** using the method described in Example **24**, Step F yield (50%).

The diastereomers were separated by chiral **HPLC** using **Chiral** Lux C-2 Semi-prep column (50% EtOH-hexane, 0.1% DEA) to provide Compound **17A** (retention time: 45 minutes) and Compound **17B** (retention time: 59 minutes).

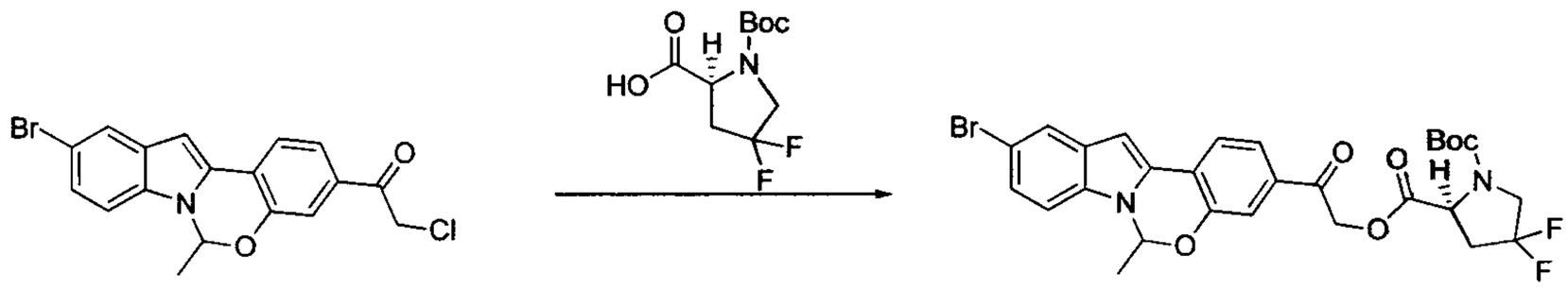
EXAMPLE 26

Preparation of Compound **23**



23

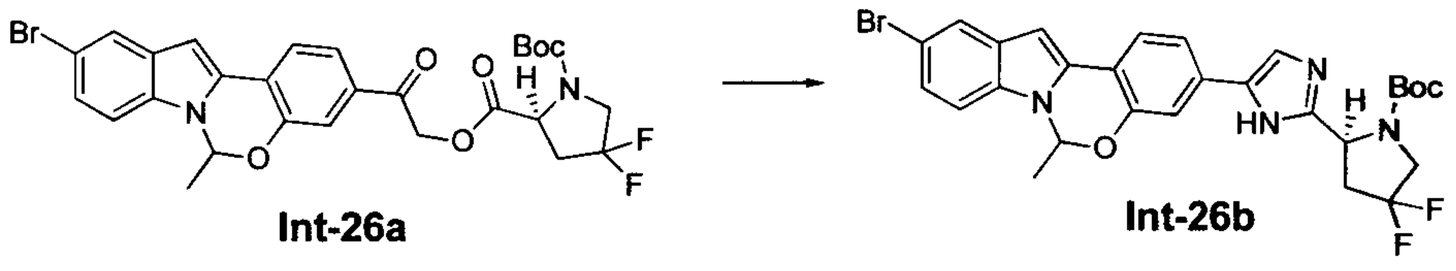
*Step A – Preparation of Compound **Int-26a***



Int-24b **Int-26a**

Compound **Int-26a** was prepared from Compound **Int-24b** using the method described in Example 24, step B (87%).

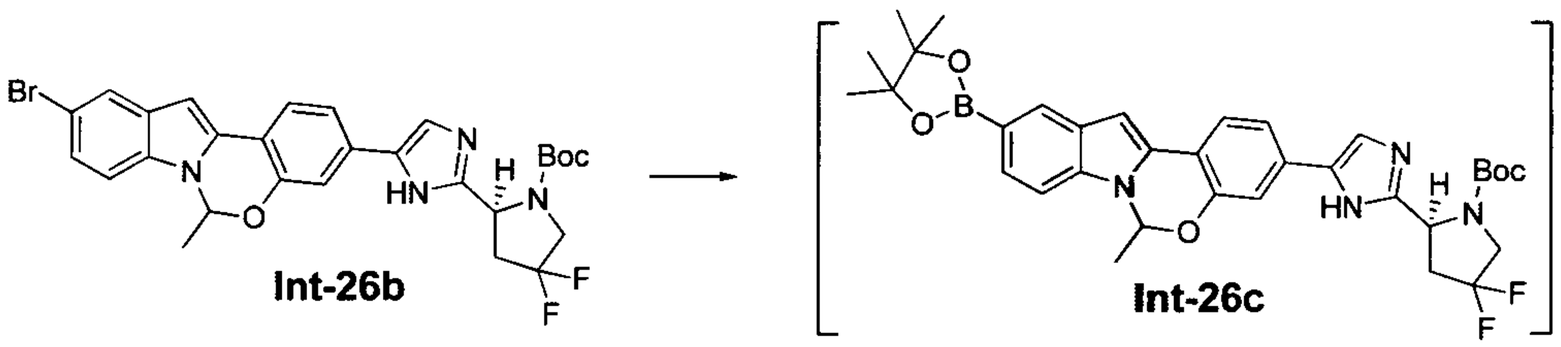
*Step B – Preparation of Compound **Int-26b***

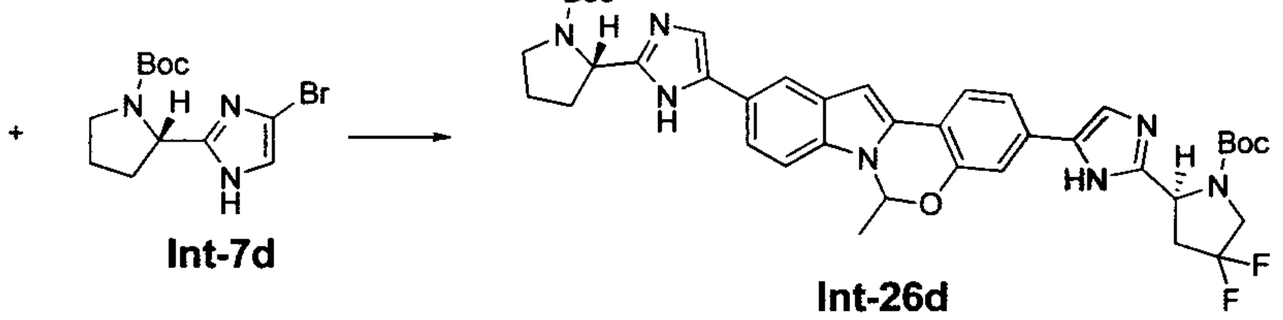


Int-26a **Int-26b**

Compound **Int-26b** was prepared from Compound **Int-26a** using the method described in Example 24, step C (72%). LRMS $(M+H)^+ = 585$.

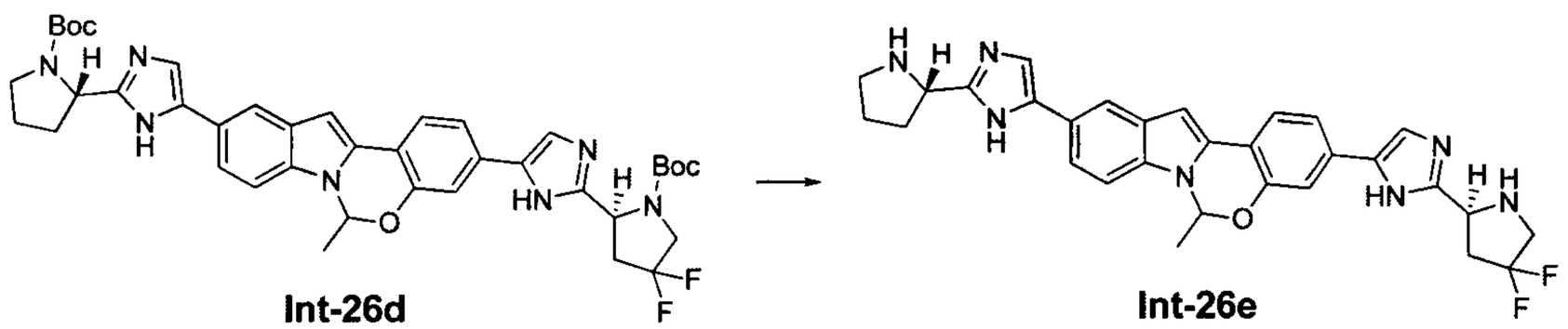
*Step C – Preparation of Compound **Int-26d***





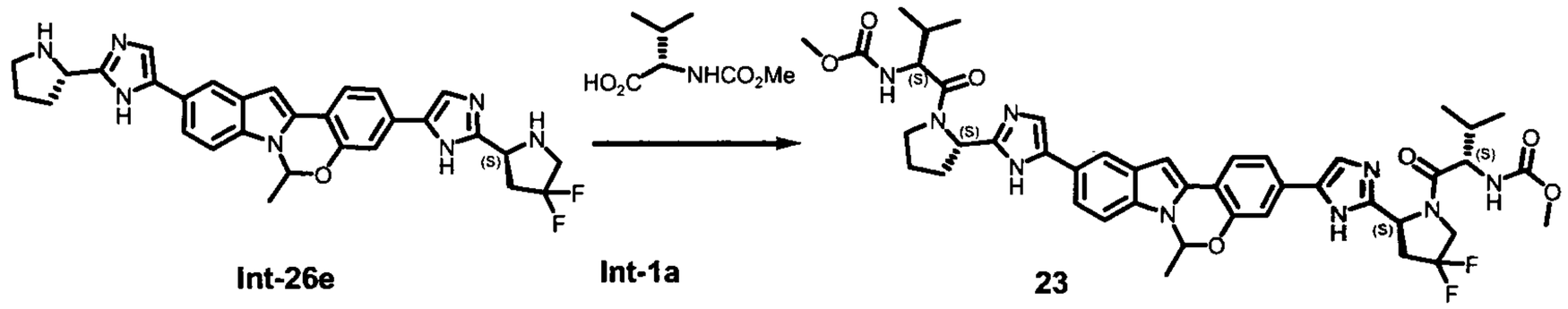
To a solution of Compound **Int-26b** (243 mg, 0.42 mmol), bis-pinacolato diborane (127 mg, 0.50 mmol), $PdCl_2(dppf)_2$ CH_2Cl_2 complex (34 mg, 0.042 mmol) in 1,4-dioxane (3 mL) was added potassium acetate (83 mg, 0.84 mmol). The mixture was degassed and allowed to stir at 100 °C for 2 hours. After being cooled to 25 °C, **Int-7d** (265 mg, 0.84 mmol), $PdCl_2(dppf)_2$ CH_2Cl_2 complex (34 mg, 0.042 mmol), and K_2CO_3 (1N aqueous solution, 1.2 mL, 1.2 mmol) were added. The mixture was degassed and allowed to stir at 90 °C for 18 hours. After being cooled to 25 °C, the mixture was diluted with EtOAc and filtered through a Celite pad. The filtrate was concentrated *in vacuo* and the residue obtained was purified using Prep TLC (5% MeOH in CH_2Cl_2) to provide **Int-26d,** 146 mg (47%). LRMS: $(M+H)^+ = 742$.

Step D – Preparation of Compound ***Int-26e***



Compound **Int-26e** was prepared from **Int-26d** using the method described in Example 24, step E (100%). LRMS: $(M+H)^+ = 542.6$.

Step E – Preparation of Compound ***23***



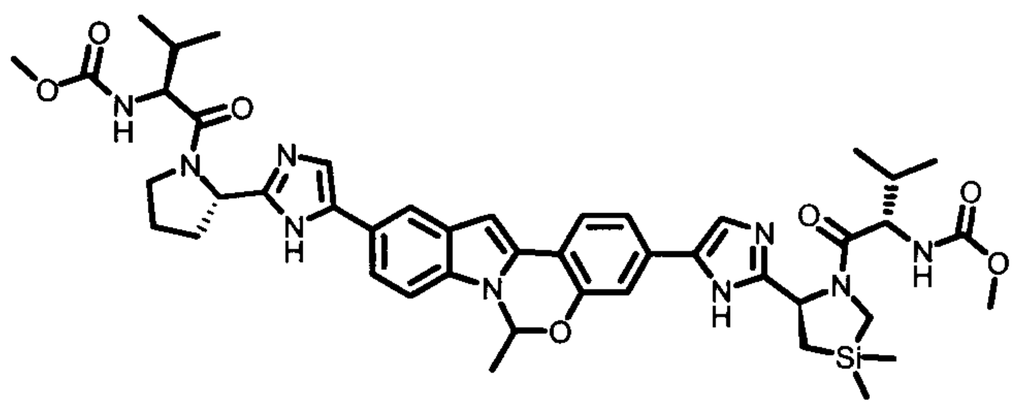
Int-26e Int-1a 23

Compound **23** (HCl salt) was prepared from Compound **Int-26e** using the method described in Example 24, step F (53%).

The diastereomers were separated by chiral HPLC using Chiral Lux C-2 Semi-prep column (50% EtOH-hexane, 0.1% DEA) to provide Compound **23A** (retention time: 16 minutes) and Compound **23B** (retention time: 27 minutes).

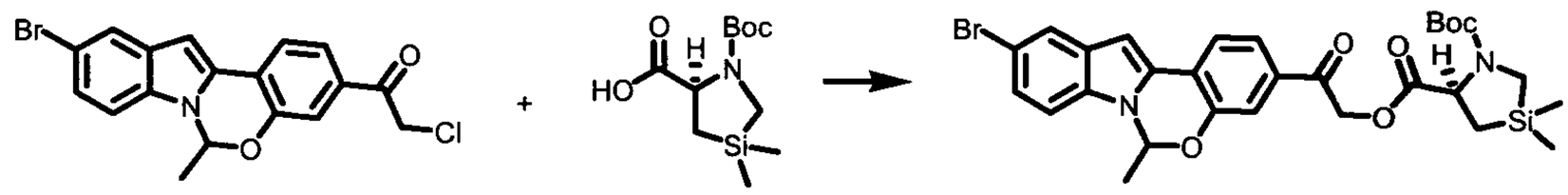
EXAMPLE 27

Preparation of Compound **26**



26

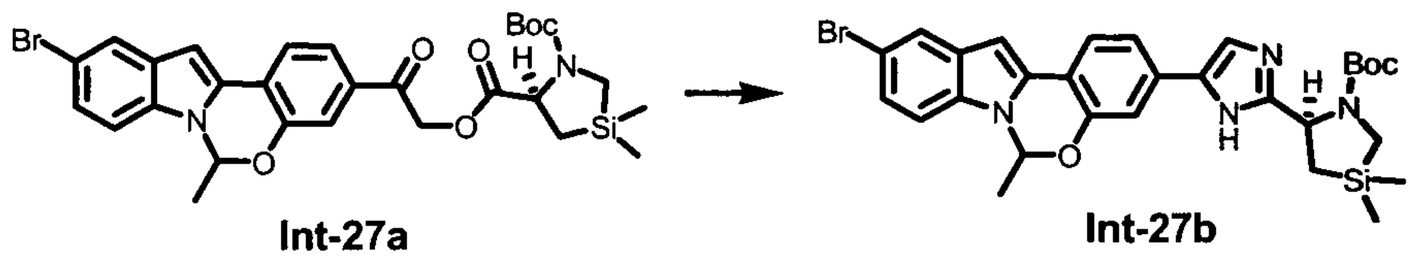
*Step A – Preparation of Compound **Int-27a***



Int-24b Int-13e Int-27a

Compound **Int-27a** was prepared from Compound **Int-24b** using the method described in Example 24, step B (85%).

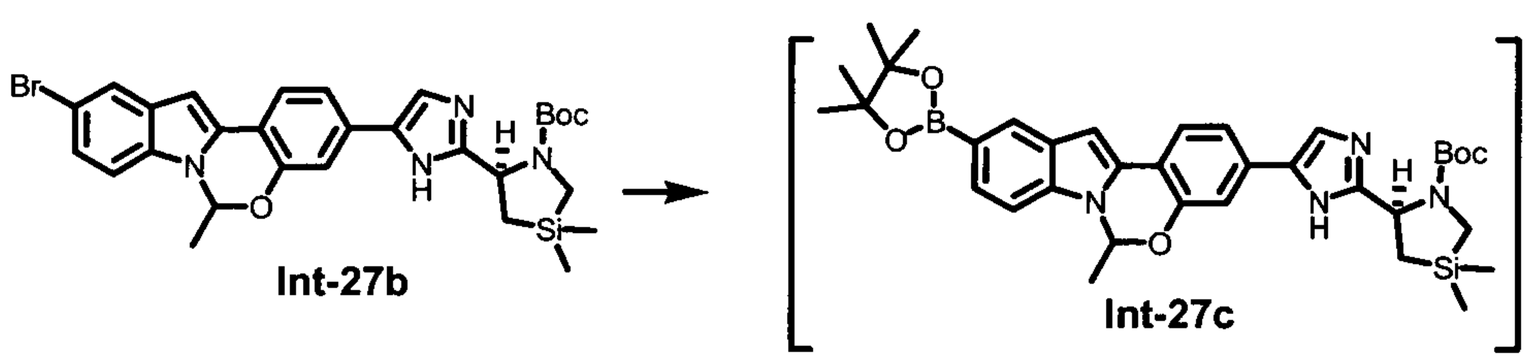
*Step B – Preparation of Compound **Int-27b***



Int-27a Int-27b

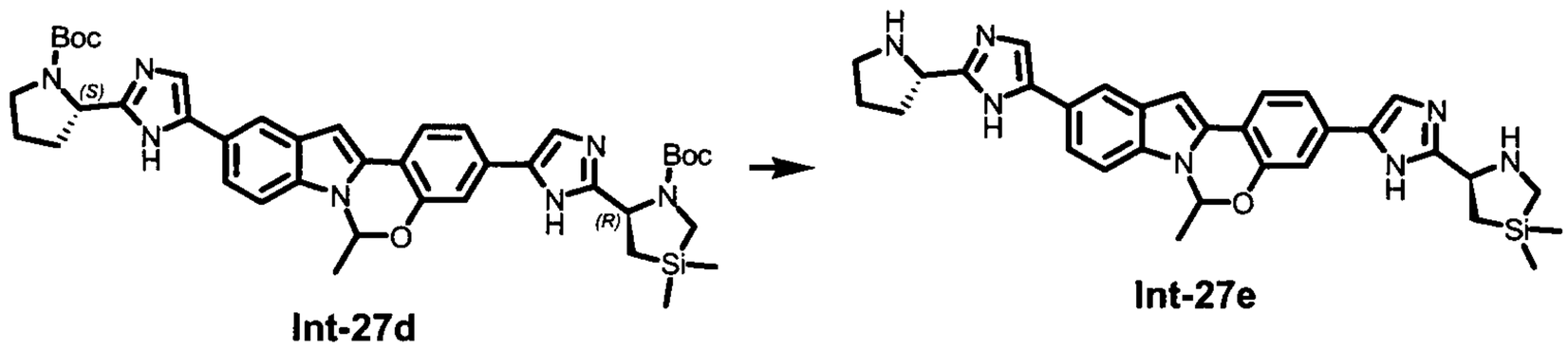
Compound **Int-27b** was prepared from Compound **Int-27a** using the method described in Example 24, step C (75%). LRMS $(M+H)^+ = 593$.

*Step C – Preparation of Compound **Int-27d***



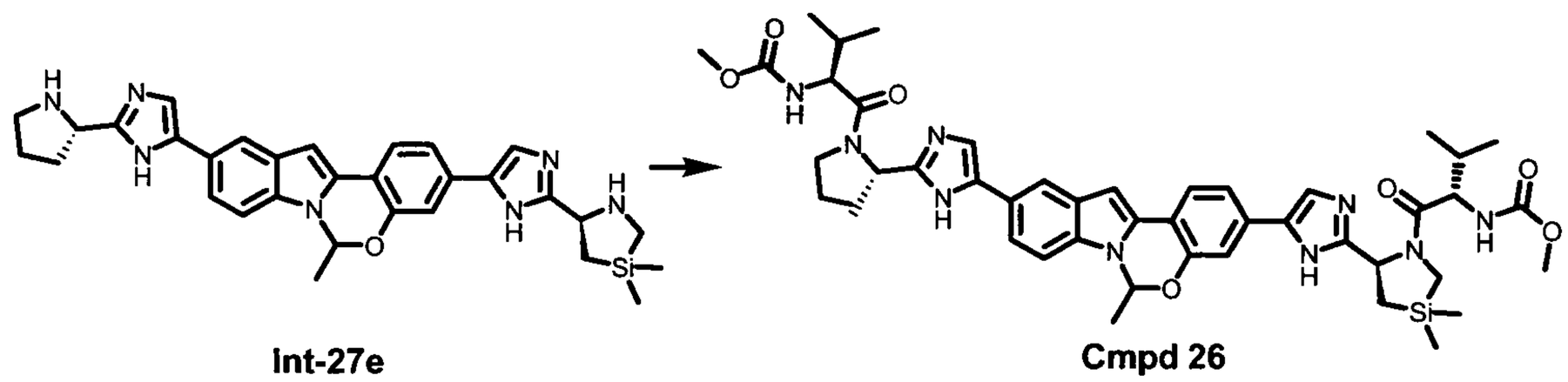
Compound **Int-27d** was prepared from Compound **Int-27b** using the method described in Example 24, step D (40%). LRMS $(M+H)^+ = 750$.

*Step D – Preparation of Compound **Int-27e***



Compound **Int-27e** was prepared from Compound **Int-27d** using the method described in Example 24, step E (100%). LRMS: $(M+H)^+ = 550$.

*Step E – Preparation of Compound **26***



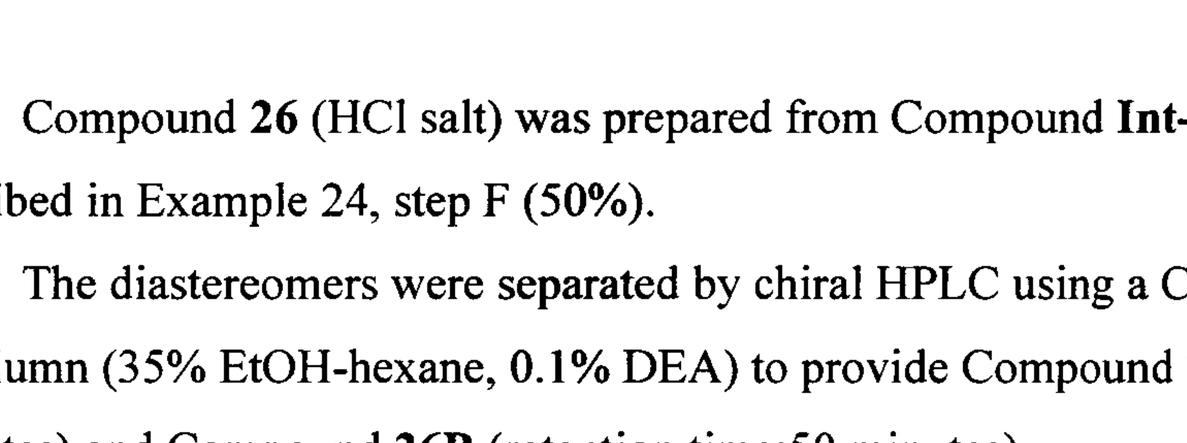
Int-27e Cmpd 26

Compound **26** (HCl salt) was prepared from Compound **Int-27e** using the method described in Example 24, step F (50%).

The diastereomers were separated by chiral HPLC using a Chiral Lux C-2 Semi-prep column (35% EtOH-hexane, 0.1% DEA) to provide Compound **26A** (retention time: 38 minutes) and Compound **26B** (retention time:50 minutes).

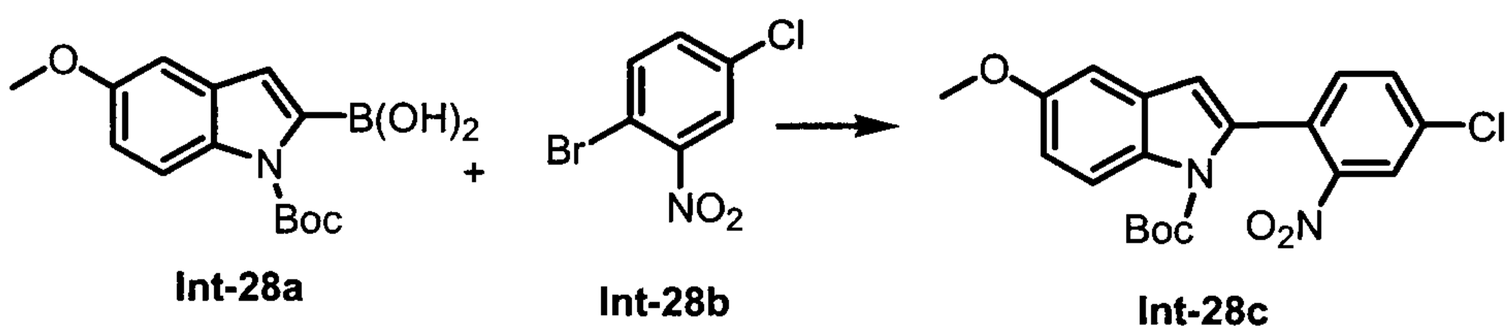
EXAMPLE 28

Preparation of Compound **240**



Cmpd 240

*Step A – Preparation of Compound **Int-28c***

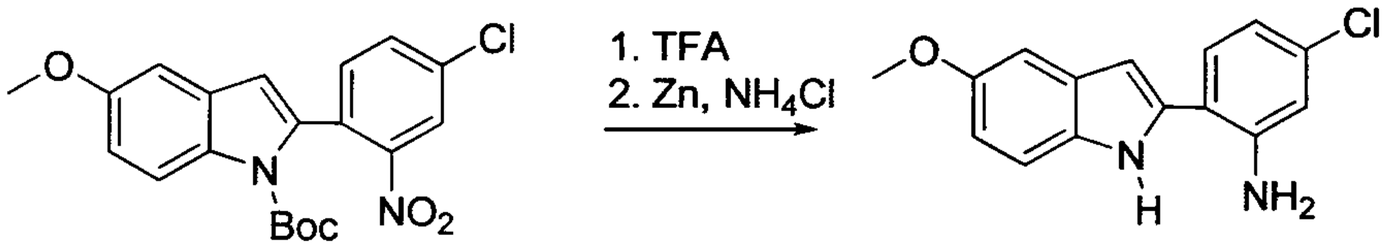


Int-28a **Int-28b** **Int-28c**

A solution of **Int-28a** (13.2 g, 46mM), **Int-28b** (9.0g, 38 mM), $Pd(PPh_3)_4$ (4.4 g, 3.8 mM), K_2CO_3 (13.1g, 95 mmol) in 28 mL H_2O and 140 mL DME was purged with nitrogen. The reaction was allowed to stir at refluxed for 3 hours. Another portion of boronic acid (0.5 equiv.), $Pd(PPh_3)_4$ (0.01 eq) were added and the reaction was allowed to stir at reflux for an additional 4 hours. The reaction mixture was diluted with EtOAc and filtered through a small Celite plug. The filtrate was concentrated *in vacuo* and the

residue obtained was purified using flash LC (0%-10% EtOAc/Hexane) to provide Compound **Int-28c** (14.5 g). MS (ESI) m / e ($M+Na^+$): 425.

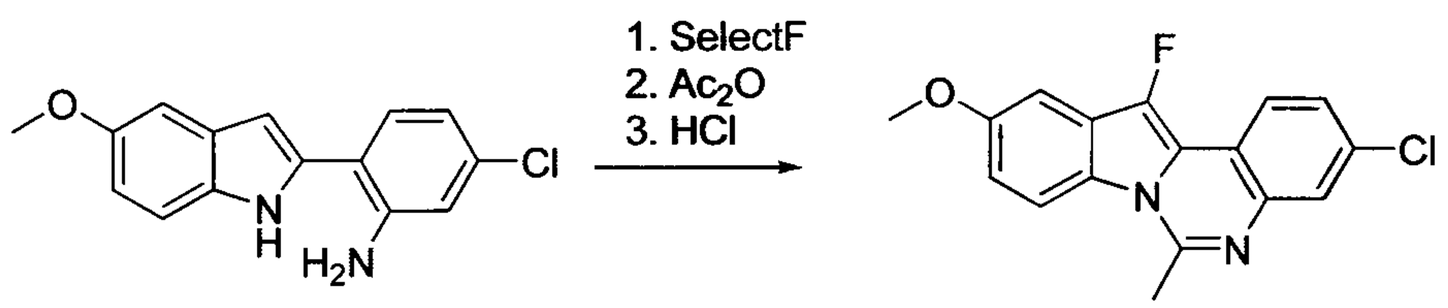
*Step B – Preparation of Compound **Int-28d***



Int-28c **Int-28d**

To a suspension of Compound **Int-28c** (2 g, 5 mM) in CH_2Cl_2 (8 mL), TFA (4 mL) was added dropwise and the reaction was allowed to stir at room temperature for 14 hours. The reaction mixture was concentrated *in vacuo* and the resulting residue was suspended in a solvent mixture of THF (25 mL), ethanol (6 mL) and water (2.5 mL). Zn dust (3.25 g, 50 mmol) and NH4Cl (1.3 g, 25 mmol) were added and the reaction was allowed to stir at reflux for 1 hour. The reaction mixture was diluted with EtOAc and filtered through a small Celite plug. The filtrate was washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide Compound **Int-28d** (1.9 g). MS (ESI) m / e ($M+H^+$): 273.

*Step C – Preparation of Compound **Int-28e***

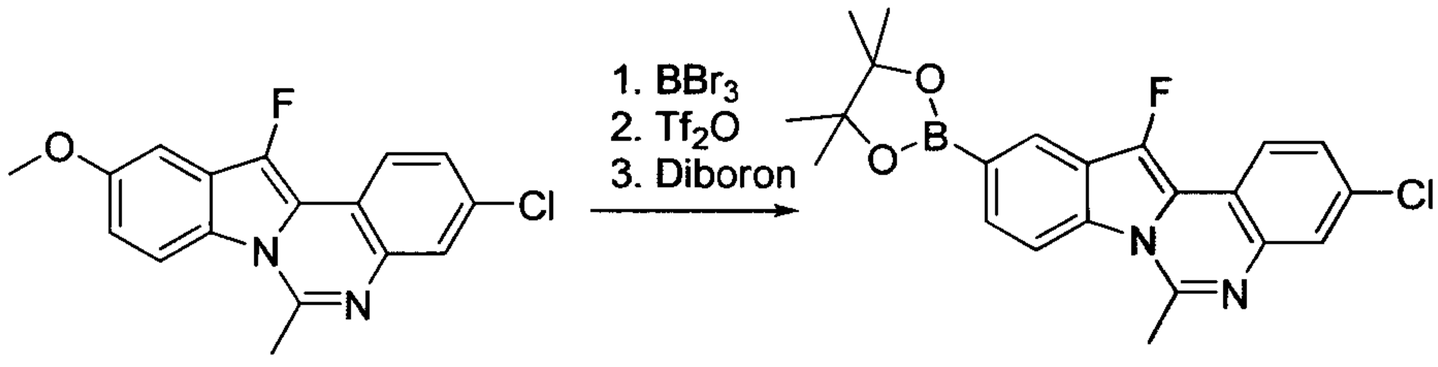


Int-28d **Int-28e**

To a suspension of **Int-28d** (1 g, 3.6 mM) in DMSO (5 mL)/ Acetonitrile (5 mL) was added Select-F (1.53 g, 4.3 mmol). The reaction was allowed to stir for 30 minutes, then was diluted with EtOAc and washed with water and brine, and the organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue obtained was suspended in acetic anhydride (4 mL) and allowed to stir at room temperature for 2 hours. The reaction mixture was then diluted with EtOAc and washed with $NaHCO_3$

solution and water. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* and the residue obtained was suspended in EtOAc (10 mL). To the resulting suspension was added 4M HCl in dioxane (4 mL) and the reaction was allowed to stir at room temperature for 2 hours. The reaction mixture was filtered and the collected solid was washed with hexane, then recrystallized from ethanol to provide Compound **Int-28e** (200 mg). MS (ESI) m / e ($M+H^+$): 315.

*Step D – Preparation of Compound **Int-28f***

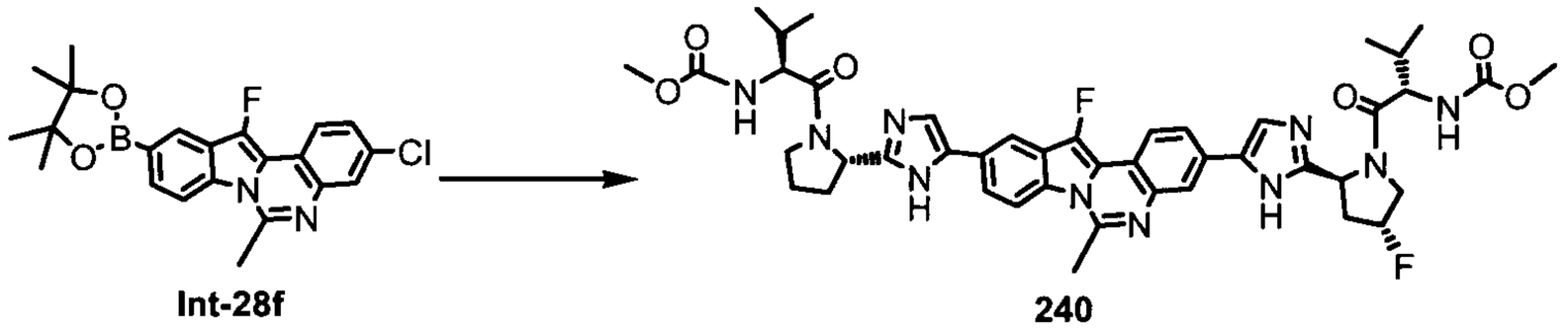


Int-28e **Int-28f**

To a 0 °C suspension of **Int-28e** (200 mg, 0.63 mM) in CH_2Cl_2 (5 mL) was added 1M solution of BBr_3 in CH_2Cl_2 (5 mL) at 0 °C. The reaction was allowed to stir at 0 °C for 1.5 hours, then an additional 5 mL of 1M solution of BBr_3 in CH_2Cl_2 was added and the reaction was heated to 40 °C and allowed to stir at this temperature for 5 hours. The reaction mixture was then diluted with EtOAc (200 mL) and the resulting solution was washed with $NaHCO_3$ solution and NaOH solution. The organic layer was then washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a residue which was subsequently suspended in CH_2Cl_2 (5 mL) cooled at 0 °C. To this solution was added Et_3N (0.6 mL) and Tf_2O (0.5 mL) and the resulting reaction was allowed to stir at 0 °C for 1.5 hours. The reaction was then diluted with dichloromethane and quenched with 10 % citric acid. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue obtained was suspended in dioxane (8 mL) and to the resulting solution was added bis-pinacolatodiborane (265 mg), $PdCl_2(dppf)_2$ CH_2Cl_2 complex (26 mg) and potassium acetate (206 mg). The mixture was degassed, purged with nitrogen and allowed to stir at 100 °C for 1.6 hours. The reaction mixture was cooled to 25 °C, diluted with EtOAc and filtered through a Celite pad. The filtrate was concentrated *in vacuo* and the residue

obtained was purified using flash LC (0-100 % EtOAc-Hex) to provide Compound **Int-28f** (100 mg).

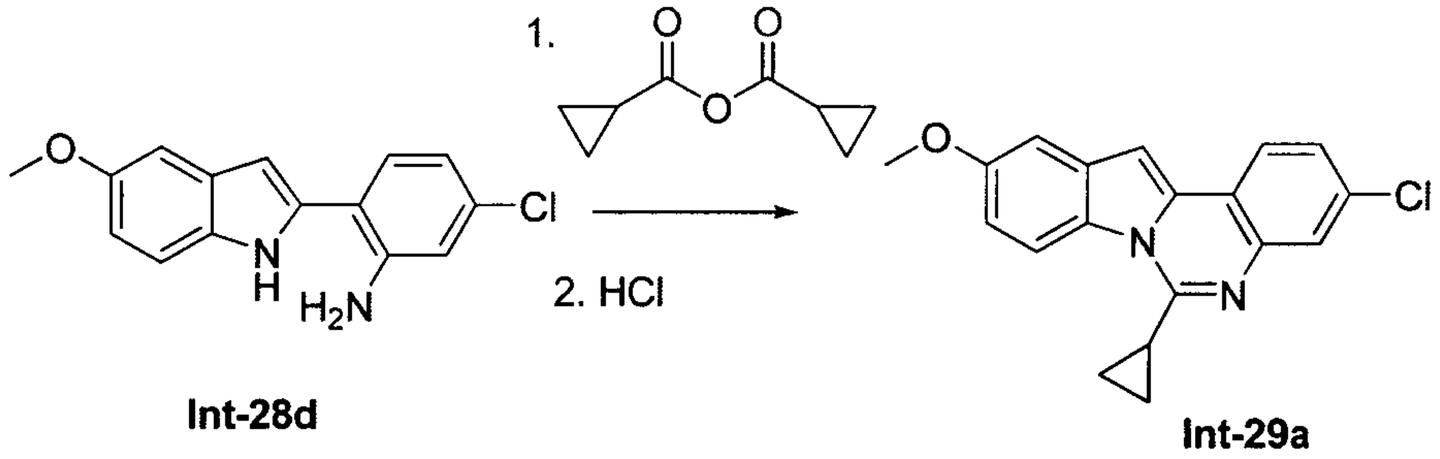
*Step E – Preparation of Compound **240***



Compound **240** was prepared from Compound **Int-28f** using the method described in Example 20.

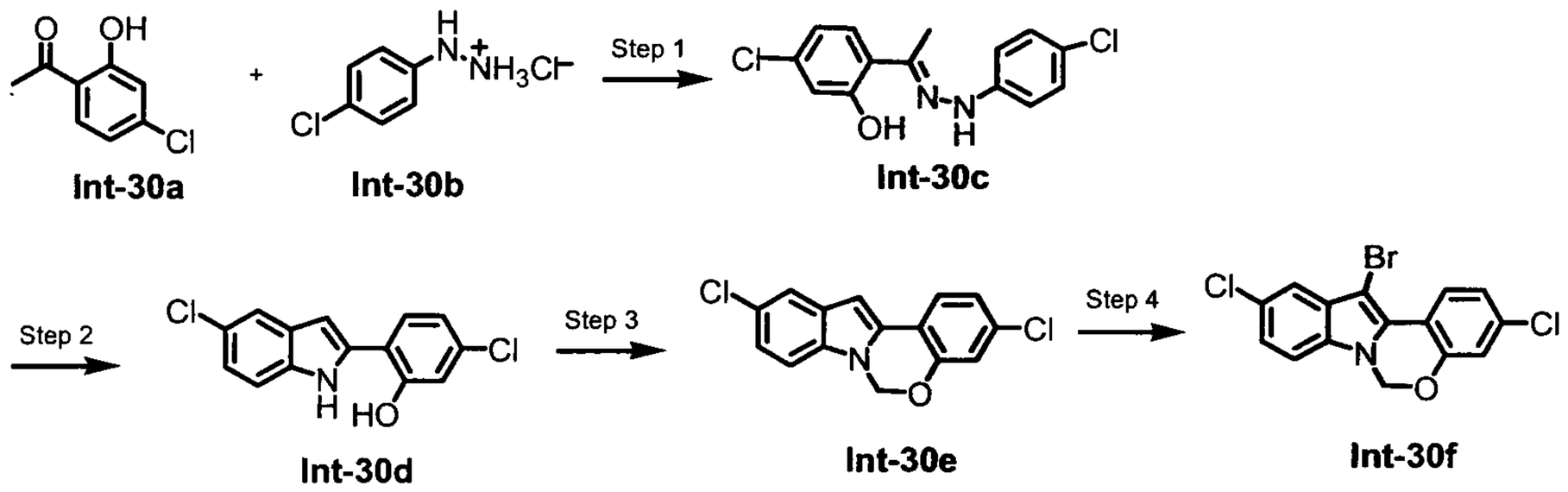
EXAMPLE 29

Preparation of Intermediate Compound **Int-29a**



To a suspension of Compound **Int-28d** (0.51 g, 1.87 mmol) in CH_2Cl_2 (3 mL) was added cyclopropyl anhydride (2 mL). The resulting reaction was allowed to stir at room temperature for 2 hours, then a solution of 4M HCl in dioxane (3 mL) was added and the reaction was allowed to stir at room temperature for 2 hours. The reaction mixture was then filtered and the collected solid was washed with hexane and dried *in vacuo* to provide Compound **Int-29a** (590 mg). MS (ESI) m / e ($M+H^+$): 323.

EXAMPLE 30



Int-30a **Int-30b** **Int-30c**

Int-30d **Int-30e** **Int-30f**

Step A

Commercially available phenol **Int-30a** (125.g, 73.3 mmol), hydrazine **Int-30b** (13.1 g, 73.3 mmol) and methanol (200 mg) were charged to a 500 mL flask. To the suspension was added potassium acetate (14.5 g, 148 mmol) and the resulting reaction mixture was allowed to stir at reflux. After 3 hours, the reaction was cooled, and the solid collected by filtration, washed with methanol (50 ml) and water (2x50 ml), and dried *in vacuo* to provide hydrazone **Int-30c** as a slightly orange solid (18.5 g, 50%).

Step B

Int-30c (18.5 g, 62.7 mmol) and polyphosphoric acid (50 g) were added to a 250 mL flask equipped with mechanical stirrer. The mixture was allowed to stir at 120 °C for 30 minutes and cooled to room temperature. To the mixture were added ice and water. The solid was collected by filtration, washed with water (2x100 ml) and then dissolved in ethyl acetate (200 ml), and washed with water (2x200 ml) again. The solution was then dried over sodium sulfate, and concentrated *in vacuo* to provide Indole **Int-30d** as a solid (17 g, 98%).

Step C

Indole **Int-30d** (18.3 g, 65.8 mmol), cesium carbonate powder (356.6 g, 117 mmol), and DMSO (100 ml) were charged into a 500 mL flask. To the resulting suspension was added diiodomethane (134.4 g, 36 mmol) via a syringe. The reaction mixture was allowed to stir at room temperature for about 15 hours, treated with water

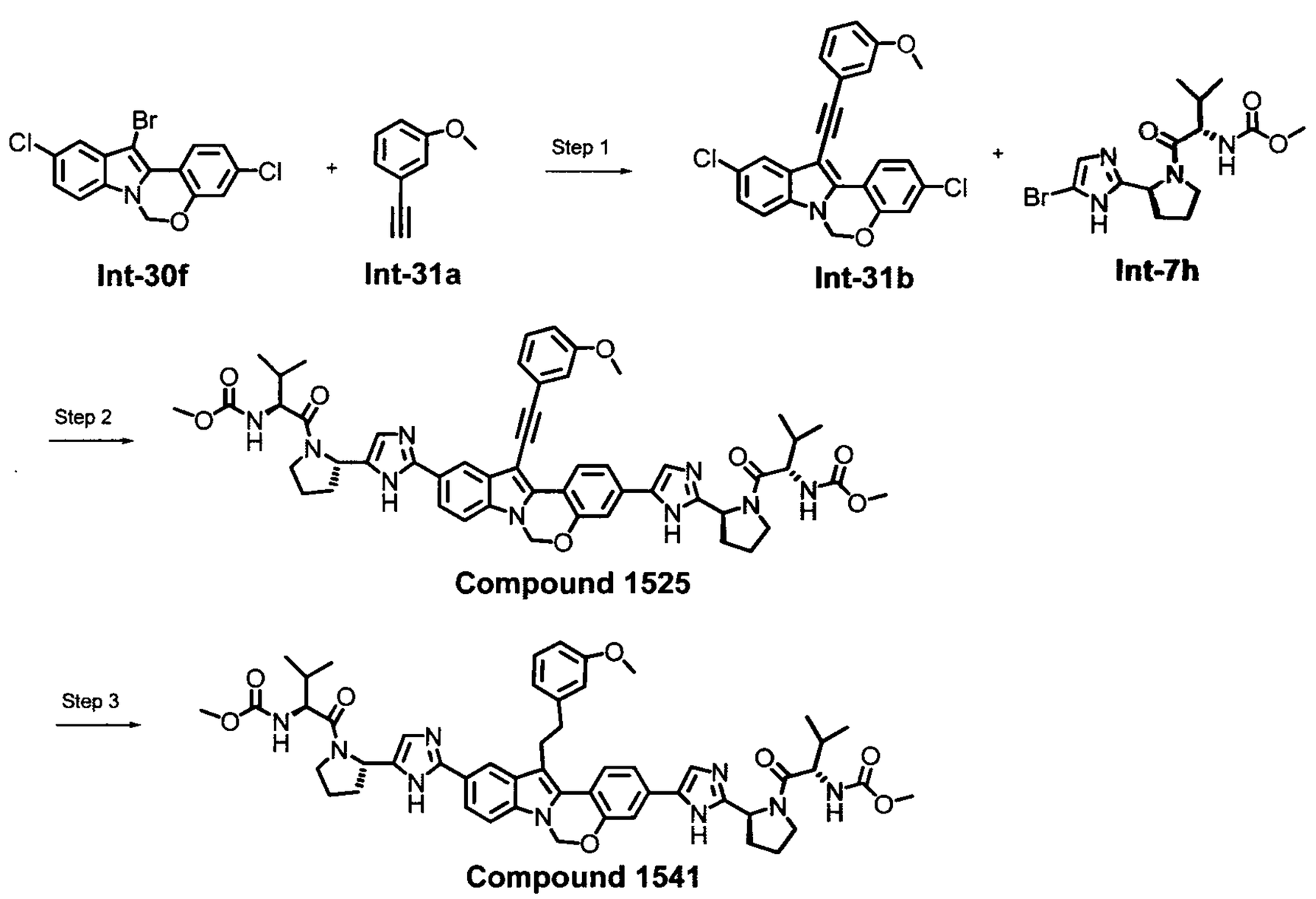
(300 ml) and filtered. The solid was purified using a 120 g silica column/Combi-Flash Rf system using a gradient of 0-20% ethyl acetate in hexanes to provide **Int-30e** as a white solid (8.5 g, 45%).

Step D

Int-30e (2.4 g, 8.27 mmol), NBS (1.47 g, 8.27 mmol), and THF (50 ml) were added to a 100 mL flask and stirred at room temperature. After 5h the reaction was concentrated *in vacuo* to a semi-solid and the residue was treated with water (100 ml), stirred at room temperature for about 15 hours, and filtered. The filter cake was washed with water (3X20 ml) and dried to provide indole **Int-30f** as a pale solid (2.7 g, 88%).

EXAMPLE 31

Preparation of Compound **1525** & Compound **1541**



Int-30f **Int-31a** **Int-31b** **Int-7h**

Compound 1525

Compound 1541

Step A

To a 35 mL microwave reaction tube were added **Int-30f** (500 mg, 1.36 mmol), bis(triphenylphosphine)palladium (II) dichloride (95 mg, 0.135 mmol), copper iodide (258 mg, 1.355 mmol), and DMF (10 mL). The resulting suspension was degassed and heated to 100 °C, and then **Int-31a** was then added in portions via a syringe. The resulting mixture was allowed to stir at 100 °C for additional 6 hours under nitrogen. After cooling, the solution was diluted with 10 mL of ethyl acetate, filtered, and concentrated *in vacuo*. The residue was purified using a 40 g silica column/Combi-Flask Rf system (0-15% ethyl acetate in hexanes eluent) to provide **Int-31b** as a wax (370 mg, 65%).

Step B

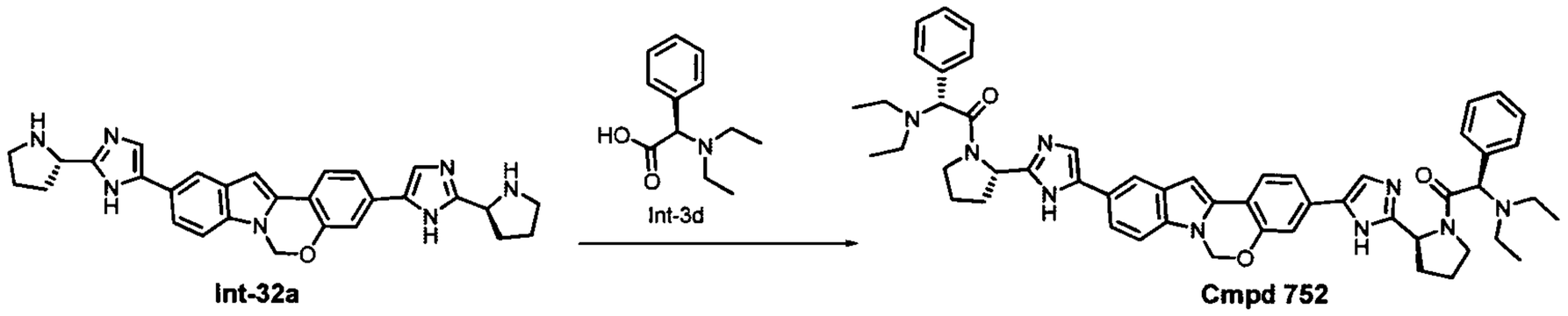
Int-31b (120 mg, 0.286 mmol), bis(pinacolato)diboron (152 mg, 0.6 mmol), potassium acetate (280 mg, 2.86 mmol), $Pd_2(dba)_3$-$CHCl_3$ (59.1 mg, 0.057 mmol), X-PHOS (54.4 mg, 0.114 mmol), and dioxane (4 ml) were added to a 35 mL microwave reaction tube. The sealed mixture was degassed and stirred at 110 °C under nitrogen atmosphere for 8 hours then cooled to room temperature. To this mixture were added bromide **Int-7h** (246 mg, 0.658 mmol), $PdCl_2$(dppf)-CH_2Cl_2 (46.7 mg, 0.0057 mmol), 1.5 M aqueous solution of sodium carbonate (1.9 ml, 2.9 mmol). The resulting mixture was degassed and stirred at 95 °C under nitrogen atmosphere for 6 hours, cooled to room temperature, concentrated, purified using Gilson reverse phase chromatography (10-80% acetonitrile in water with 0.1% TFA eluent) to provide Compound **1525** as a wax (68 mg, 20%). LC/MS anal. calcd. for: $C_{52}H_{53}N_9O_8$ 935.4; Found: 937.1 $(M+H)^+$.

Step C

Compound **1525** (16 mg, 0.014 mmol) and 10% palladium on activated carbon (5 mg, 4.7 μM) were added to 8 mL of methanol in a 250 mL pressure vessel and the reaction was shaken at room temperature under 35 psi hydrogen atmosphere using PARR hydrogenation apparatus for 6 hours. The reaction mixture was filtered through celite, concentrated *in vacuo* to provide Compound **1541** as a solid (15 mg, 93%). LC/MS anal. calcd. for: $C_{52}H_{61}N_9O_8$ 939.4; Found: 939.7 $(M+H)^+$.

EXAMPLE 32

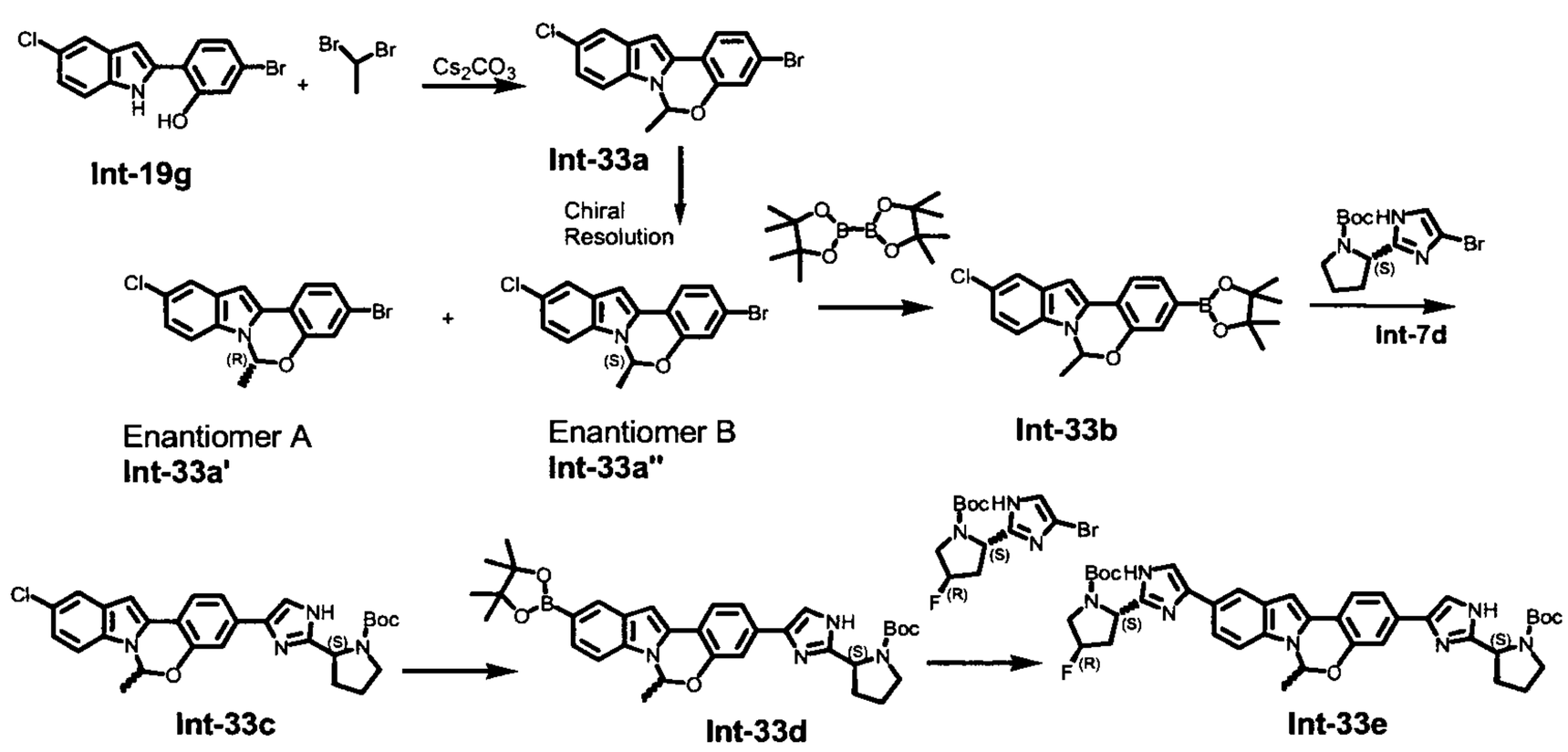
Preparation of Compound **752**

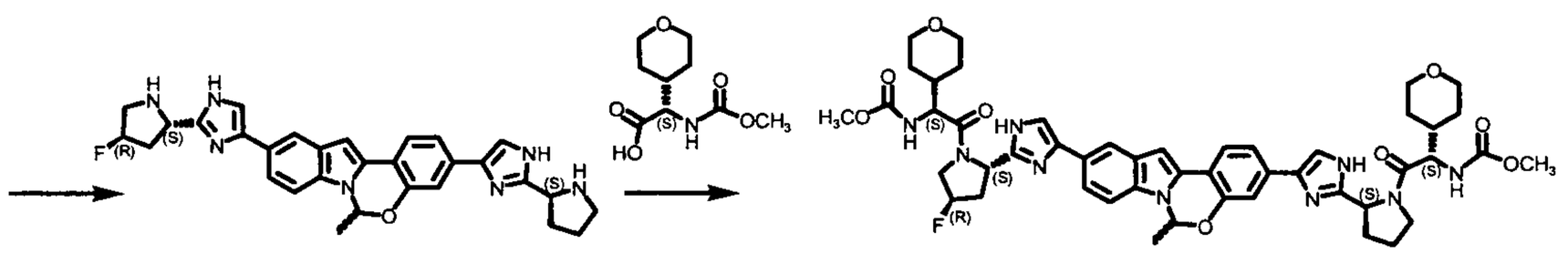


A round bottom flask was charged with **Int-32a** (89 mg, 0.14 mmol), (*R*)-2-(diethylamino)-2-phenylacetic acid hydrochloride (66 mg, 0.32 mmol), HATU (58 mg, 0.153 mmol) and 2 mL DMF provided 50 mg (34%) of the title Compound 752 using the capping procedure as in Step D of Compound **752**. LC-MS (M+H) = 946.8.

EXAMPLE 33

Preparation of Compound **1359**





Step A

Cs_2CO_3 (48.5g, 150 mmol)and dibromoethane (28g, 150mmol) was added to a stirred, solution of **Int-19g** (9.6g, 30mmol) in DMSO (100 mL) and the mixture was allowed to stir at 90 °C for for about 15 hours. The mixture was cooled, diluted with water (~200 mL). and extracted with EtOAc (3 x 100mL). The combined organic extracts and a EtOAc washing was washed with brine (1 x 80 mL), dried over Na_2SO_4. The dried layer was evaporated, the solid residue solid was triturated with methylene chloride, filtered to provide first crop of **Int-33a** as off white solid (4.33g). The filtrate was purified using column chromatography on silica gel 330g column, eluting with Hex/EtOAc (0 to 10% then 20%) to provide the 2nd crop of **Int-33a** as a off white solid (2.5g) yield 62.3%.

Step B

Int-33a (6.4g) was resolved on SFC (Chiral AD, 30% MeOH/AcCN (2:1) in CO_2, to provide **Int-33a'** (~3g) and **Int-33a"** (~2.8g).

Step C

Int-33a" (0.51 g, 1.463 mmol), bis(pinacolato)diboron 0.446 g, 1.755 mmol), KOAc(0.431 g, 4.40 mmol) and $PdCl_2(dppf)_2$ (0.107 g, 0.146 mmol) were added into a microwave tube. After the flask was flashed with N_2, dioxane (5 mL) was added. The mixture was allowed to stir at 95 °C for 4 hours. The crude **Int-33b** was used in the next step without purification

Step D

Int-7d (0.51 g, 1.61 mmol), $PdCl_2(dppf)_2$ (0.107 g, 0.146 mmol) and K_2CO_3 (1 N aq., 5 ml) were added to the reaction mixture of above mentioned **Int-33b** . The tube was sealed and degassed and heated to 100 °C for about 15 hours. After cooling, EtOAc (30mL) was added and it was extracted with Brine (30 mL). The organic layer was separated and dried and concentrated *in vacuo*. The crude material was purified on a ISCO column (40 g) and eluted with Hex:EtOAc 0% to 70% to provide the **Int-33c** (350 mg, 45%).

Step E

Int-33c (160mg, 0.317 mmol), $Pd_2(dba)_3$, (44mg, 0.048 mmol), X-phos (45.3mg, 0.095 mmol), KOAc (93mg, 0.950 mmol), bis(pinacolato)diboron (88 mg, 0.349 mmol) and dioxane (3 mL) are added into a 25 mL sealed tube. After the tube was degassed *in vacuo* followed by flashing with N_2 for three times. The mixture was allowed to stir at 120 °C for for about 15 hours. LC-MS indicated that the reaction was complete, the crude product **Int-33d** was used in the next step without further purification.

Step F

Int-33d (131 mg, 0.392mmol), $PdCl_2(dppf)_2$, (26 mg, 0.036mmol) and 1M K_2CO_3 (~3 mL) were added to the above mentioned mixture of **Int-7e**. The mixture was allowed to stir at 90 °C for 4 hours. After cooling down, the aqueous layer was separated and extracted with 10 mL EtOAc. The organic layers were combined and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated *in vacuo*. The product was purified using SiO_2 chromatography (24 g, solvent A: DCM; solvent B:0-50%) to provide **Int-33e** as desired product (95 mg, 37%).

Step G

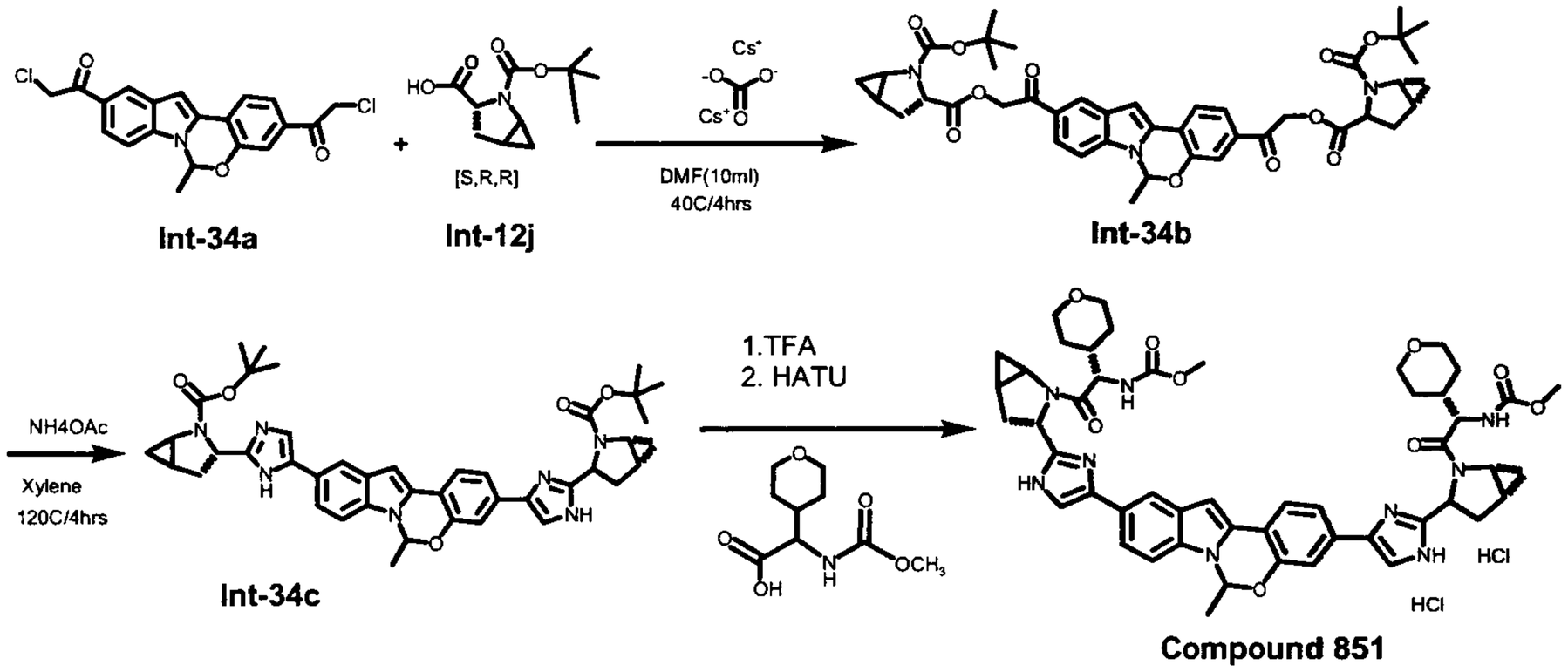
Int-33e (95 mg) was allowed to stir in dioxane (10 mL). HCl (4N in dioxane, 3 mL) was added and it was allowed to stir at room temperature for 1.5 hr. The solvent was removed and the **Int-33f** was isolated without further purification (95 mg, 100%).

Step H

Int-33f (50 mg, 0.075 mmol) was dissolved in DMF (1.5 mL) and cooled to 0°C. HATU(68.2 mg, 0.179 mmol) Compound 10A (34.1 mg, 0.157 mmol were added followed by addition of Hunig's base (0.062 mL, 0.45 mmol). The reaction was allowed to stir at 0°C for 45 minutes. Water was added to quench the reaction. The mixture purified using RP_HPLC (AcCN/H2O,0-80%) to provide title Compound 1359 11 45 mg (52.4%).

EXAMPLE 34

Preparation of Compound **851**



Step A

A mixture of **Int-34a** (0.3G,0.773 mmol), cesium carbonate (0.755g, 2.318mmol) and 1R,3S,5R)-2-(tert-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (0.386g, 1.7mmol) in DMF(10ml) were combined in a microwave tube and heated at 40 °C. After 4 hrs. TLC indicated complete reaction. The reaction was diluted with EtOAc (30ml) washed with water (3x20ml), brine(1x20ml), dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide **Int-34b** as red oil. **Int-34b** was used in the next step with out additional purification.

Step B

Int-34b (0.59g, 0.766mmol), ammonium acetate (1.182g, 15.33mmol) and xylenes (15ml) were charged in a microwave tube and heated at 120 °C (oil bath) for 4 hrs. (Note*: This reaction should be carried out in a fume-hood with shield protection*). The reaction was cooled and then diluted with EtOAc (25ml) and water (25ml). The organic layer were washed with water (2x20ml), brine (1x20ml), dried (Na2SO4), filtered and concentrated to provide crude **Int-34c** which was purified on a ISCO chromatography system using 5%MeOH/ CH_2Cl_2 .The relevant fraction were collected

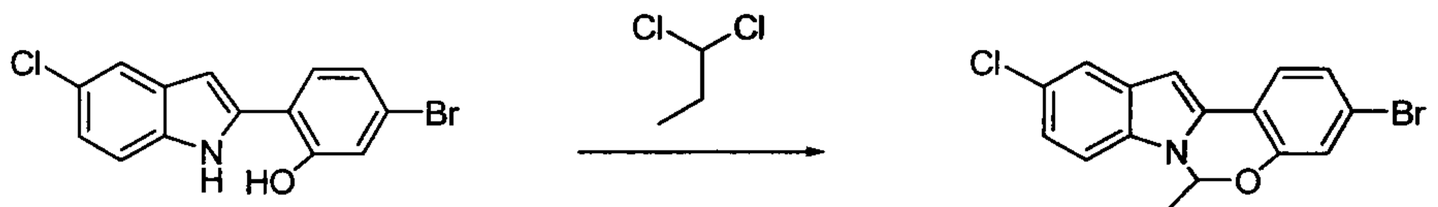
and concentrated to provide **Int-34c** as an orange solid,

Step C

Standard capping procedure was used as for the Compound **851** from **Int-34c** as above (41%).

EXAMPLE 35

Preparation of Intermediate Compound **Int-35e**



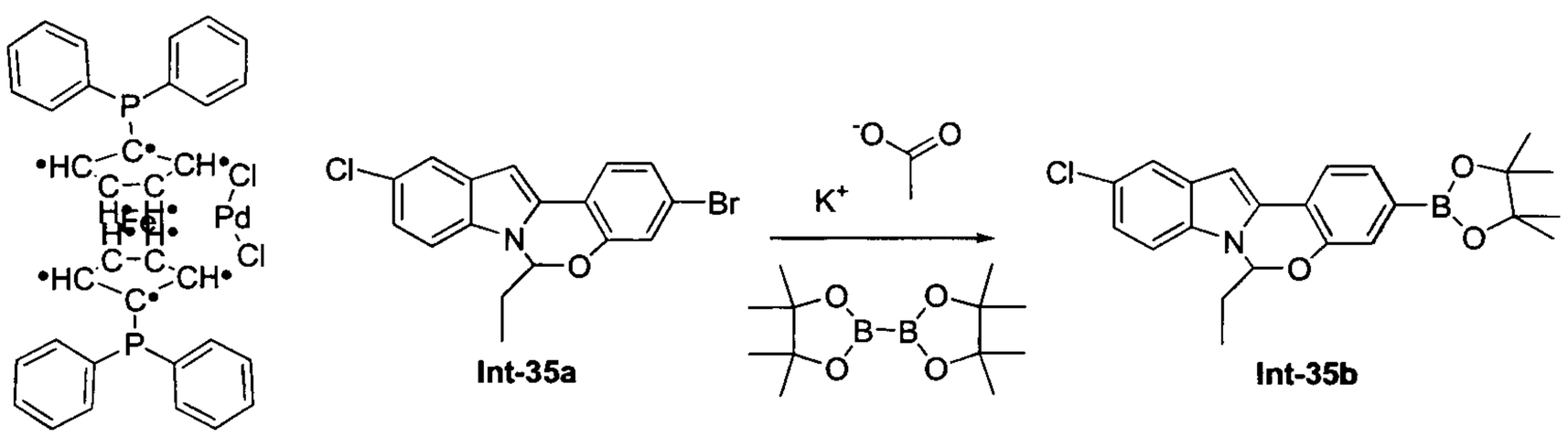
Int-19g **Int-35a**

Step A

The indole phenol **Int-19-g** (10.0 g, 31.0 mmol), cesium carbonate (40.g, 123 mmol), and DMSO (77 ml) were added to a 500 mL round bottomed pressure flask equipped with a stir bar. 1, 1-Dichloropropane (10.09 g, 89 mmol) was added to the reaction mixture, N_2 was blown over the reaction mixture, and the flask was capped. The flask was placed in a 90 °C oil bath which was then heated to 110 °C. After ~16 hours at 110 °C, the reaction mixture was allowed to cool to room temperature. Additional 1,1-dichloropropane was added (4 g, 35 mmol), the reaction mixture was blanketed with N_2 and reheated to 110 °C. After 4.5 hours, the reaction was cooled to room temperature, and poured into 300 mL of water. EtOAc was added (500 mL) and the layers were separated. The aq. layer was extracted with additional EtOAc. The combined organic layer was washed with water and brine, gravity filtered and dried over $MgSO_4$. The mixture was filtered and the solvent concentrated under reduced pressure to provide 11.62 g of a tan solid. The crude product **Int-35a** was dissolved in CH_2Cl_2 , Silica gel was added (62 g) and the mixture was concentrated *in vacuo*. The silica gel containing the crude product was dry loaded on a silica gel column (262 g) that had been packed with hexanes. The column was eluted with an EtOAc/hexanes gradient (0%-1.5%). The

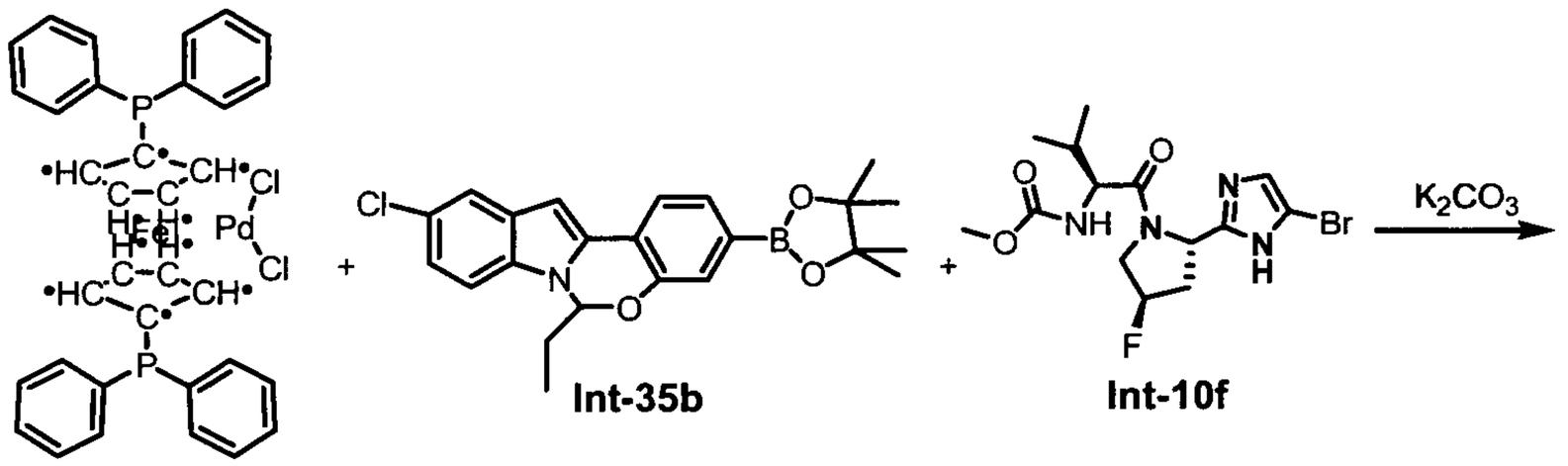
first major peak was collected as product to provide **Int-35a** as an off white solid (3.11 g). LC/MS. Obsd. M+H = 361.8.

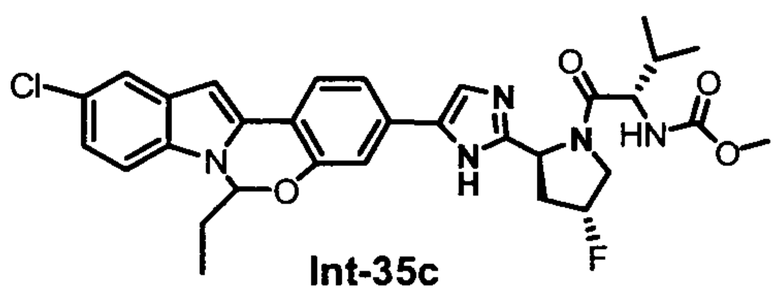
Step B



Int-35a (1.59 g, 4.38 mmol), $PdCl_2$(dppf) (0.493 g, 0.674 mmol), Bis(pinacolato)diboron (1.08 g, 4.26 mmol), and potassium acetate (1.49 g, 15.18 mmol) were added to a 20 mL microwave vial equipped with a stir bar. The vial was cycled between vacuum and nitrogen five times. Dioxane (16 ml) was added via syringe, and the vial was cycled between vacuum and nitrogen three more times. The vial was placed in a preheated reaction block and the reaction mixture was left stirring at 85 °C. After 2.5 hours, the reaction mixture was allowed to cool to room temperature. The reaction mixture was diluted with ethyl acetate and water and the layers separated. The organic layer was washed with water and brine, filtered through a pad of Celite, dried with $MgSO_4$, and filtered again. The solvent was evaporated under reduced pressure to provide **Int-35b** as a yellow oil. The crude product was further purified via silica gel column chromatography on an 80 g Isco Gold SiO_2 cartridge, using a $MeOH/CH_2Cl_2$ gradient (0%-5%) as the mobile phase to provide **Int-35b** (1.29 g) as an off white foam. LC/MS. Obsd M+H = 410.11.

Step C



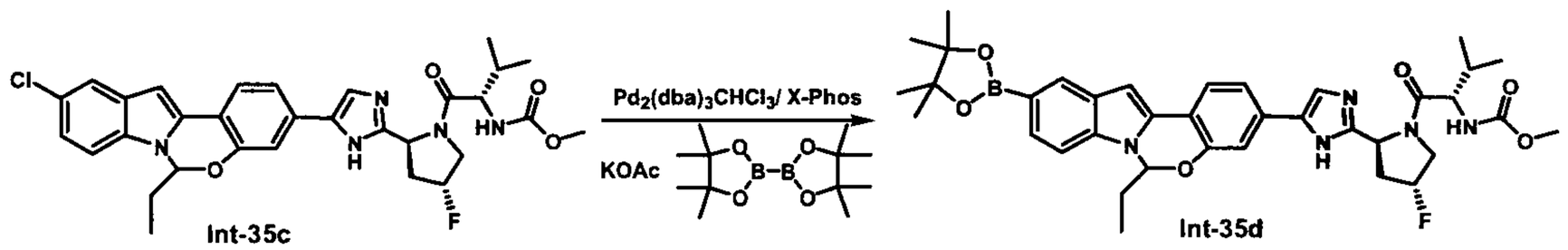


Int-35c

Int-35b (0.66 g, 1.611 mmol), **Int-10f** (0.658 g, 1.682 mmol) and $PdCl_2$(dppf) (0.120 g, 0.164 mmol) were added to 100 mL round bottomed flask equipped with a stir bar. The flask was capped with a septum, connected to a vacuum line via needle and tubing and cycled between vacuum and nitrogen five times. Dioxane (8 ml) was added via syringe, and the flask was cycled between vacuum and nitrogen three more times. Aqueous 2.0 M potassium carbonate (2.8 ml, 5.60 mmol) was added and the flask was cycled between vacuum and nitrogen five times and the flask was heated at 85 °C in a heating block. After 16.5 hours, the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate and water and the layers were separated. The organic layer was washed with water and brine, gravity filtered, dried with $MgSO_4$, and filtered again. The solvent was evaporated under reduced pressure to provide **Int-35c** (1.16 g) as a brown foam. The crude product was purified further via flash silica gel column chromatography on an ISCO 80 g SiO_2 Gold cartridge, using a $MeOH/CH_2Cl_2$ (0%-5%) gradient as the mobile phase. The major peak was isolated as product to provide **Int-35c** (0.41 g) as a tan foam.

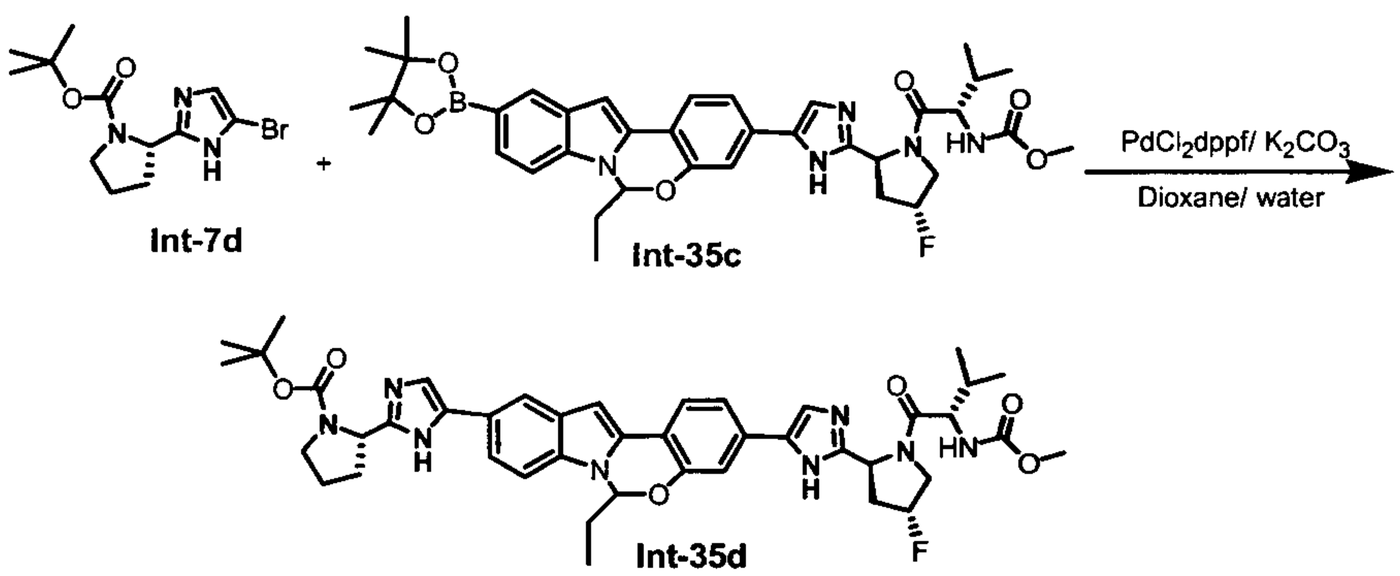
LC/MS- Obsd M+H = 594.2.

Step D



X-Phos (0.116 g, 0.243 mmol), $Pd_2(dba)_3$ chloroform adduct (0.110 g, 0.106 mmol), Bis-(pinacolato)diboron (0.175 g, 0.689 mmol), and potassium acetate (0.254 g, 2.59 mmol) were added to a 5 mL microwave tube equipped with a stir bar. The tube was capped and connected to a vacuum line via needle and tubing. The tube was cycled between vacuum and nitrogen five times. Dioxane (0.3 mL) was added via syringe and the tube was cycled between vacuum and nitrogen five times. After five minutes, a solution of **Int-35c** (0.44 g, 0.741 mmol) in 2.2 mL of dioxane was added via syringe. The tube was cycled between vacuum and nitrogen five more times and the tube was placed in a heating block at 120 °C. After 4h the reaction mixture was allowed to cool to room temperature and was used in the next step without further purification.

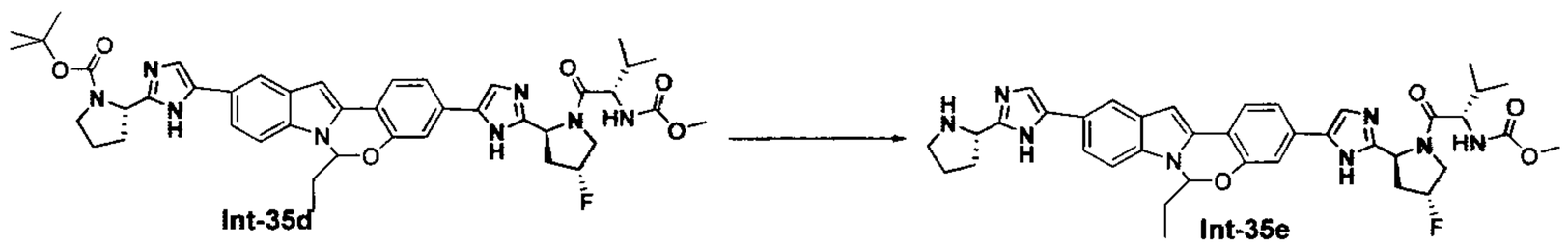
Step E



$PdCl_2(dppf)$ (81 mg, 0.111 mmol) and **Int-7d** (246 mg, 0.777 mmol) were added to a 5 mL microwave tube equipped with a stir bar. The tube was capped and connected to a vacuum line via needle and tubing. The tube was cycled between vacuum and nitrogen five times. The crude **Int-35c** was added via syringe to the tube containing the Suzuki reaction. The tube was cycled between vacuum and nitrogen three times. Aq. 2.0 M potassium carbonate (1.480 ml, 2.96 mmol) was added via syringe. The tube was cycled between vacuum and nitrogen three more times. The tube was placed in an 85 °C heating block and left stirring for about 15 hours. After ~16h, the reaction was cooled and the aq layer was removed via pipette. The remaining organic layer was diluted with 1.5 mL of DMF and 0.3 mL of water. The resulting material was passed through a micron syringe filter while injecting it directly onto an ISCO Gold C-18 cartridge. The cartridge had been conditioned with 15% acetonitrile in water. TFA (0.1%) was added to

each component of the mobile phase. The column was eluted with an acetonitrile/water gradient (15%-90% with and isocratic hold at 45% acetonitrile while the main peak eluted. **Int-35d** was obtained as an off white solid (262 mg). LC/MS Obsd M+H = 795.3.

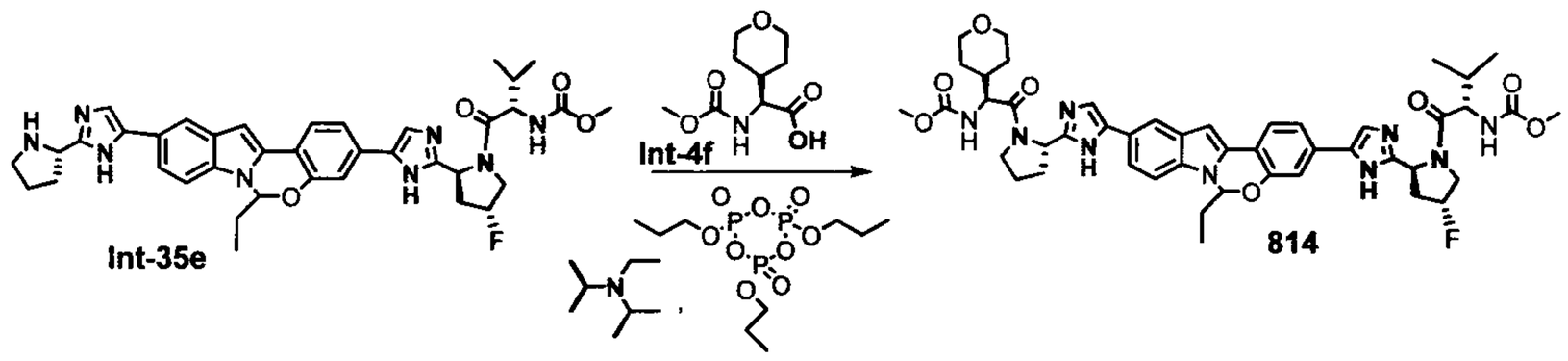
Step F



Int-35d (257 mg, 0.323 mmol) and Methanol (15 ml) were added to a round bottomed flask equipped with a stir bar. HCl in Dioxane (4.0 M) (5 ml, 20.00 mmol) was added, and the reaction mixture stirred at room temperature. After ~ 45 minutes the reaction mixture was concentrated *in vacuo*. **Int-35e** was obtained as a colored solid (**Int-5060**. LC/MS. Obsd M+H = 695.3. The product was used in the subsequent reactions without further purification.

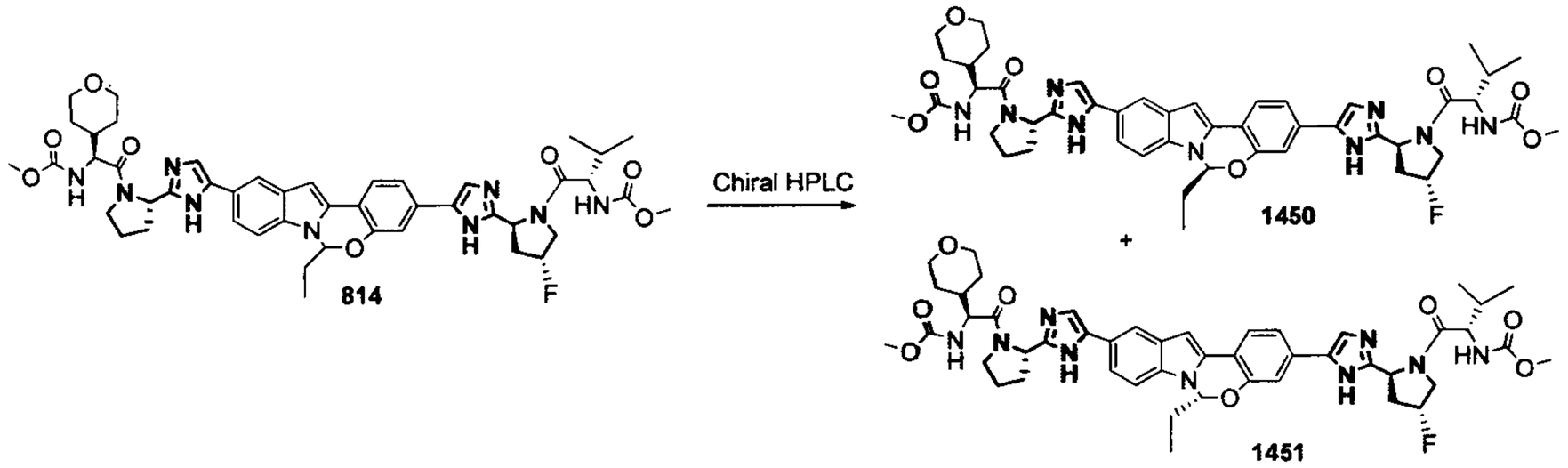
EXAMPLE 36

Preparation of Compounds **814, 1450,** and **1451**



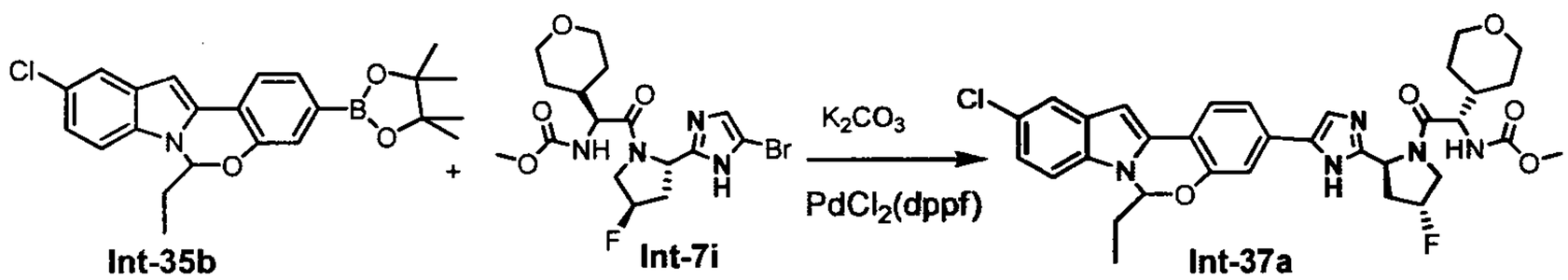
Amino acid **Int-4f** (44.6 mg, 0.205 mmol) and a solution containing **Int-35e** (57 mg, 0.082 mmol), acetonitrile (410 µl), THF (410 µl), and DIPEA (71.6 µl, 0.410 mmol) were added to a 1 dram vial equipped with a stir bar. Propylphosphonic anhydride (aka T3P) (164 µl, 0.246 mmol) was added, and the reaction mixture was allowed to stir at room temperature. After 4 hours, the reaction mixture was diluted with EtOAc and water and the layers were separated. The organic layer was washed with water and brine, dried with $MgSO_4$, filtered, and concentrated to a brown oil. The aqueous layer was then basified with 2.0 M potassium carbonate and extracted with EtOAc and CH_2Cl_2. The

combined organic layer was filtered, dried with $MgSO_4$, filtered again, and concentrated to dryness. The crude product was purified via silica gel column chromatography on an ISCO 4 g SiO_2 cartridge, using a MeOH/ CH_2Cl_2 gradient as the mobile phase to provide an off white solid Compound **814** LC/MS. Obsd. M+H = 894.3.

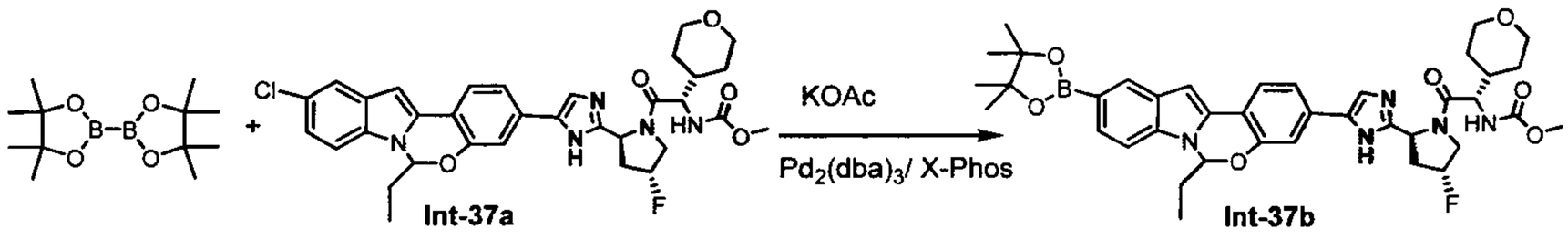


Compound **814** (isomer mixture at ethyl position) was separated on a Chiralcel OD column using 30% ethanol in hexanes as the mobile phase. Diethyl amine (0.1% by volume) was added to each component of the mobile phase. Two peaks were isolated that contained a molecular ion at 894.4 in the LC/MS. LC/MS. Obsd. M+H = 895.0. Peak A = Compound **1450;** Peak B = Compound **1451.**

EXAMPLE 37



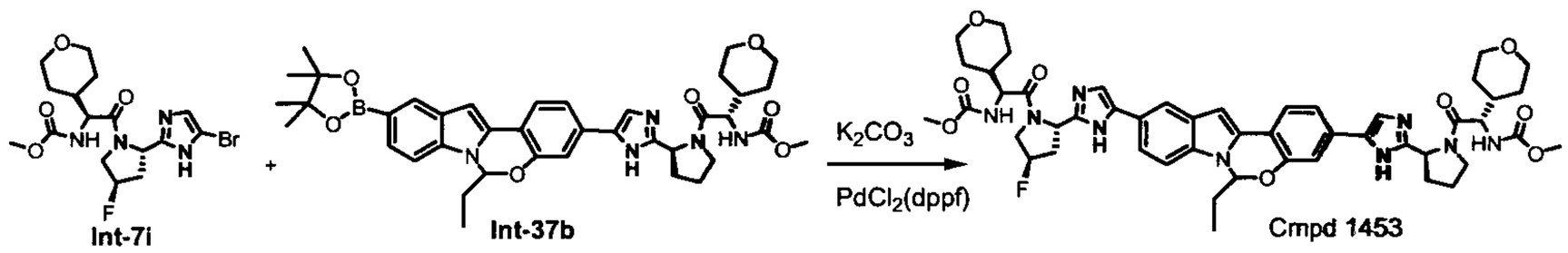
Int-35b (113 mg, 0.276 mmol), **Int-7b** (103 mg, 0.238 mmol), and $PdCl_2(dppf)$ (26 mg, 0.036 mmol) were added to a 2 mL microwave vial equipped with a stir bar. Using the procedure for Example 35, Step C provided 129 mg of **Int-37a** as a clear oil. LC/MS. Obsd M+H = 636.1



X-Phos (30 mg, 0.063 mmol), $Pd_2(dba)_3$ (31 mg, 0.034 mmol), Bis(pinacolato)-diboron (47mg, 0.185 mmol), and potassium acetate (65 mg, 0.662 mmol) were added to a 2 mL microwave vial equipped with a stir bar. The vial was capped and connected to a vacuum line via needle and tubing. The vial was cycled between vacuum and nitrogen five times. A solution of **Int-37a** (125 mg, 0.197 mmol) in dioxane (800 µl) was added via syringe, and the vial was cycled between house vacuum and nitrogen five times. The vial was placed in a preheated reaction block and the reaction mixture was left stirring at 120 °C, for 3.5 hours. The reaction mixture was allowed to cool to room temperature and left stirring for about 15 hours at room temperature. The crude reaction mixture, which contains intermediate compound **Int-37b**, was used without further purification.

EXAMPLE 38

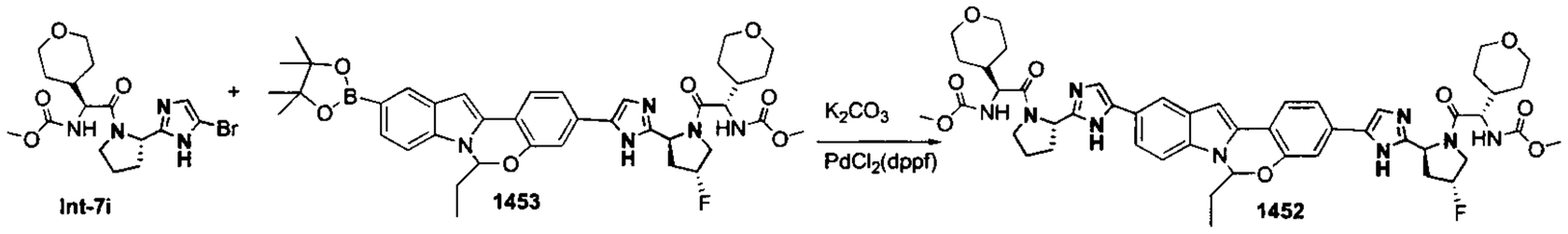
Preparation of Compound **1453**



The microwave vial containing the **Int-37b** crude reaction mixture was charged with **Int-7i** (0.063 g, 0.145 mmol) and $PdCl_2(dppf)$ (17 mg, 0.023 mmol). The vial was recapped, and connected to a vacuum line via syringe needle and tubing. Using the procedure for Example 35, step C provided Compound **1453** as a tan solid-(43 mg). LC/MS. Obsd. M+H = 936.4.

EXAMPLE 39

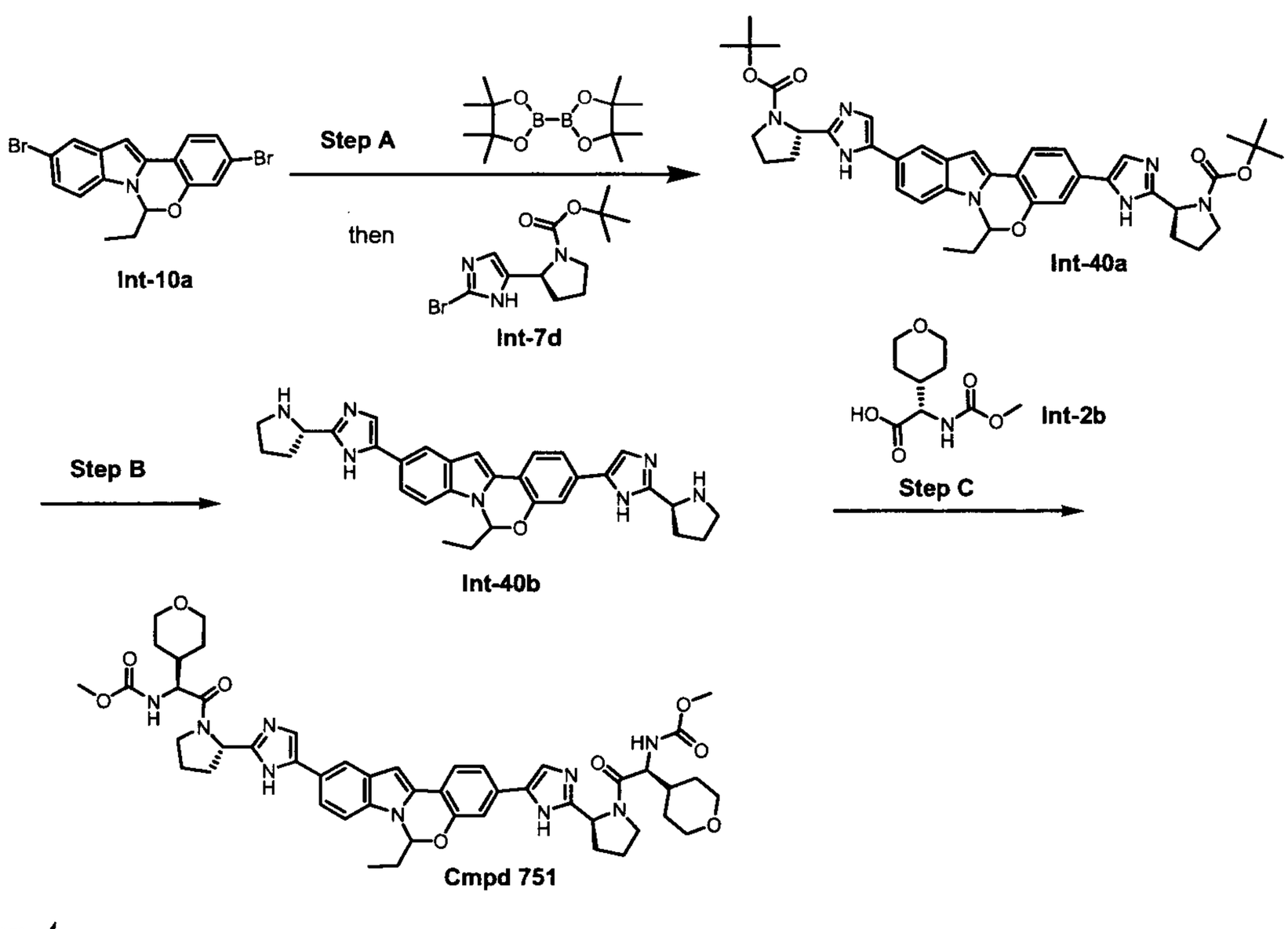
Preparation of Compound **1452**



Int-7i (0.070 g, 0.169 mmol) and $PdCl_2(dppf)$ (0.024 g, 0.033 mmol) were added to a 2 mL microwave tube equipped with a stir bar. The vial was capped and connected to a vacuum line via needle and tubing. The vial was cycled between vacuum and nitrogen five times. A solution of compound **1453** (0.135 g, 0.185 mmol) in dioxane (0.9 mL) was added via syringe into the reaction vial. Using the procedure for Example 35, step C provided Compound **1452** as a tan solid-(49 mg). LC/MS. Obsd. M+H = 936.4.

EXAMPLE 40

Preparation of Compound **751**



Step A

Using the method described in Example 35, step B, **Int-10a** (0.34 g, 0.83 mmol) was converted to **Int-40a** (0.24 g , 40% yield) as a brown solid. LC/MS Obs M+H = 720.4.

Step B

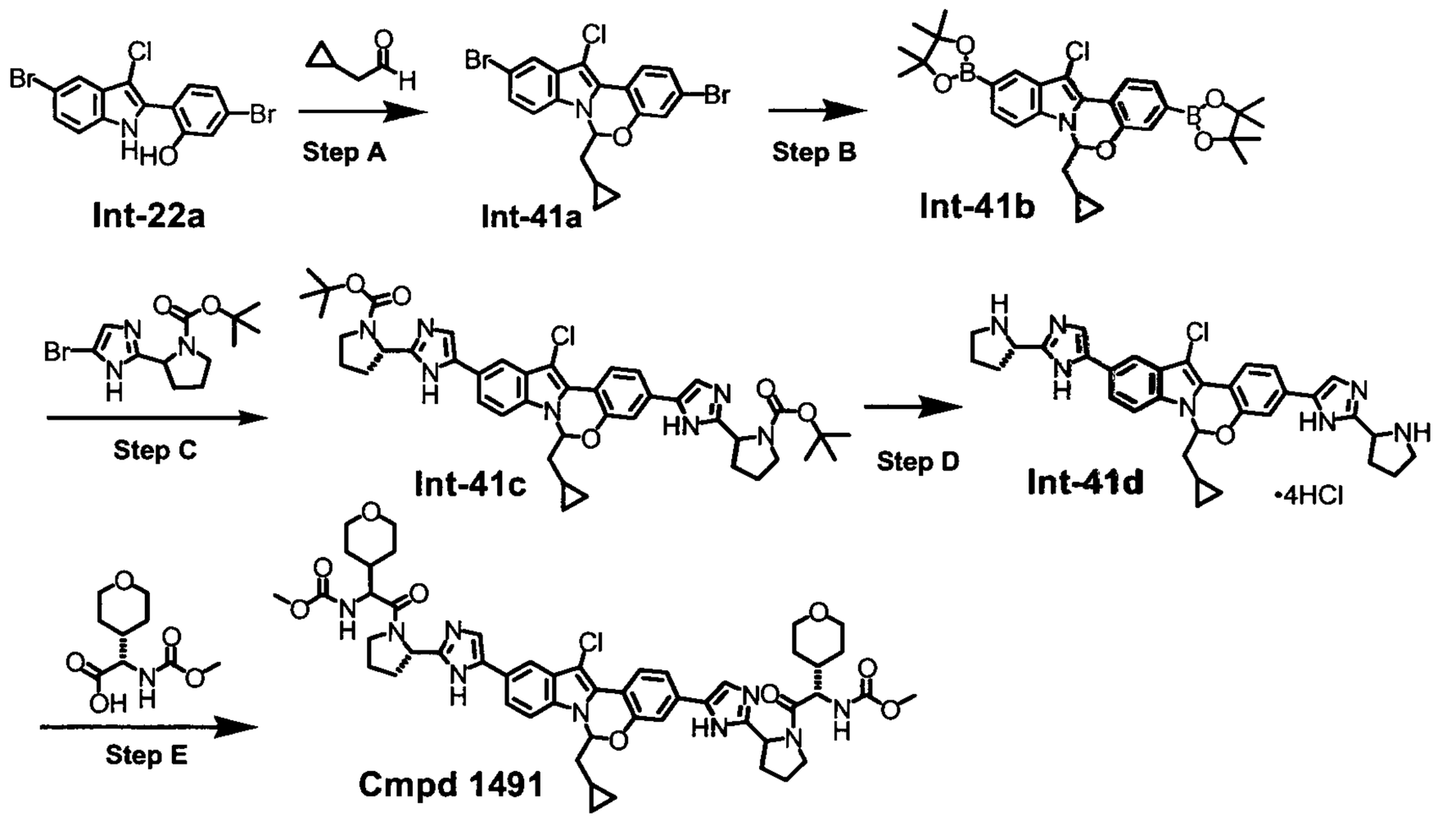
Using the method described in Example 35, step F, **Int-40a** (78 mg, 0.11 mmol) was converted to **Int-40b** 72 mg (99%) as a dihydrochloride salt. LC/MS Obs M+H = 521.2.

Step C

Using the method described in Example 36, step A, **Int-40b** (72 mg, 0.11 mmol) was treated with **Int-2b** (49 mg, 0.23 mmol) to provide Compound **751** (80 mg, 75% yield) as the dihydrochloride salt. LC/MS Obs M+H = 918.5.

EXAMPLE 41

Preparation of Compound **1491**



Step A

In a 20-mL Biotage® microwave tube, cyclopropylacetaldehyde (2.0 g, 24 mmol) was dissolved in toluene (10 mL) to provide a milky mixture. **Int-22a** (1.78 g, 4.43 mmol) was added and the resulting red-brown suspension was allowed to stir at room temperature for 10 minutes. *p*-Toluenesulfonyl chloride (85 mg, 0.443 mmol) and

toluene (2 mL) were added and the tube was flushed with nitrogen. The sealed reaction was heated and stirred under microwave conditions (Biotage® Initiator 8, reaction temperature = 170 °C; total heating time = 12 h), after which the reaction mixture was allowed to cool to room temperature . The reaction mixture was concentrated under reduced pressure (bath temperature ~50-60 °C) and then coevaporated with EtOAc (2 x 100 mL) to provide a dark-brown semi-solid as crude product. The crude product was adsorbed onto 6.0 g silica gel and purified using flash silica gel chromatography (ISCO®; 200 g RediSep® Gold silica gel column; Eluent of 0-30% EtOAc/hexanes gradient @ 150 mL/min) to provide **Int-41a** as a light orange-yellow solid (710 mg, 34% yield).

Step B

In a 125-mL round-bottom flask, **Int-41a** (0.707 g, 1.51 mmol), bis(pinacolato)-diboron (0.806 g, 3.18 mmol), (dppf)$PdCl_2$•CH_2Cl_2 (111 mg, 0.151 mmol) and KOAc (445 mg, 4.54 mmol) were admixed. A magnetic stir bar was added, the flask was sealed and alternately evacuated and refilled with nitrogen (5x). Dry dioxane (7.5 mL) was added and the flask was immersed in a preheated 90 °C oil bath. After 1.5 hours the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (~100 mL) and washed with brine (~50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure (water bath temperature ~50-60 °C) to provide a dark brown semi-solid as crude product. The crude product was purified using flash silica gel chromatography (ISCO®; 120 g RediSep® Gold silica gel column; Eluent 0-70% EtOAc/hexanes gradient @ 85 mL/min) to provide **Int-41b** as a beige solid (630 mg, 74% yield).

Step C

In a 125-mL round-bottom flask, **Int-41b** (618 mg, 1.10 mmol), bromo-imidazole **Int-7d** (731 mg, 2.31 mmol), (dppf)$PdCl_2$•CH_2Cl_2 (81 mg, 0.110 mmol) were admixed. A magnetic stir bar was added and the flask was sealed with a rubber septum. The flask was alternately evacuated and refilled with nitrogen (5x). Dioxane (11 mL) was added and the reaction mixture was allowed to stir at room temperature for 5 minutes after which aqueous potassium carbonate solution (5.5 mL, 1 M aqueous, 5.5 mmol) was

added. The reaction mixture was allowed to stir at 90 °C for 18 hours. The reaction mixture was allowed to cool to room temperature and was diluted with EtOAc (~100 mL). The resulting solution was poured into a separatory funnel containing EtOAc (~50 mL) and water (~50 mL). The organic layer was washed with brine (~50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide an orange-brown as crude product. The crude product was purified using flash silica gel chromatography (ISCO®; 80 g RediSep® Gold silica gel column; 0-100% EtOAc-hexanes gradient @ 60 mL/min). Product-containing fractions were collected, concentrated, and re-purified using reverse-phase chromatography (Gilson®; Phenomenex Gemini 150 x 21.20 mm x 5 μm column; Eluent of 10-70% MeCN/water (+0.1% TFA) gradient over 20 minutes) to provide **Int-41c** as a beige solid (467 mg, 54% yield).

Step D

In a 50-mL round-bottom flask, **Int-41c** (411 mg, 0.527 mmol) was dissolved in methanol (5.0 mL) and hydrogen chloride solution (1.5 mL, 4 M in dioxane, (1.8 g, 6 mmol) was added. The reaction mixture was allowed to stir at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure to provide **Int-41d** as a beige (396 mg, quantitative yield).

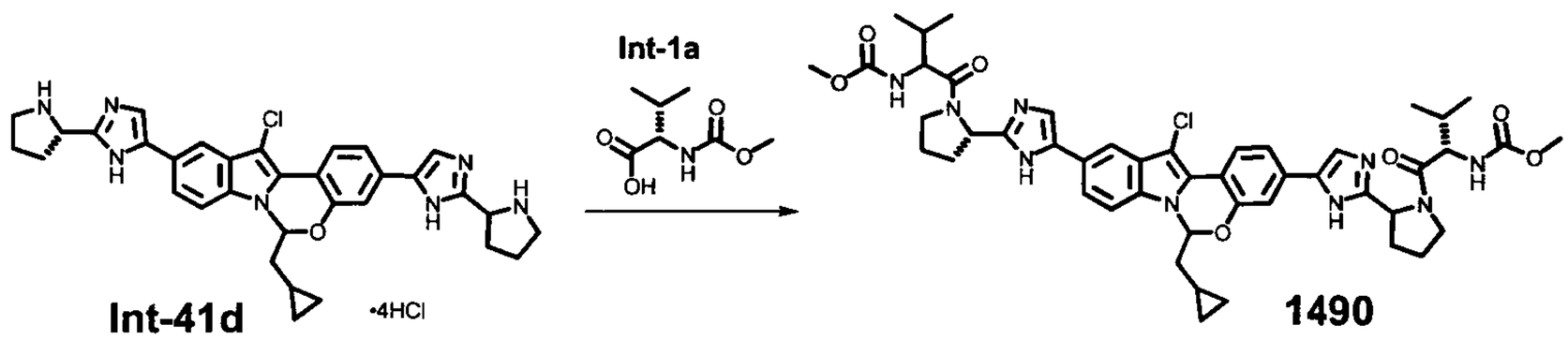
Step E

Int-4f (85 mg, 0.392 mmol), was weighed into a pre-tarred vial and transferred to a 50-mL round-bottom flask containing **Int-41d** (142 mg, 0.196 mmol) with the aid of dry DMF (4 x 500 μL). Diisopropylamine (200 μL, 148 mg, 1.15 mmol) was added by syringe. The mixture was allowed to stir at room temperature for ~1 minutes, during which time all solids dissolved. The flask was cooled in an ice-water bath for ~10 minutes. Solid HATU (157 mg, 0.412 mmol) was added in one portion at 0 °C but gradually allowed to warm to room temperature as the cooling bath expired. After 24 hrs methanol (2 mL), water (0.2 mL) and potassium carbonate (135 mg, 0.980 mmol) were added sequentially. The reaction mixture was extracted with EtOAc (2 x 50 mL), the combined extracts were washed with brine (~50 mL), and dried over anhydrous

$MgSO_4$. After filtration, the organic layer was concentrated under reduced pressure to provide a light brown solid as the crude product. Further purification by reverse-phase chromatography (Gilson®; Phenomenex® Gemini 150 x 21.20 mm x 5 µm column; 10-70% MeCN/water (+0.1% TFA) gradient over 15 minutes) provided Compound **1491** as a beige solid (164 mg, 86% yield).

EXAMPLE 42

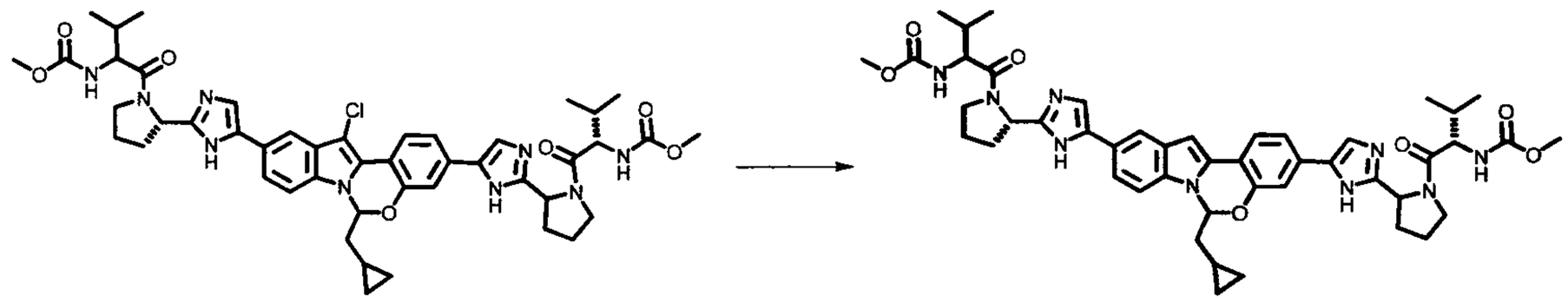
Preparation of Compound **1490**



In a 50-mL round-bottom flask, **Int-41d** (196 mg, 0.270 mmol) and **Int-1a** (95 mg, 0.540 mmol) were admixed. A magnetic stir bar was added and the solids were dissolved in dry DMF (2.7 mL). Diisopropylethylamine (283 µL, 209 mg, 1.62 mmol) was added, the reaction mixture cooled to 0 °C (ice-water bath) and then stirred for 15 minutes. Solid HATU (216 mg, 0.567 mmol) was added in one portion and the reaction mixture was allowed to stir at 0 °C for 24 hours. Methanol (2 mL), water (0.2 mL) and potassium carbonate (187 mg, 1.35 mmol) were added and the reaction was allowed to stir at room temperature for 18 hours. Water (20 mL) was added and the reaction mixture was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (~50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide a light brown solid as crude product. The crude product was purified directly by reverse-phase chromatography (Gilson®; Phenomenex® Gemini 150 x 21.20 mm x 5 µm column; 10-70% MeCN/water (+0.1% TFA) gradient over 15 minutes to provide Compound **1490** as a beige solid (151 mg, 63% yield).

EXAMPLE 43

Preparation of Compound **1499**

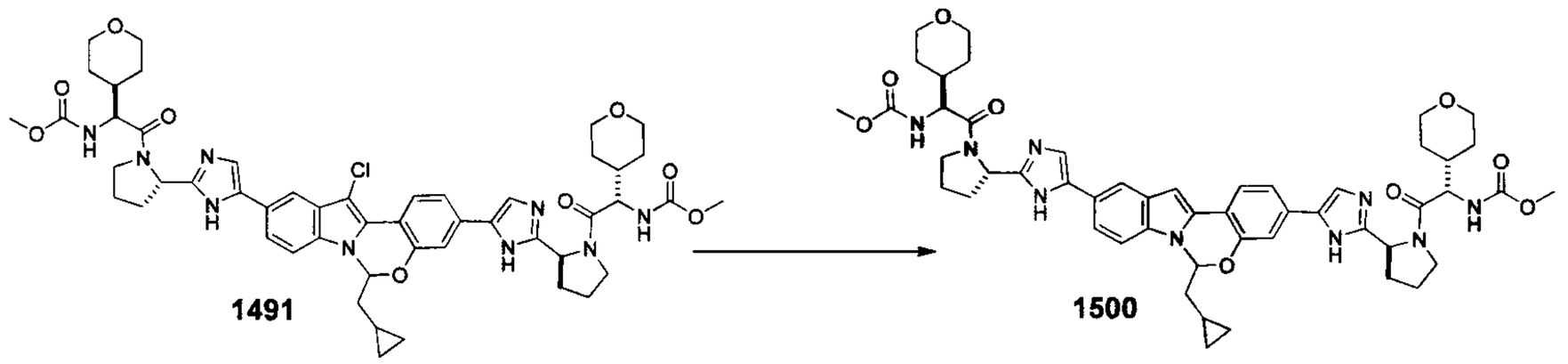


1490 1499

In a 5-mL Biotage® microwave tube, Compound **1490** (128 mg, 0.143 mmol), bis(pinacolato)diboron (73 mg, 0.286 mmol), $Pd_2(dba)_3$•$CHCl_3$ (15 mg, 0.014 mmol) and X-Phos (14 mg, 0.029 mmol) were admixed. A magnetic stir bar was added and the tube was alternately evacuated and back-filled with nitrogen (5x). Dry dioxane (1.0 mL) was added and the reaction mixture immersed into a preheated 120 °C oil bath. After 2 hours the reaction mixture was diluted with EtOAc (~50 mL) and washed with brine (~25 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide an orange-red as crude product. The crude product was purified using reverse-phase chromatography (Gilson®; Phenomenex® Gemini 150 x 21.20 mm x 5 μm column; 10-70% MeCN/water (+0.1% TFA) gradient over 15 minutes) to provide Compound **1499** as a beige solid (75 mg, 61% yield).

EXAMPLE 44

Preparation of Compound **1500**

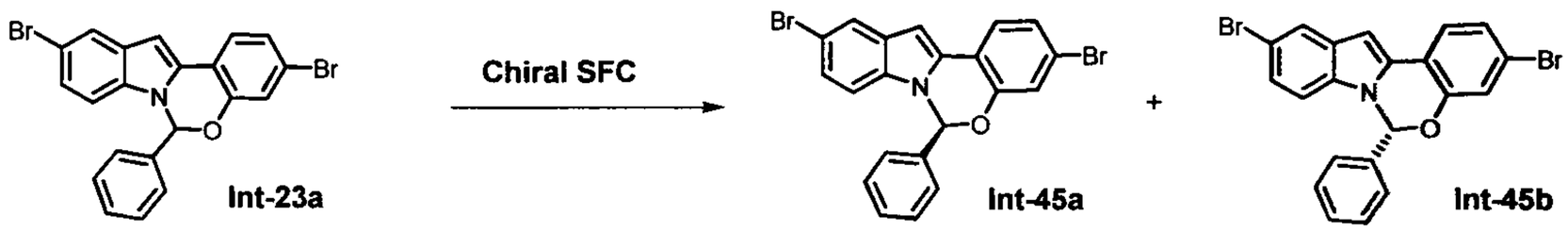


1491 1500

Using the method described in Example 43, Compound **1491** was transformed to Compound **1500** and the crude product was purified directly by reverse-phase chromatography (Gilson®; Phenomenex® Gemini 150 x 21.20 mm x 5 μm column; 10-70% MeCN/water (+0.1% TFA) gradient over 15 minutes) to provide Compound **1500** as a beige solid (89 mg, 64% yield).

EXAMPLE 45

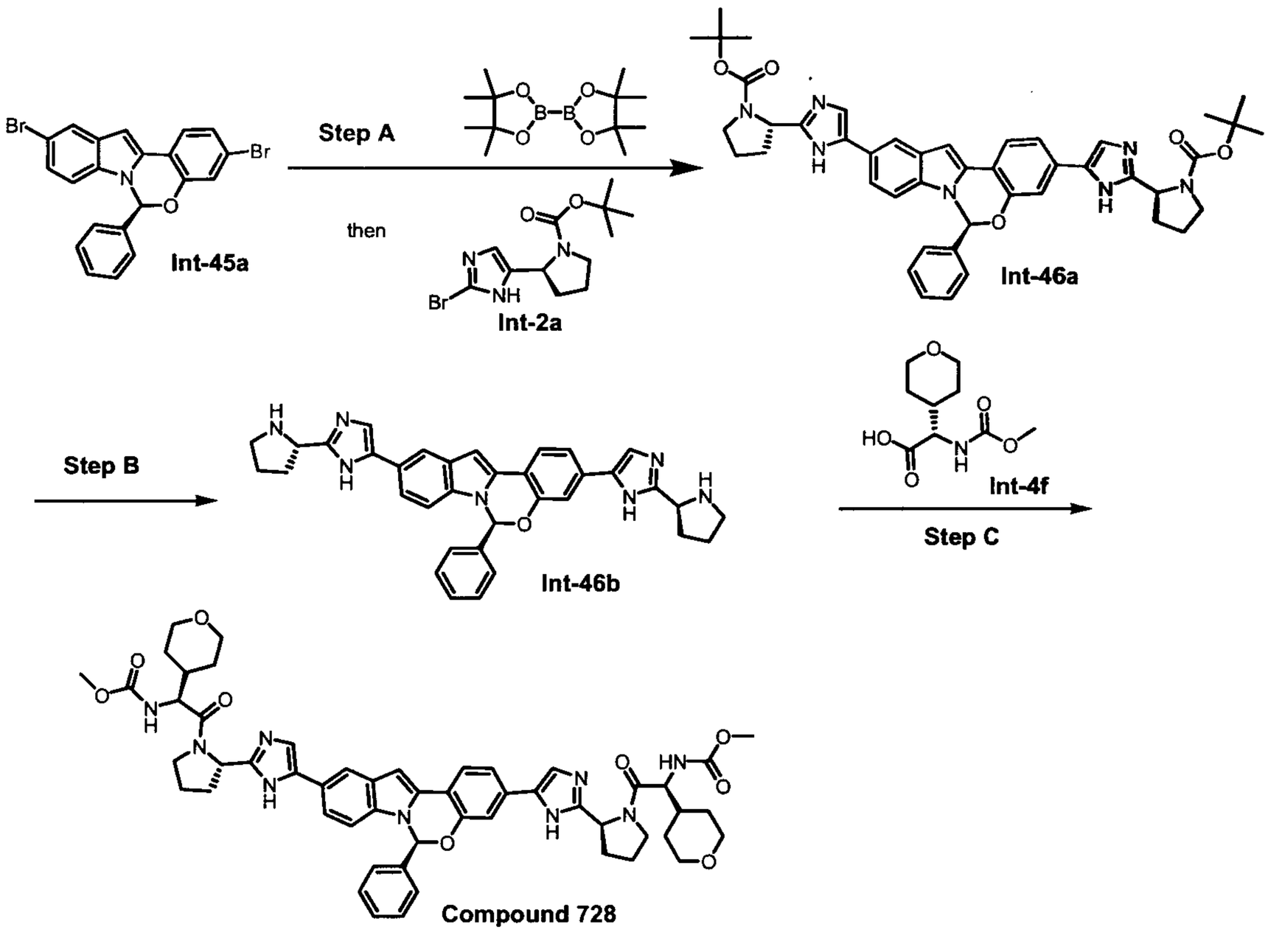
Preparation of **Int-45a** and **Int-45b**



Chiral SFC separation (Chiral AD, 30% MeOH/AcCN (2:1) **in** CO_2) of **Int-23a** yielded Compounds **Int-45a** and **Int-45b**.

EXAMPLE 46

Preparation of Compound **728**



Step A

To a 250 mL round bottomed flask with a stir bar under N_2 was added dibromoindole **Int-45a** (3 g, 6.6 mmol) followed by bis(pinacolato)diboron (3.7 g, 14.5

mmol), KOAc (1.9 g, 20 mmol), and $PdCl_2$ (dppf)·CH_2Cl_2 (1.6 g, 2.0 mmol). Dioxane (~45 mL) was added to the mixture which was degassed six times under house vacuum filling with N_2 after each evacuation. The reaction flask was affixed with a reflux condenser and the mixture was heated to 90 °C. After 5 hours the mixture was deemed to be complete by LC-MS, and the crude bisboronate used as is.

To a cooled flask containing the crude bisboronate above was added bromo imidazole **Int-4f** (4.6 g, 14.5 mmol), $PdCl_2$dppf·CH_2Cl_2 (1.6 g, 1.98 mmol), and 1 M K_2CO_3 (~20 mL). The flask was flushed with N_2, capped, and heated to 95 °C. After 12 hours at 95 °C and the mixture was cooled to room temperature and the mixture diluted with EtOAc (100 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 75 mL). The organic layers were combined and were washed with brine (1 x 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified using RS ISCO Gold 220 gm column using a gradient of 100% CH_2Cl_2 to 92/8 % CH_2Cl_2/MeOH to provide 2.0 (39%) of **Int-46a** as a brown solid.

LC-MS M+H = 769.2.

Step B

To a solution of **Int-46a** (0.11 g, 0.14 mmol) in CH_2Cl_2 (1.5 mL) under N_2 was added excess TFA (1 mL) and the resultant mixture stirred at room temperature for 2 hours. The reaction was concentrated *in vacuo* and then taken up in ~ 2-3 mL 4.0 M HCl in dioxane and concentrated to dryness to yield **Int-46b** (75 mg, 99% yield) as the HCl salt.

LC-MS M+= 568.2.

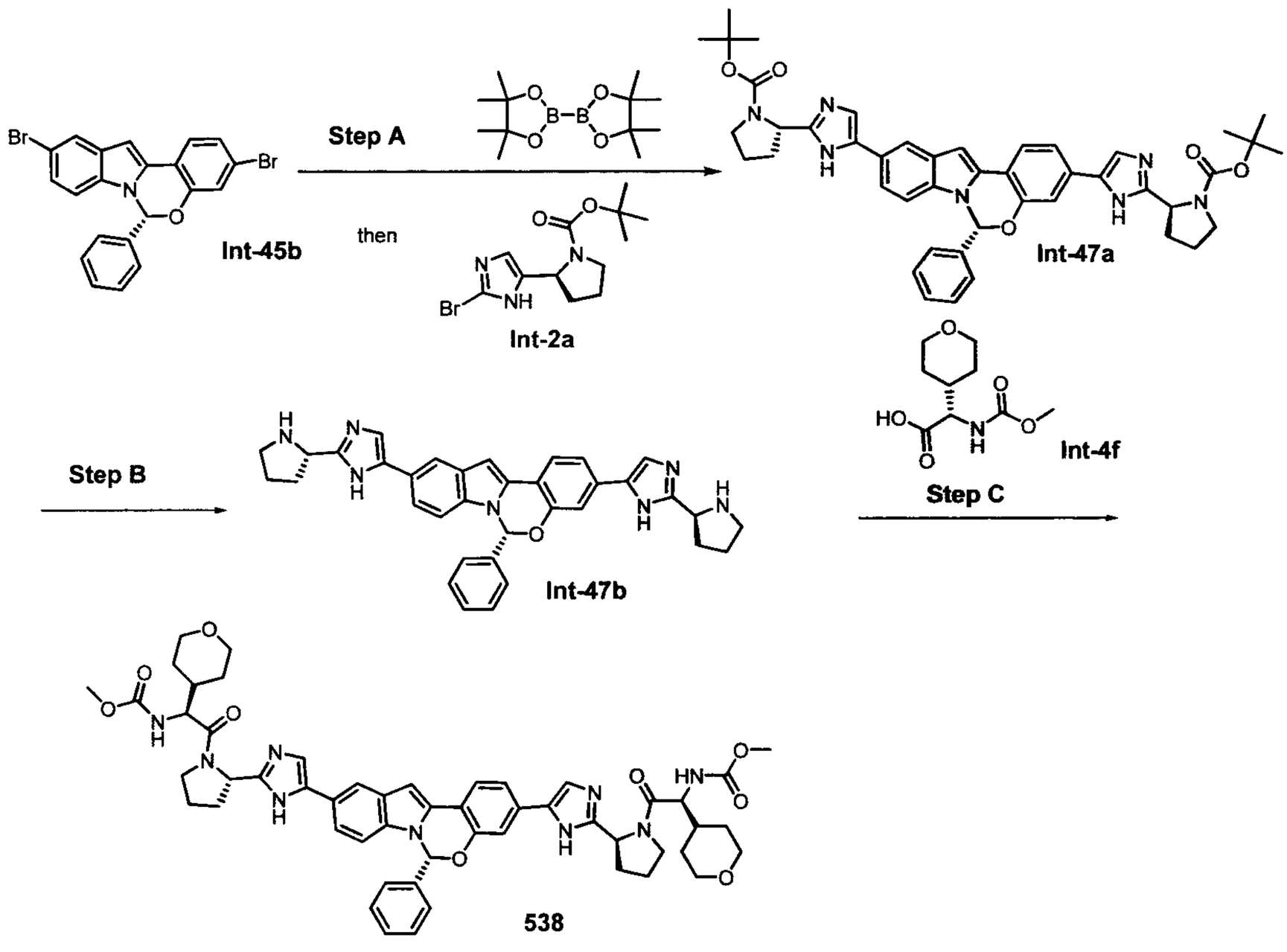
Step C

To a solution of **Int-46b** (75 mg, 0.13 mmol) in 1.5 mL DMF (1.5 mL) at -15 °C was added (*S*)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid **Int-4f** (60 mg, 0.28 mmol) and HATU (0.105 g, 0.277 mmol). The mixture was allowed to stir for ~ 15 minutes whereupon DIPEA (0.17 mL, 0.925 mmol) was added. The mixture was allowed to stir at - 15 °C for 90 minutes whereupon H_2O (3 mL) and EtOAc

(15 mL) were added. The organic layer was washed with H_2O (3 X 3 mL), brine (3 x 3 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified using reverse-phase HPLC (Gilson) using a C18 column with a gradient: 0% ACN to 90% ACN/10% water (both with 0.1% TFA) to provide 120 mg (87%) of the title Compound **728** as a light yellow dihydrochloride salt after treatment with HCl. LC-MS (M+H) = 966.6.

EXAMPLE 47

Preparation of Compound **538**



Step A

Using the procedure for the preparation of **Int-46a**, **Int-45b** (2.5 g, 5.5 mmol) was converted to 2.5 g (56%) of **Int-47a** as a brown solid. LC-MS M+H 768.4.

Step B

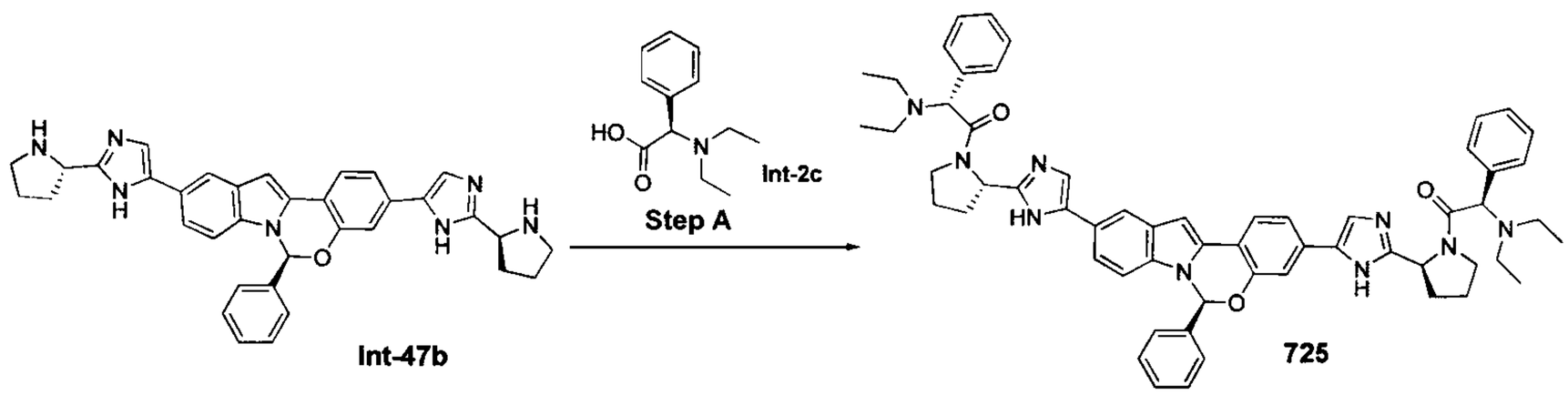
Using the procedure for the preparation of **Int-46b**, **Int-47a** (0.10 g, 0.14 mmol) was converted to 98 mg (99%) of **Int-47b** as the hydrochloride salt. LC-MS (M+H) = 568.3.

Step C

Using the method described in Example 46, step C, **Int-47b** (98 mg, 0.14 mmol) was treated with (*S*)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid **Int-4f** (65 mg, 0.30 mmol) to provide 39 mg (26%) of **Compound 538** as the dihydrochloride salt after HCl treatment. LC-MS M+H 966.4.

EXAMPLE 48

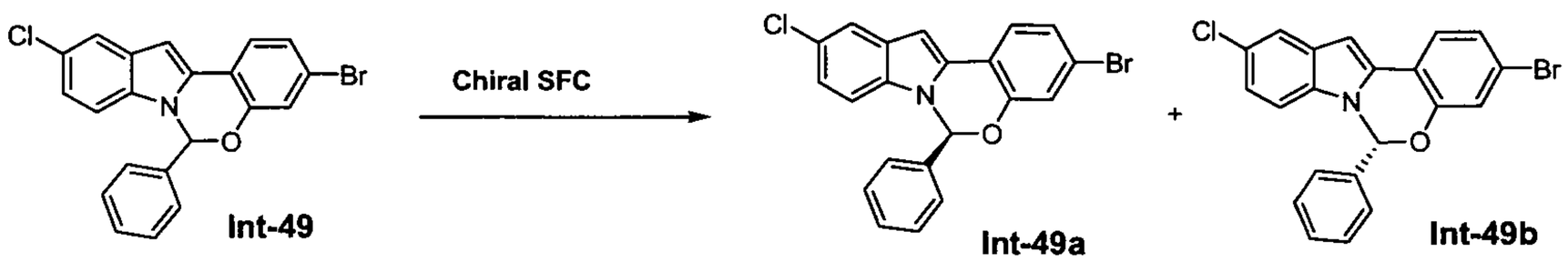
Preparation of Compound **725**



Step A

Following the procedure for Example 46, Step C, treatment of **Int-47b** (75 mg, 0.13 mmol) with (*R*)-2-(diethylamino)-2-phenylacetic acid hydrochloride **Int-2c** (68 mg, 0.28 mmol) provided 0.12 g (83%) of the title Compound **725.** LC-MS (M+H) = 946.8.

EXAMPLE 49

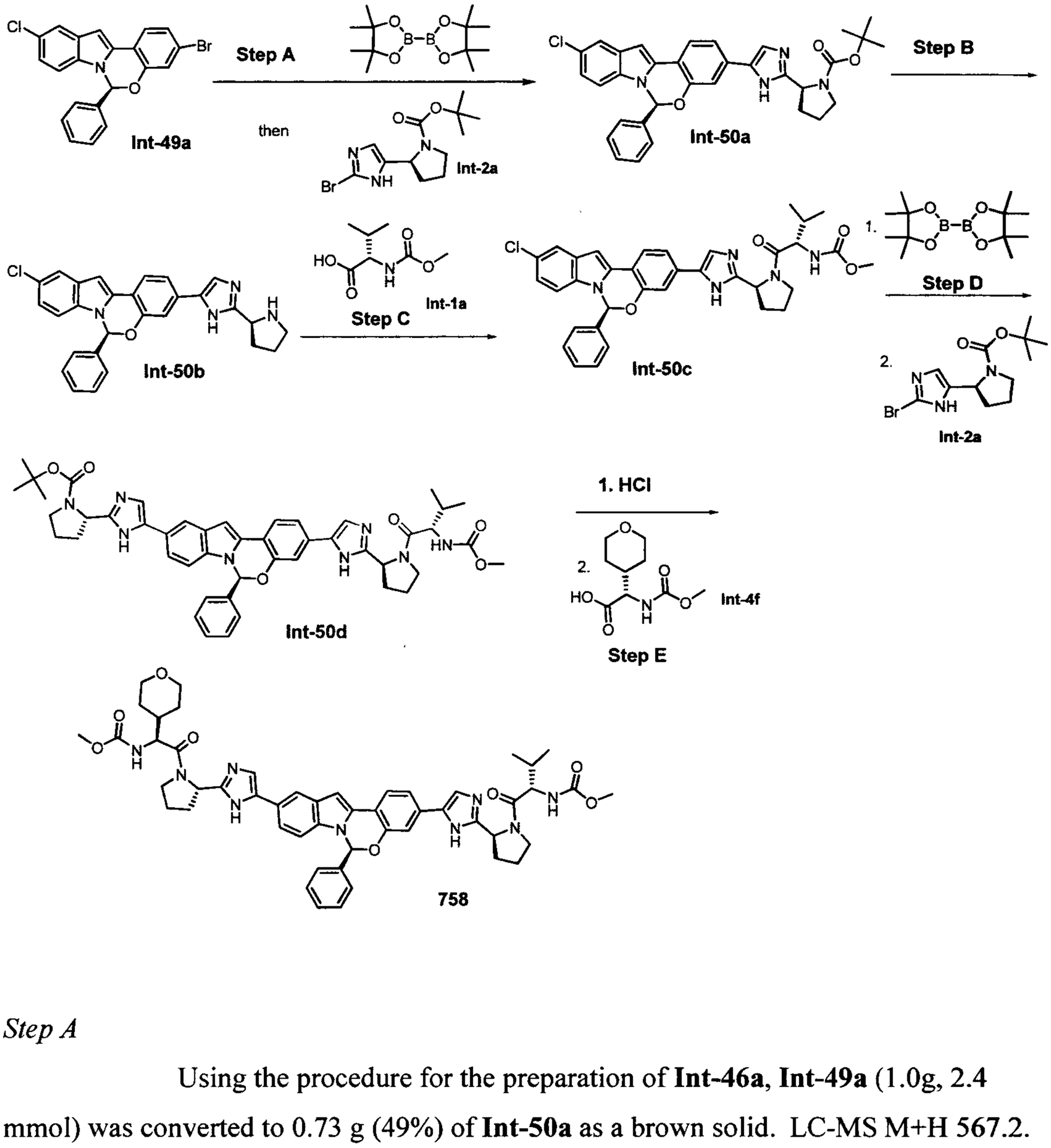


Chiral SFC separation (Chiral AD, 30% MeOH/AcCN (2:1) in CO_2) of **Int-49** yielded Compounds **Int-49a** and **Int-49b**.

Optical rotation: Int-49b $[\alpha]_D^{23}$ -362.4°

EXAMPLE 50

Preparation of Compound **758**



Step A

Using the procedure for the preparation of **Int-46a**, **Int-49a** (1.0g, 2.4 mmol) was converted to 0.73 g (49%) of **Int-50a** as a brown solid. LC-MS M+H 567.2.

Step B

To a round bottom flask charged with **Int-50a** (0.25 g, 0.44 mmol) **and a** stir bar was added MeOH (1 mL) to provide a yellow, heterogeneous mixture. 4 N HCl

in dioxane (~1 mL) was added dropwise and the resulting solution was allowed to stir for 2.5 hours at room temperature. The mixture was concentrated under reduced pressure to provide an orange solid. The solid was triturated with Et_2O (4 x 4 mL), concentrated under reduced pressure, and placed under high vacuum to provide **Int-50b** (206 mg ,99%) of a light yellow solid. LC-MS M+H = 467.2. This material was taken without any further characterization or purification.

Step C

To a solution of **Int-50b** (0.24 g, 0.44 mmol) in DMF (2.5 mL) at -10 °C (ice/acetone) was added (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid **Int-2d** (85 mg, 0.49 mmol), HATU (0.18 g, 0.49 mmol), followed by dropwise addition of DIPEA (0.23 mL, 1.3 mmol) to provide an orange, homogenous solution. The resulting solution was allowed to stir for 1 hour at -10 °C whereupon the reaction mixture was diluted with water (1.5 mL) and EtOAc (4 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 4 mL) and the organic layers were combined. The organic layer was washed with brine (1 x 3 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting orange/brown semisolid was placed under high vacuum to provide a yellow semisolid. The crude material was taken up in CH_2Cl_2 (2 mL) and was loaded onto a 40 g silica gold column. A gradient of 100% CH_2Cl_2 to 85% CH_2Cl_2/15% MeOH was run over roughly 35 minutes. The major fraction that was collected was concentrated under reduced pressure to provide 0.27 g (95%) of **Int-50c** an off-white solid. LC-MS (M+H) = 624.2.

Step D

To a 20 mL pressure tube with a stir bar was added **Int-50c** (0.30 g, 0.48 mmol) in dioxane (4 mL). Bis(pinacolato)diboron (0.13 g, 0.53 mmol), KOAc (0.14 g, 1.4 mmol), and $Pd_2(dba)_3.CHCl_3$ (75 mg, 0.07 mmol), and X-phos (69 mg, 0.14 mmol) were added to the tube to provide a heterogeneous mixture. The reaction mixture was degassed under house vacuum and filled with N_2 five times. The tube was capped, the reaction was heated to 120 °C. After 4 hours LC-MS (M+H 716.2) in dicated that the reaction was complete. To the cooled pressure tube containing the crude boronate was

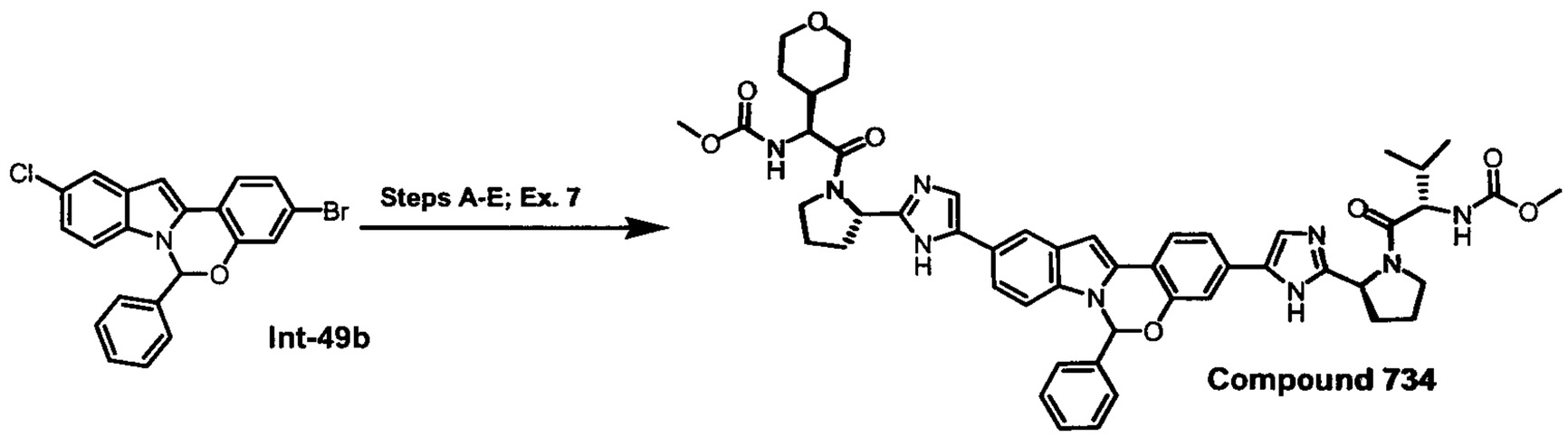
added bromo imidazole **Int-2a** (0.18 g, 0.58 mmol), $PdCl_2dppf{\cdot}CH_2Cl_2$ (79 mg, 0.096 mmol), and 1 M K_2CO_3 (1.4 mL). The tube was flushed with N_2, capped, and heated to 95 °C for 12 hours. The reaction was then cooled to room temperature, diluted with EtOAc (100 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 75 mL). The organic layers were combined and were washed with brine (1 x 50 mL). dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified using RS ISCO Gold 40 gm column using a gradient of 100% CH_2Cl_2 to 90/10 % CH_2Cl_2/MeOH to provide 0.16 (37%) of **Int-50d** as a brown solid. LC-MS (M+H) = 825.4.

Step E

Using the procedure for the preparation of **Int-3b**, **Int-50d** (71 mg, 0.086 mmol) was converted to 71 mg (99%) of the free diamine as the hydrochloride salt. LC-MS (M+H) = 726.2.

Using the procedure in example 45, step C, The diamine intermediate **Int-50d'** (71 mg, 0.086 mmol) was treated with (*S*)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid **Int-4f** (20 mg, 0.094 mmol) to provide 70 mg (82%) of Compound **758** as the dihydrochloride salt after HCl treatment. LC-MS (M+H) = 966.4.

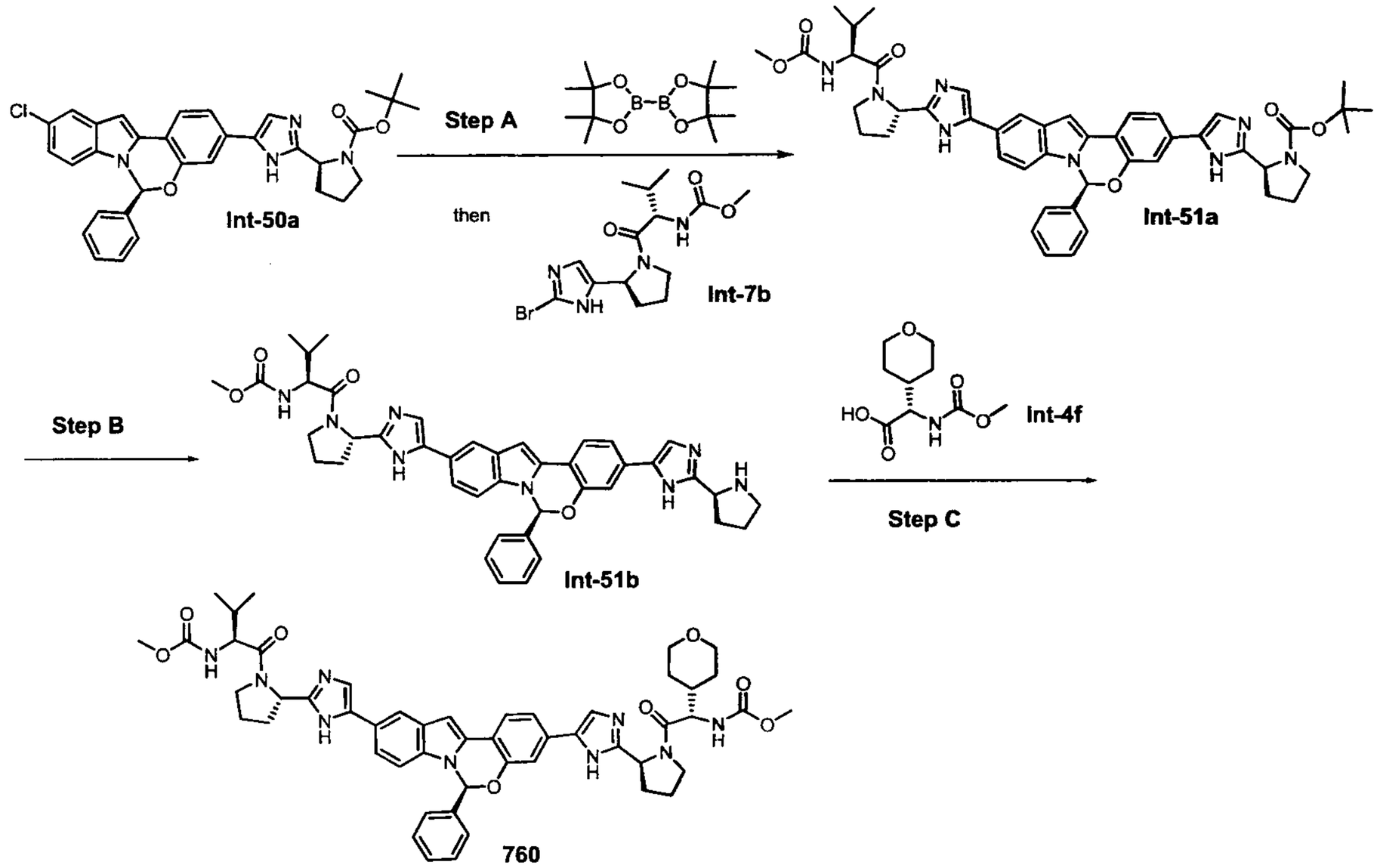
Preparation of Compound **734**



Using the methods described in Example 7, Steps A-E, compound **Int-49b** was converted into Compound **734.** LC-MS (M+H) = 925.3.

EXAMPLE 51

Preparation of Compound **760**



Step A

Using the method described in Example 50, **Int-50a** (0.40 g, 0.71 mmol) was treated with **Int-7b** (0.32 g, 0.85 mmol) after initial boronate formation to provide 0.27 g (44%) of **Int-51a** as an off-white solid. LC-MS (M+H) = 825.2.

Step B

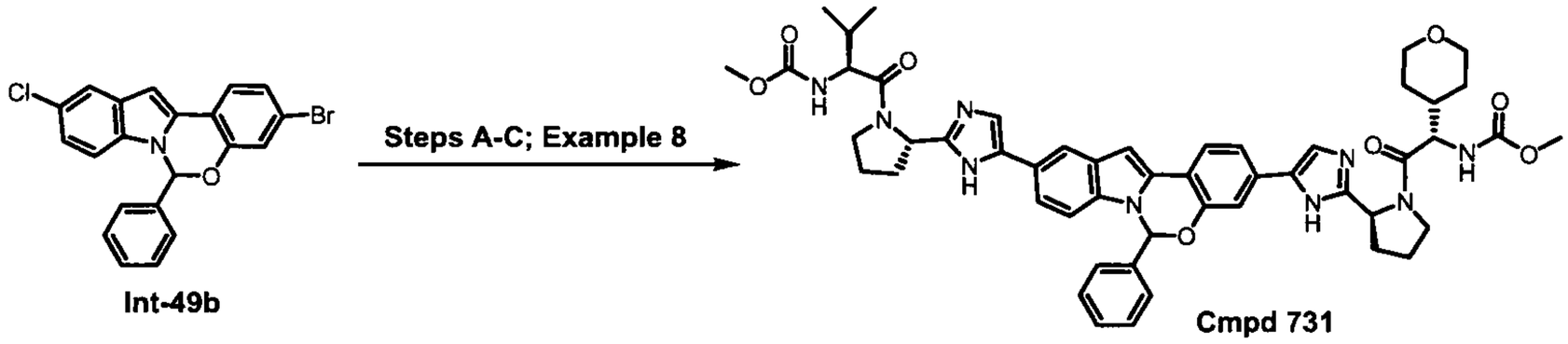
Using the method described in Example 5o, **Int-51a** (86 mg, 0.10 mmol) was converted to 86 mg (99%) of **Int-51b** as the hydrochloride salt. LC-MS (M+H) = 725.4.

Step C

Using the procedure in example 50, **Int-51b** (86 mg, 0.10 mmol) was treated with (*S*)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid **Int-**

4f (25 mg, 0.12 mmol) to provide 65 mg (62%) of Compound **760** as the dihydrochloride salt after HCl treatment. LC-MS (M+H) = 924.5.

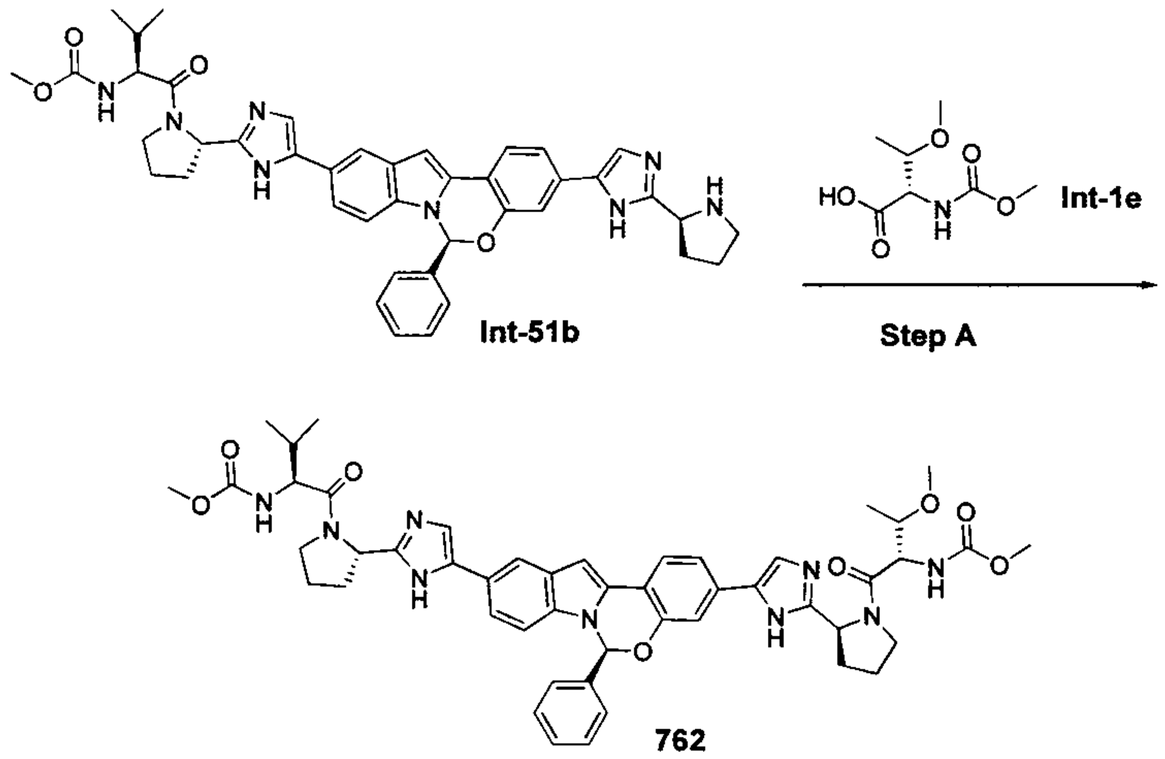
Preparation of Compound **731**



In an analogous procedure, **Int-50a** was converted into Compound **731.** LC-MS (M+H) = 924.5.

EXAMPLE 52

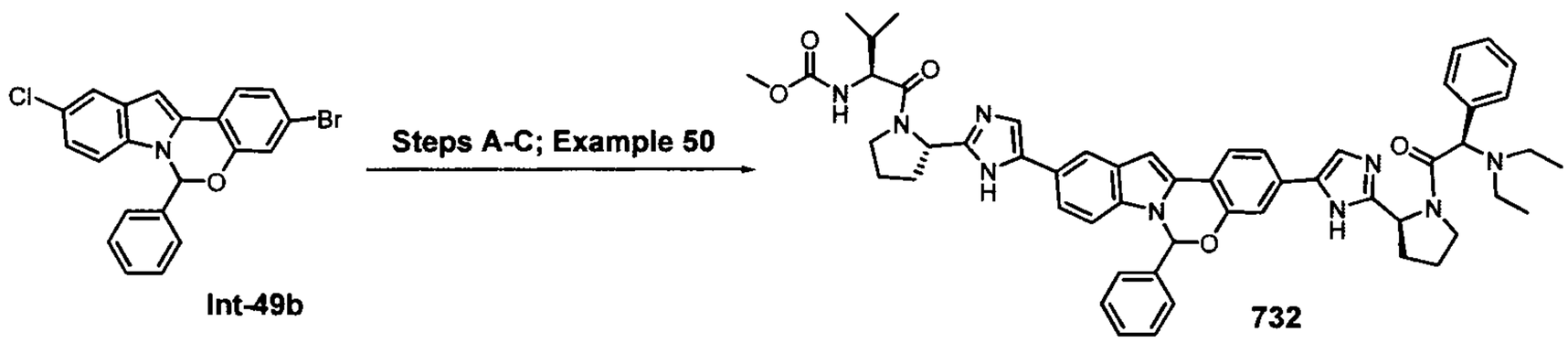
Preparation of Compound **762**



`Using the method described in Example 50, **Int-51b** (86 mg, 0.10 mmol) was treated with (2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid **Int-1e** (22 mg, 0.12 mmol) to provide 70 mg (69%) of Compound **762** as the dihydrochloride salt after HCl treatment. LC-MS (M+H) = 899.4.

EXAMPLE 53

Preparation of Compound **732**

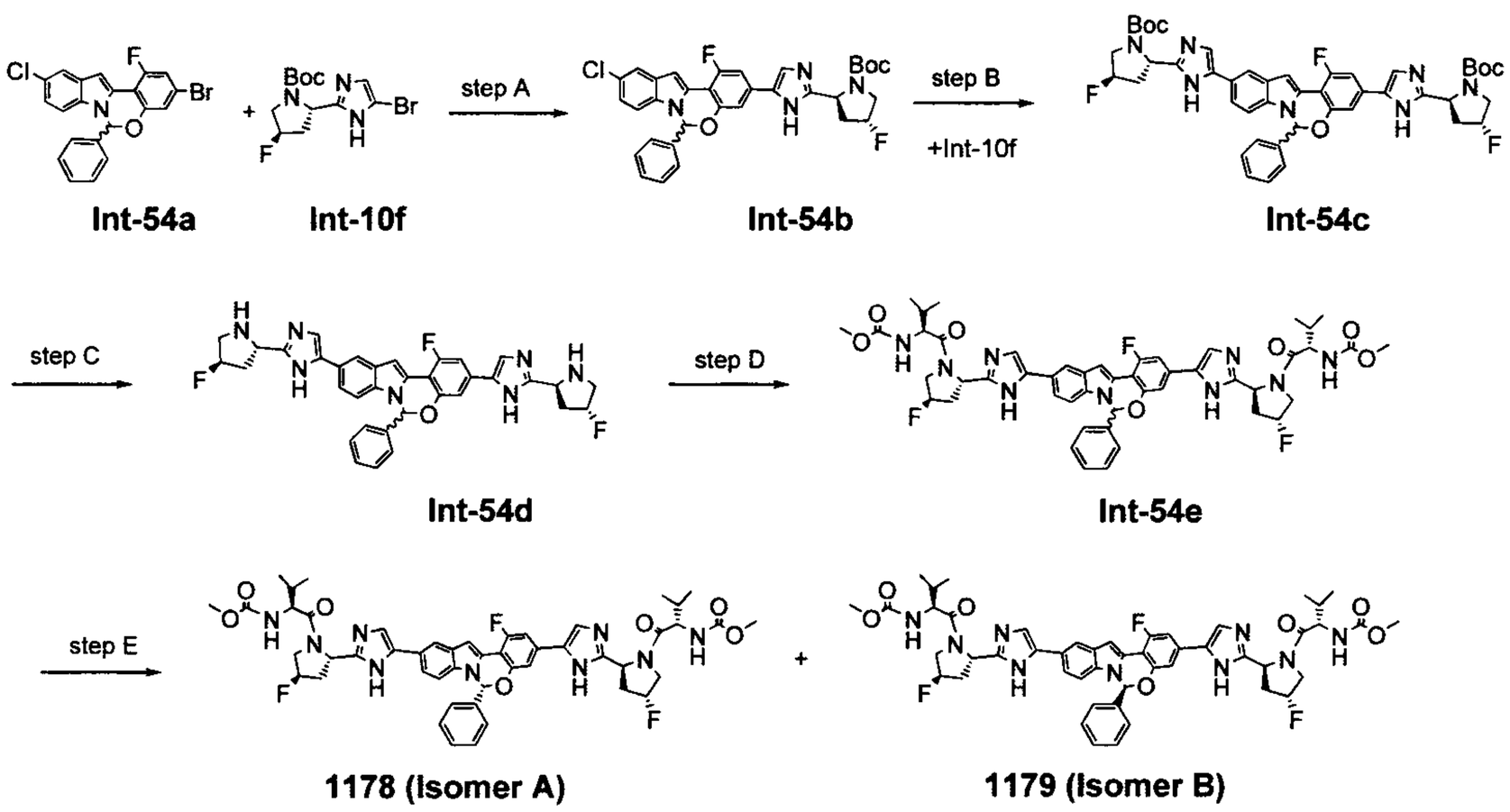


Int-49b **732**

In an analogous procedure to Example **50** using (*R*)-2-(diethylamino)-2-phenylacetic acid hydrochloride **Int-2c**, and **Int-49b** was converted into Compound **732.** LC-MS (M+H) = 914.4.

EXAMPLE 54

Preparation of Compound **1178** & compound **1179**



Int-54a **Int-10f** **Int-54b** **Int-54c**

Int-54d **Int-54e**

1178 (Isomer A) **1179 (Isomer B)**

Step A

Int-54a (prepared from **Int-19i**, 800 mg, 1.87 mmol), bis(pinacolato)diboron (474 mg, 1.87 mmol), $PdCl_2(dppf)_2$ (273 mg, 0.37 mmol), and KOAc (549 mg, 5.6 mmol) were added into a 100 mL flask. After the flask was flashed with N_2, dry dioxane (18 mL) was added and the reaction was allowed to stir at 90 °C for 2 hours. After cooling down, **Int-10f** (624 mg, 1.87 mmol), $PdCl_2(dppf)_2$ (136 mg, 0.19 mmol) and 1M K_2CO_3 solution (1M, 5.6 mL, 5.6 mmol) were added. The mixture was allowed to stir at 90 °C for 4 hours and allowed to cool to room temperature . The aqueous layer was separated and extracted with 10 mL EtOAc. The organic layers were combined

and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified using silica-gel chromatography (80 g, Eluent:EtOAc in Hexane: 0% to 80%) to provide **Int-54b** (791 mg, 70.3%).

Step B

Int-54b (791 mg, 1.31 mmol), bis(pinacolato)diboron (333 mg, 1.31 mmol), $Pd_2(dba)_3$ (120 mg, 0.13 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (125 mg, 0.262) and KOAc (386 mg, 3.93 mmol) were added into a 100 mL flask. After the flask was flashed with N_2, dioxane (13 mL) was added. The mixture was allowed to stir at 110 °C for 2 hours. After cooling down, Compound **Int-10f** (438 mg, 1.31 mmol), $PdCl_2$ $(dppf)_2$ (96 mg, 0.13 mmol) and 1M K_2CO_3 solution (1M, 3.9 mL, 3.9 mmol) were added. The mixture was allowed to stir at 90 °C for an additional 4 hours and allowed to cool to room temperature. The aqueous layer was separated and extracted thrice with 10 mL EtOAc. The combined organic extracts, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified using silica-gel chromatography (40 g, Eluent: EtOAC (10% MeOH) in CH_2Cl_2: 0% to 80% to provide **Int-54c** (364 mg, 33.8%).

Step C

Int-54c was charged in a 50 mL flask, MeOH (0.5 mL) was added and the reaction was allowed to stir at room temperature for 1 minutes. HCl (4M in dioxane, 6.6 mL, 26.4 mmol) was then added and the solution was allowed to stir at room temperature. After 1 hr the solution was concentrated and the residue was dried *in vacuo* to provide **Int-54d** (364 mg, 100%) which were used in the next step without further purification.

Step D

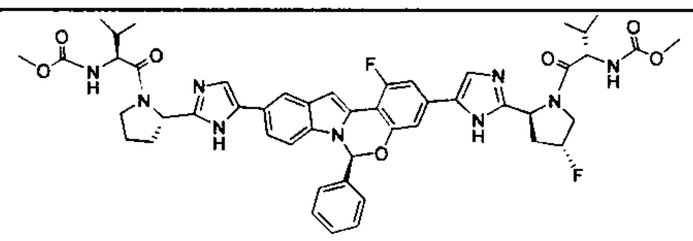
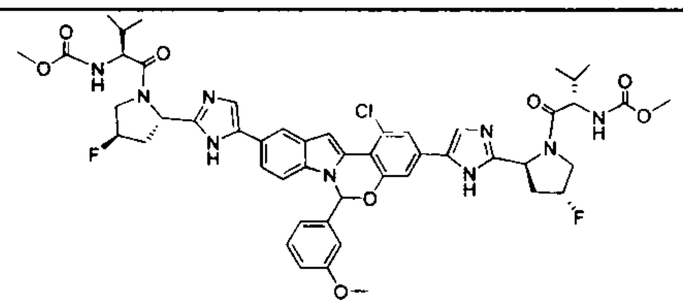
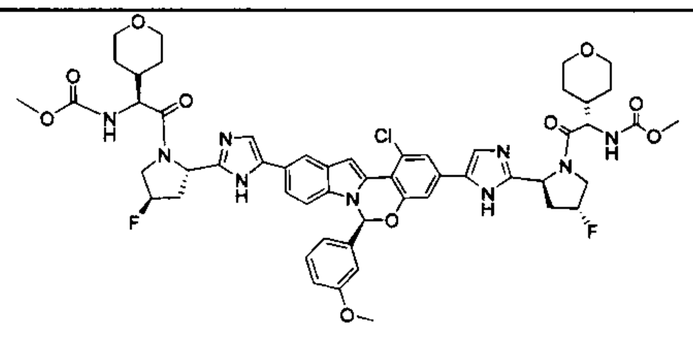
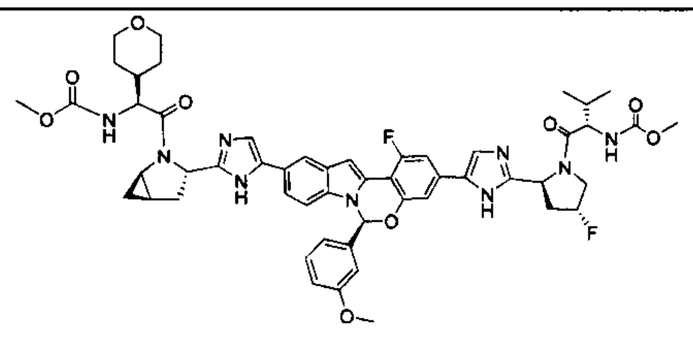
Int-54d (364 mg, 0.443 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (155 mg. 0.886 mmol), HATU (337 mg, 0.886 mmol), and DMF (4.5 mL) were added into a 40 mL flask. The reaction mixture was cooled to 0 °C and DIPEA (0.55 mL, 3.1 mmol) was added. After 1 hour, water (0.7 mL) and TFA (0.7 mL) were added at 0 °C. The solution was then stirred at room temperature for an additional 30 minutes, before concentration to an oil.. The

solution was purified using C18 column (80 g, CH_3CN/water 10% to 70%, with 0.05% TFA) to provide **Int-54e** (312 mg, 60.5%).

Step E

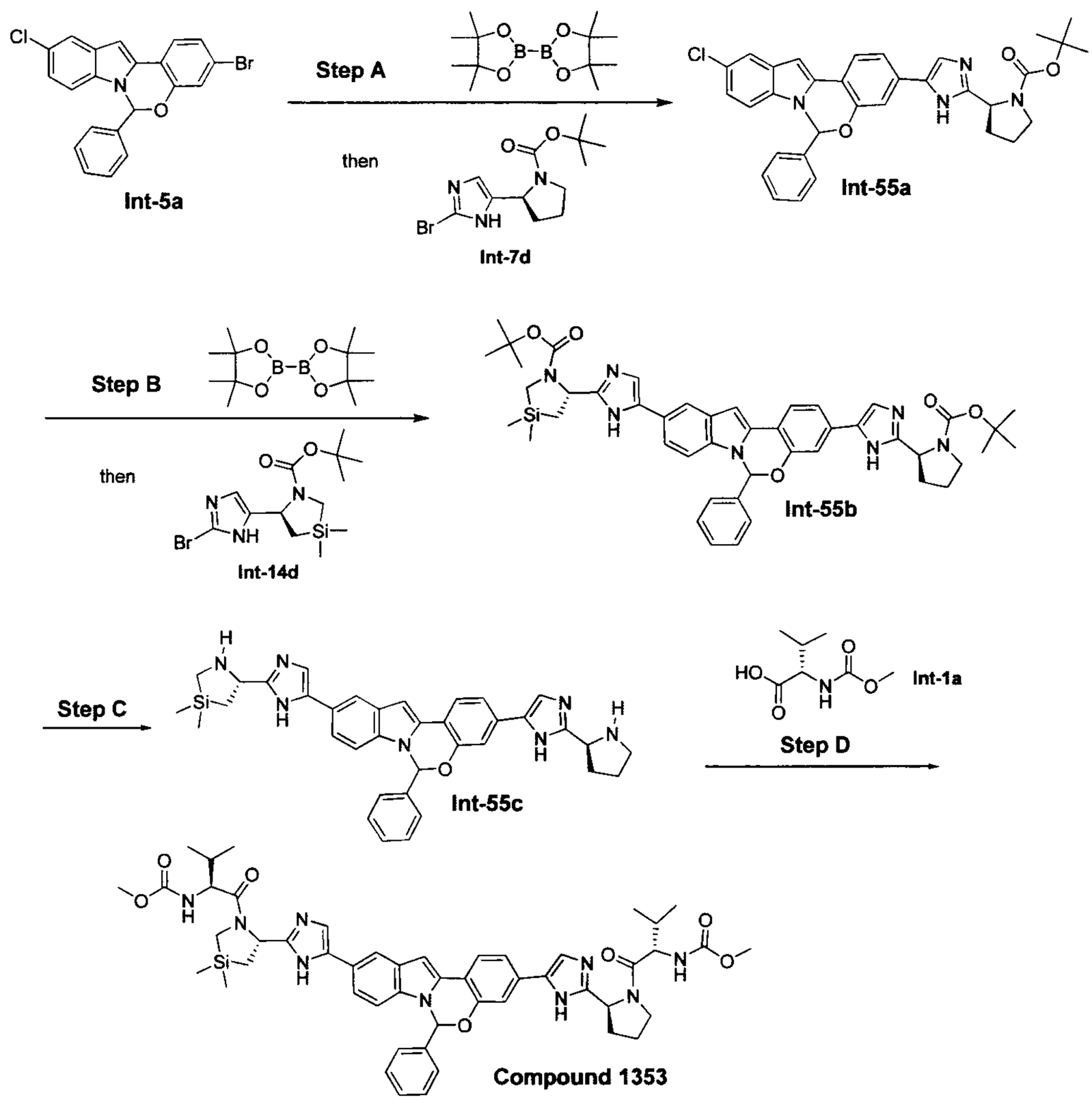
Int-54e was resolved by Chiral SFC (Chiracel AS-H, 20x250 mm, Eluent: 40% MeOH (0.2% DEA)/CO_2, 50 mL/min) to provide isomer A (Compound **1178**, 1st peak, 110 mg, 35.2%) and B (Compound **1179**, 2nd peak, 108 mg, 34.6%).

The following Compounds were prepared as described above

1463		single isomer
1198		mixture of two isomers
1507		mixture of two isomers
1508		single isomer

EXAMPLE 55

Preparation of Compound **1353**



Step A

Using the method described in Example 50 step A, **Int-5a** (1.0 g, 2.4 mmol) was converted to the boronate and was treated with **Int-7d** (0.92 g, 2.9 mmol) to provide 0.92 g (67%) of **Int-55a** as a brown solid. LC-MS (M+H) = 566.7.

Step B

Using the method described in Example 50, **Int-55a** (0.70 g, 0.1.2 mmol) was converted to the intermediate boronate followed by treatment with **Int-7d** (0.53 g, 1.5 mmol) to provide 0.25 g (25%) of **Int-55b**. LC-MS (M+H) = 811.6.

Step C

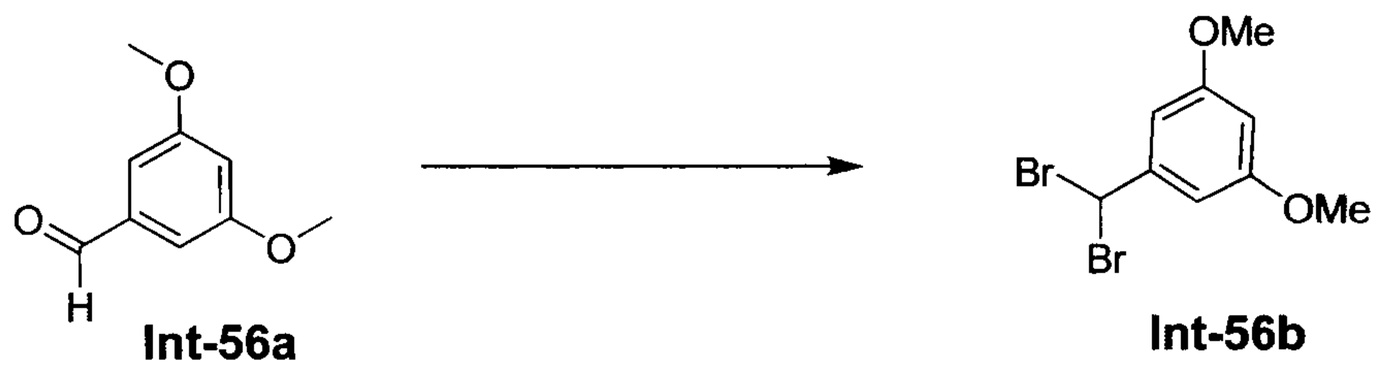
Using the method described in Example 50, **Int-55b** (0.25 g, 0.31 mmol) was converted to 0.23 g (99%) of **Int-55c** as the hydrochloride salt. LC-MS (M+H) = 611.8.

*Step D Preparation of Compound **1353***

Using the procedure Example 50 step E, **Int-55c** (23 mg, 0.31 mmol) was treated with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid **Int-1a** (0.11 g, 0.65 mmol) to provide 0.19 g (66%) of Compound **1353** as the dihydrochloride salt. LC-MS (M+H) = 926.2.

EXAMPLE 56

Preparation of Intermediate Compound **Int-56b**

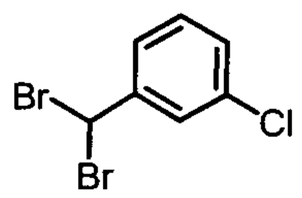


Int-56a **Int-56b**

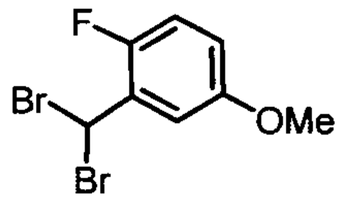
A 500-mL round-bottom flask was charged with triphenyl phosphite (31 mL, 37 g, 120 mmol), dichloromethane (250 mL) and cooled for 15 minutes in a dry ice-acetone bath that was maintained at -50 to -60 °C. Bromine (6.2 mL, 19 g, 120 mmol) was added dropwise over 15 minutes through an addition funnel. Triethylamine (19 mL, 13 g, 132 mmol) and 3,5-dimethoxybenzaldehyde (**Int-56a;** 10.0 g, 60.2 mmol) were added sequentially. The reaction mixture was allowed to stir at -60 °C for 1 hour. The cold bath was removed and the reaction mixture was allowed to stir for a further 18 hours as the temperature was allowed to reach RT. The reaction mixture was concentrated by rotary evaporation under reduced pressure (water bath temperature ~50-60 °C) to provide a dark brown, viscous liquid as crude product. The crude product was taken up in EtOAc (~100 mL) and filtered. The filtrate was concentrated under reduced pressure (water bath temperature ~50-60 °C) to provide a dark brown, crude Int-56b as a viscous liquid. **Int-56b** was loaded directly onto a pre-equilibrated 330 g RediSep® Gold silica gel column

and purified using flash chromatography (Isco®; Eluent: 0-5% EtOAc/hexanes gradient, to 5-70% EtOAc/ hexane to provide **Int-56b** as a white solid (12.8 g, 68% yield).

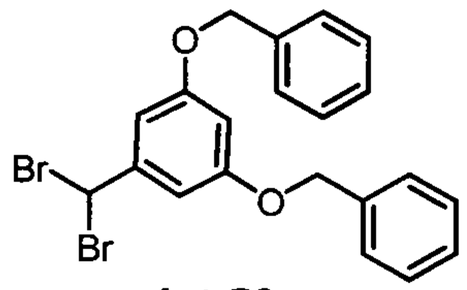
In the same manner, the following 1,1-dibromo intermediates were prepared from the corresponding aldehydes.



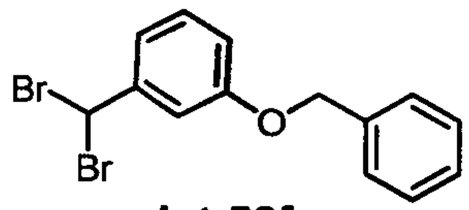
Int-56c



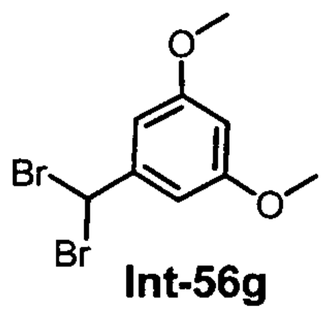
Int-56d



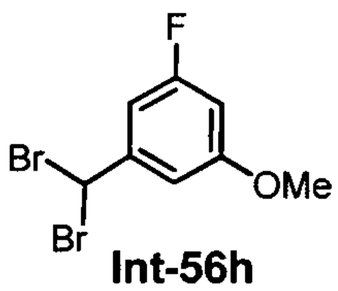
Int-56e



Int-56f



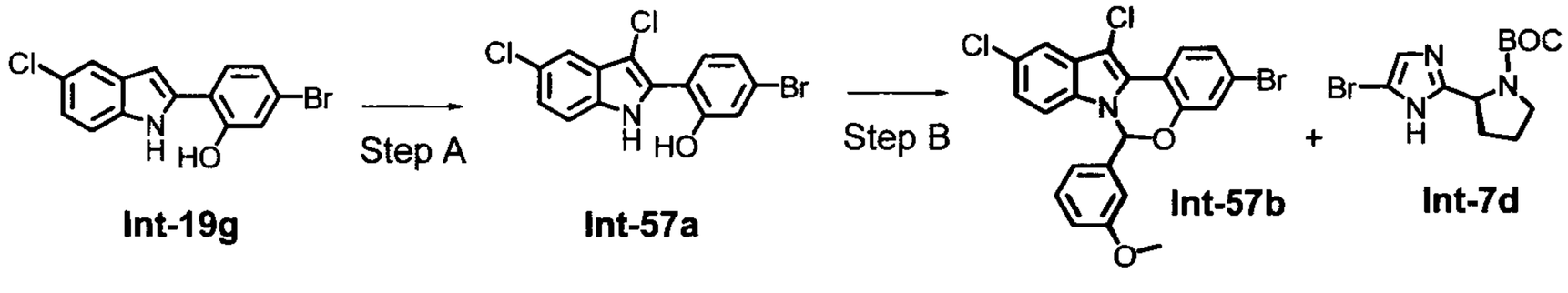
Int-56g

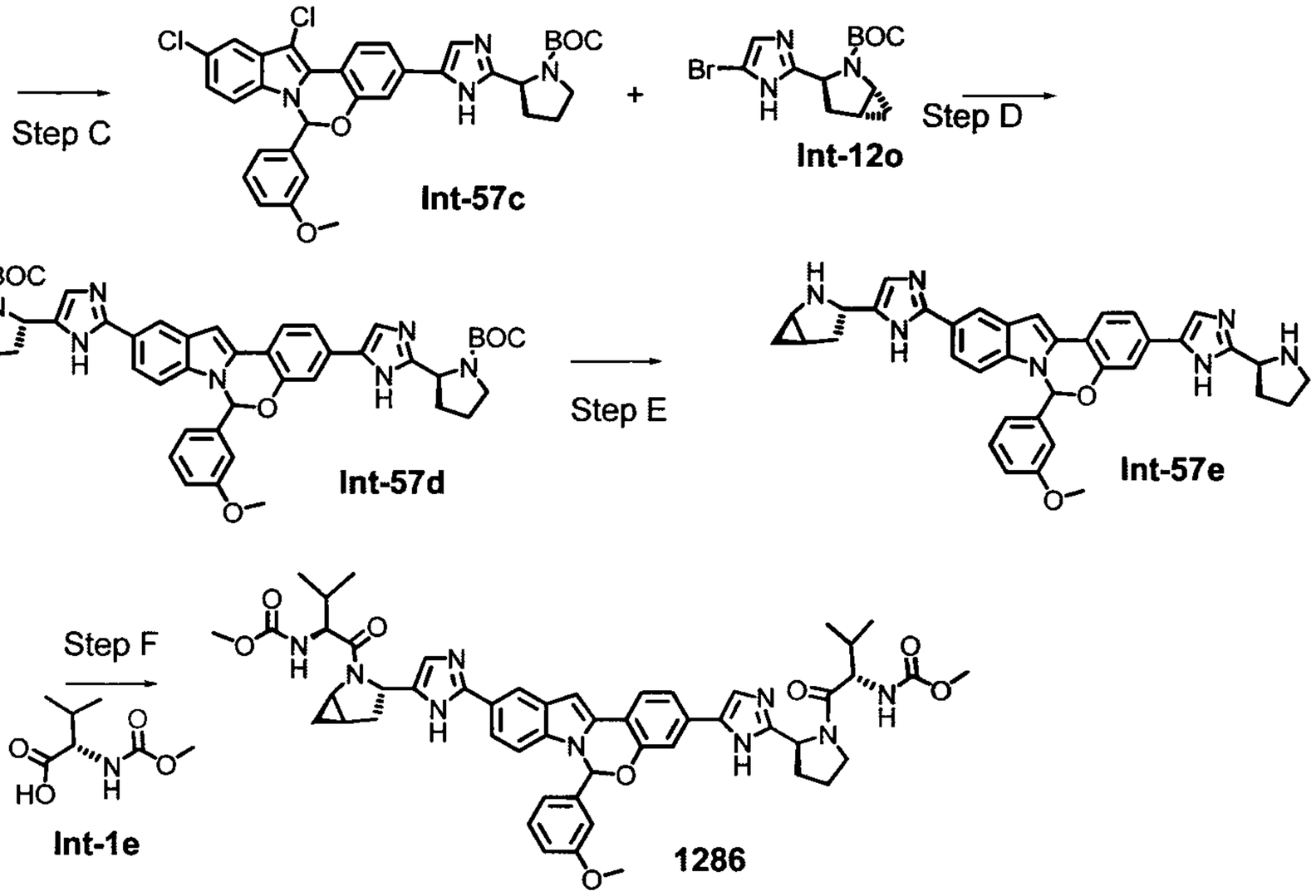


Int-56h

EXAMPLE 57

Preparation of Compound **1286**





Step A

Int-19g (10.0 g, 31 mmol), NCS (4.14 g, 31 mmol), dichloromethane (300 ml), and THF (300 ml) were added to a 1 L flask and the resulting mixture was allowed to stir at 0 °C for 1 hour and then at room temperature for 2 hours. The reaction mixture was then concentrated to a semi-solid and the residue was suspended in dichloromethane (150 ml) and filtered. The solid was washed with dichloromethane (2x15 ml) and dried to provide **Int-57a** as a solid (6.4 g, 58%).

Step B

Int-57a (1.0 g, 2.8 mmol), 3-methoxybenzaldehyde (0.572 g, 0.58 mmol), *p*-toluenesulfonic acid (0.0053 g, 0.28 mmol), and *o*-xylene (10 ml) were added to a 35 mL pressure vessel. The resulting mixture was allowed to stir at 170 °C for about 15 hours under protection of a shield, cooled to room temperature, and purified on a 80 g

silica column/ Combi-Flash Rf system (Eluent: 0-5% ethyl acetate in hexanes eluent) to provide **Int-57b** as a gel (0.2 g, 15%).

Step C

Int-57b (200 mg, 0.421 mmol), bis(pinacolato)diboron (118 mg, 0.421 mmol), potassium acetate (207 mg, 2.1 mmol), $PdCl_2$(dppf)-CH_2Cl_2 (34.4 mg, 0.042 mmol), and dioxane (5 ml) were added to a 35 mL microwave reaction tube. The sealed tube was degassed and stirred at 95 °C under nitrogen atmosphere for 4 hours then cooled to room temperature. To this mixture were added bromide **Int-7d** (160 mg, 0.505 mmol), $PdCl_2$(dppf)-CH_2Cl_2 (34.4 mg, 0.042 mmol), 1.5 M aqueous solution of sodium carbonate (1.4 ml, 2.1 mmol). The resulting mixture was degassed and stirred at 95 °C under nitrogen atmosphere for 6 hours, cooled to room temperature, concentrated, purified using a 12 g silica column on Combi-Flash Rf system (0-60% ethyl acetate in hexanes eluent) to provide **Int-57c** as a wax (114 mg, 43%).

Step D

Int-57c (65 mg, 0.103 mmol), bis(pinacolato)diboron (57.5 mg, 0.226 mmol), potassium acetate (101 mg, 1.03 mmol), $Pd_2(dba)_3$-$CHCl_3$ (21.3 mg, 0.02 mmol), X-PHOS (19.6 mg, 0.04 mmol), and dioxane (3 ml) were added to a 35 mL microwave reaction tube. The sealed mixture was degassed and stirred at 110 °C under nitrogen atmosphere for 8 hours then cooled to room temperature. To this mixture were added bromide **27** (85 mg, 0.258 mmol), $PdCl_2$(dppf)-CH_2Cl_2 (16.8 mg, 0.02 mmol), 1.5 M aqueous solution of sodium carbonate (0.7 ml, 1.05 mmol). The resulting mixture was degassed and stirred at 95 °C under nitrogen atmosphere for 6 hours, cooled to room temperature, concentrated, purified using a 4 g silica column / Combi-Flash Rf system (0-100% ethyl acetate in hexanes eluent) to provide **Int-57d** as a solid (39 mg, 47%).

Step E

Int-57d (39 mg, 0.048 mmol), TFA (1 ml) and dichloromethane (1 ml) were added to a 25 mL flask and stirred at room temperature for 4 hours and concentrated *in vacuo*. The residue was dissolved in methanol (2 ml), treated with 0.1 mL of 4.0 M

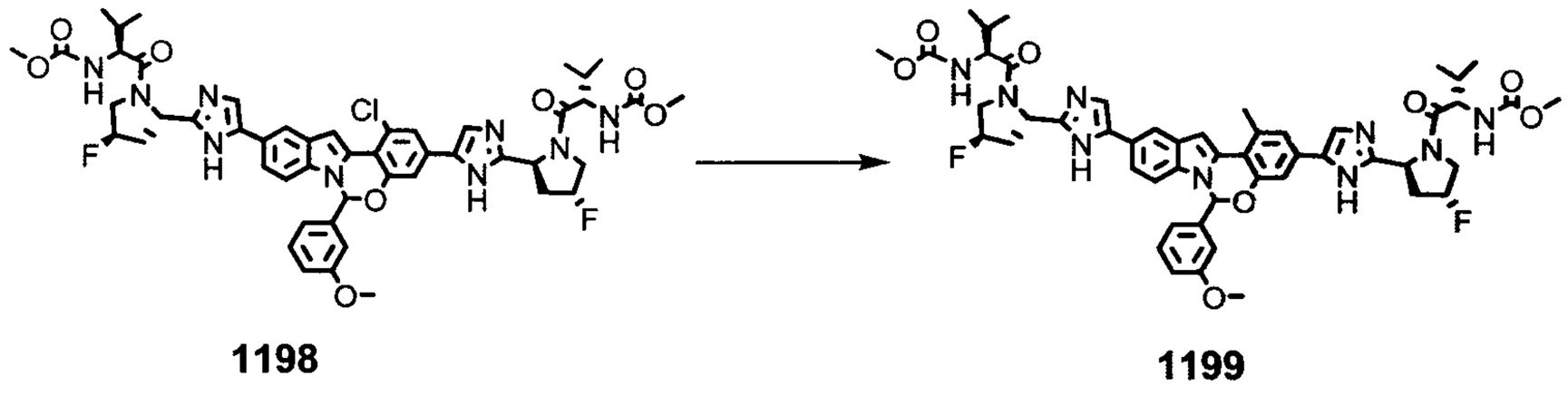
HCl (0.4 mmol) solution in dioxane and concentrated again *in vacuo* to provide **Int-57e** as a white solid. This crude product was used for the next reaction without purification.

Step F

Diamine **Int-57e** , Valine-MOC acid **Int-1a** (14.3 mg, 0.081 mmol), and DMF (1 ml) were added to a 50 mL flask and cooled to 0 °C. To this cooled solution was added HATU (30 mg, 0.08 mmol) and the reaction was allowed to stir at 0 °C over a period of 1 hour, quenched with water (3 drops). The reaction mixture was purified using reverse phase chromatography (0-90% acetonitrile in water with 0.1% TFA eluent) to provide Compound **1286** as a wax (13 mg, 31%). LC/MS anal. calcd. for: $C_{51}H_{57}N_9O_8$ 923.4; Found: 924.5 $(M+H)^+$.

EXAMPLE 58

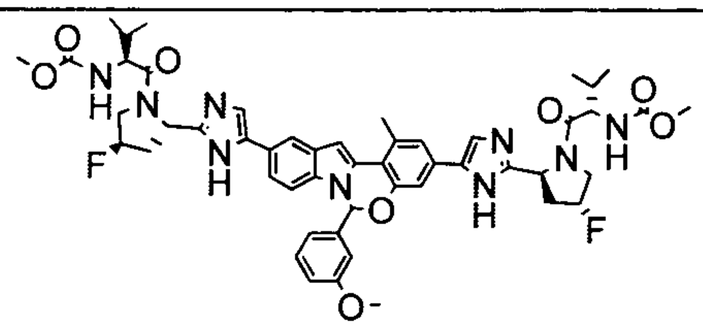
Preparation of Compound **1198** & Compound **1199**



1198 **1199**

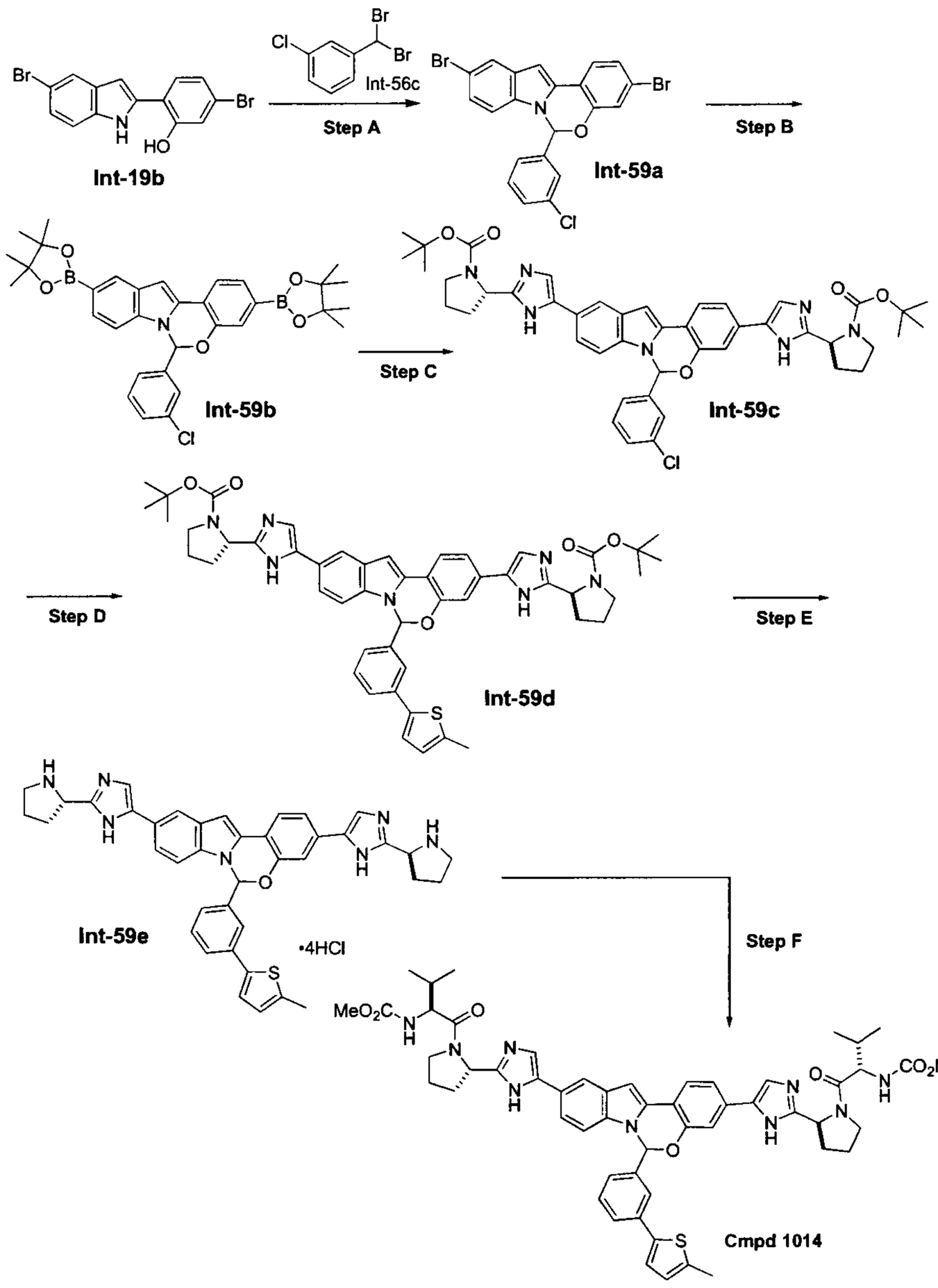
Compound **1198** (20 mg, 0.020 mmol), trimethylboroxine (7.67 mg, 0.061 mmol), $Pd_2(dba)_3$ (3.73 mg, 4.07 μmol), and dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (3.88 mg, 8.14 μmol) are added into a 50 mL flask. After the flask was flashed with N_2, 1,4-Dioxane (204 μl) and K_2CO_3 (61.1 μl, 0.061 mmol) was added. The mixture was allowed to stir at 110 °C for 16 hours. After cooling down, the aqueous layer was separated and extracted with 5 mL EtOAc. The organic layers were combined and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated *in vacuo*. The solution was concentrated and purified using SiO_2 chromatography (24 g, MeOH (Eluent: 10% concentrated $MeOH/NH_3{\cdot}H_2O$) in CH_2Cl_2, 0% to 80%) to provide Compound **1199** (15 mg, 77%).

The following compound was made using the method described in the Example above:

1199		mixture of two isomers

EXAMPLE 59

Preparation of Compound **1014**



Step A

In a 250-mL round-bottom flask, **Int-19b** (2.006 g, 5.47 mmol) was dissolved in DMSO (22 mL). Neat dibromide **Int-56c** (1.710 g, 6.01 mmol) was added, followed by solid cesium carbonate (5.34 g, 16.4 mmol). The reaction mixture was immersed into a preheated 90 °C oil bath and stirred for 18 hours, then allowed to cool to room temperature, and poured into water (~100 mL), whereupon a tan solid precipitated. The aqueous mixture was extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with brine (~50 mL), then dried over anhydrous $MgSO_4$, filtered,

and concentrated *in vacuo* to provide a tan-brown solid as crude product. The crude product was purified using flash silica gel chromatography (Isco®; 220 g RediSep® Gold silica gel column; Eluent: 0-30% EtOAc/hexanes gradient to provide **Int-59a** as a pale yellow solid (683 mg, 26% yield).

Step B

In a 20-mL Biotage® microwave tube was charged with stir basr was added **Int-59a** (670 mg, 1.37 mmol), bis(pinacolato)diboron (695 mg, 2.74 mmol), (dppf)$PdCl_2$•CH_2Cl_2 (68 mg, 0.083 mmol) and potassium acetate (403 mg, 4.11 mmol). The tube was alternately evacuated and back-filled with nitrogen 5 times. Dioxane (14 mL) was added and the tube was immersed into a preheated 90 °C oil bath. After 1.5 hours, then reaction was allowed to cool to room temperature, diluted with EtOAc (~20 mL) and filtered through a Celite® pad. The pad was rinsed with EtOAc (~50 mL) and the combined filtrate were washed with brine (~25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide an light brown solid as crude product. The crude product was purified using flash silica gel chromatography (Isco®; 40 g RediSep® Gold silica gel column; Eluent 0-50% EtOAc/hexanes gradient) to provide **Int-59b** as a beige solid (705 mg, 88% yield).

Step C

A 20-mL Biotage® microwave tube was charged with a stir bar, **Int-59b** (700 mg, 1.20 mmol), bromoimidazole **Int-7d** (834 mg, 2.64 mmol), and (dppf)$PdCl_2$•CH_2Cl_2 (49 mg, 0.060 mmol). The tube was alternately evacuated and refilled with nitrogen (5x). Dioxane (8 mL) was added and the reaction mixture was allowed to stir at room temperature for 5 minutes. Aqueous potassium carbonate solution (6 mL, 1 M aqueous, 6 mmol) was then added and the reaction was immersed into a preheated 90 °C oil bath. After 18 hours the reaction was allowed to cool to room temperature and was diluted with EtOAc (~50 mL), filtered through a polyethylene filter frit and the filtrate was washed with brine (~25 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide an orange-brown solid as crude product. The crude product was purified using flash silica

gel chromatography (Isco®; 120 g RediSep® Gold silica gel column; Eluent 0-10% MeOH/CH2Cl2 gradient) to provide **Int-59c** as a beige solid (719 mg, 75% yield).

Step D

A 5-mL Biotage® microwave tube was charged with a stir bar, **Int-59c** (130 mg, 0.162 mmol), $(dba)_3Pd_2 \cdot CHCl_3$ (25 mg, 0.024 mmol) and X-Phos (23 mg, 0.049 mmol). The tube was sealed and alternately evacuated and back-filled with nitrogen (5x). 5-methylthienyl-2-boronate (36 mg, 0.16 mmol), dissolved in dioxane (1.6 mL), and potassium carbonate (0.8 mL, 1 M aqueous; 0.8 mmol) were added by syringe. The tube was immersed in preheated 120 °C oil bath and stirred for 4 hours. The reaction mixture was then cooled, diluted with EtOAc (~50 mL), filtered, and washed with brine (~25 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product as a golden yellow solid. Further purification by reverse-phase chromatography (Gilson®; Phenomenex® Gemini 150 x 21.20 mm x 5 μm column; 10-70% MeCN/water (+0.1% TFA) gradient over 20 minutes) to provide **Int-59d** as a beige solid (26 mg, 19% yield).

Step E

In a 50-mL round-bottom flask **Int-59d** (20 mg, 0.03 mmol) was dissolved in methanol (500 μL) and HCl solution (60 μL, 4 M in dioxane, 0.240 mmol) was added. The clear, pale yellow tinged solution was allowed to stir at room temperature for 24 hours. The reaction mixture was concentrated *in vacuo* to provide **Int-59e** a beige solid (15.6 mg, 83% yield).

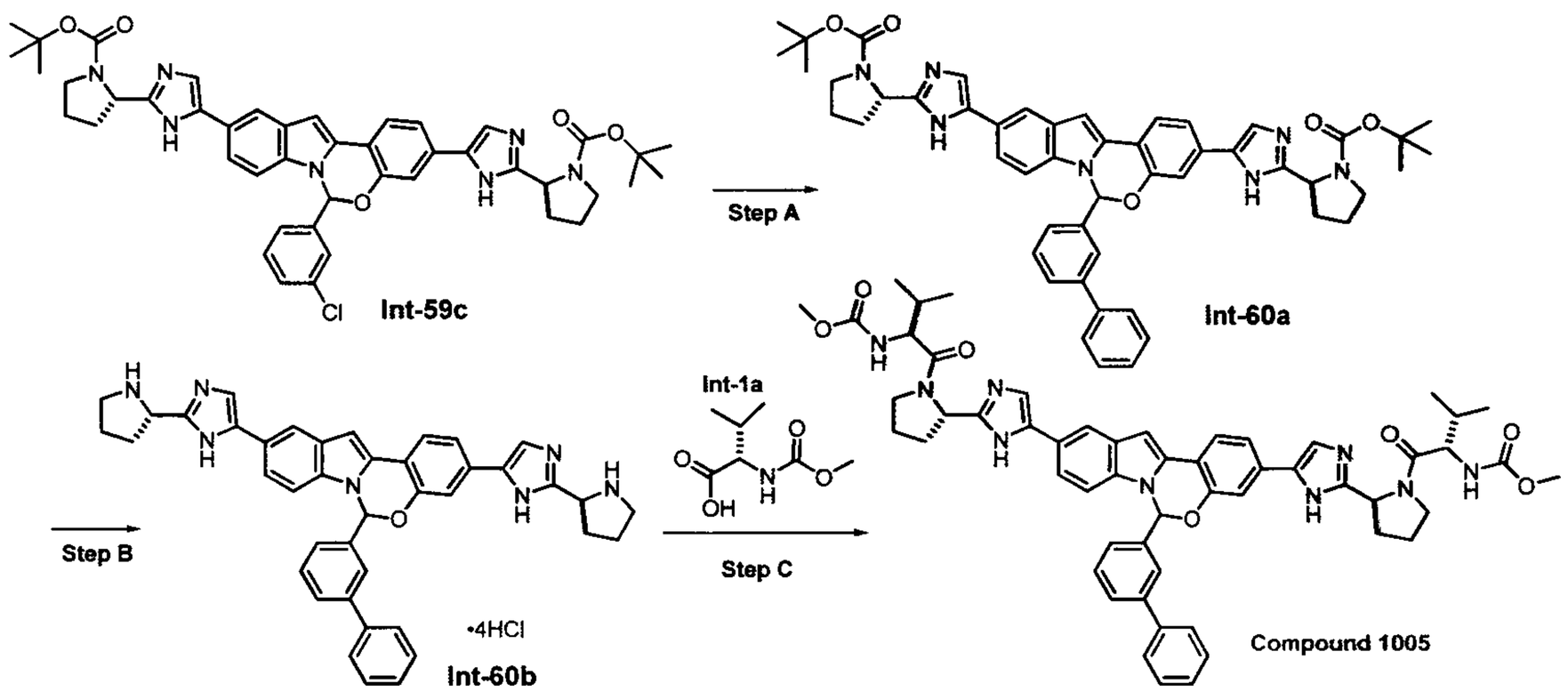
Step F

In a 50-mL round-bottom flask, **Int-59e** (16 mg, 0.019 mmol) and **Int-1a** (7 mg, 0.040 mmol) were dissolved in DMF (200 μL). Diisopropylethylamine (20 μL, 15 mg, 0.118 mmol) was added and the reaction mixture was cooled in an ice-water bath for 15 minutes. Solid HATU (15 mg, 0.039 mmol) was added slowly and the reaction allowed to warm slowly to room temperature. After 3 hours the reaction was purified directly by reverse-phase chromatography (Gilson®; Phenomenex® Gemini 150 x 21.20

mm x 5 μm column; 10-70% MeCN/water (+0.1% TFA) gradient over minutes) to provide Compound **1014** as a beige solid (12 mg, 62% yield).

EXAMPLE 60

Preparation of Compound **1005**



Step A

A 5-mL Biotage® microwave tube equipped with a magnetic stir bar was added, **Int-59c** (254 mg, 0.317 mmol), phenylboronic acid (77 mg, 0.634 mmol), $Pd_2(dba)_3$•$CHCl_3$ (66 mg, 0.063 mmol) and X-Phos (61 mg, 0.127 mmol). The tube was sealed and alternately evacuated and back-filled with nitrogen (5x). Dioxane (3 mL) and potassium carbonate (0.78 mL, 1 M aqueous; 0.78 mmol) were added and the reaction immersed in a preheated 110 °C oil bat. After 22 hours the reaction was allowed to cool, diluted with EtOAc (~30 mL), and washed sequentially with water (~20 mL) and brine (~20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to provide the crude product as a light brown solid. The crude product was purified using flash silica gel chromatography (Isco®; 40 g RediSep® Gold silica gel column; Eluent 0-10% MeOH/CH_2Cl_2 gradient) to provide **Int-60a** (134 mg, 50% yield) as a pale yellow-orange solid.

Step B

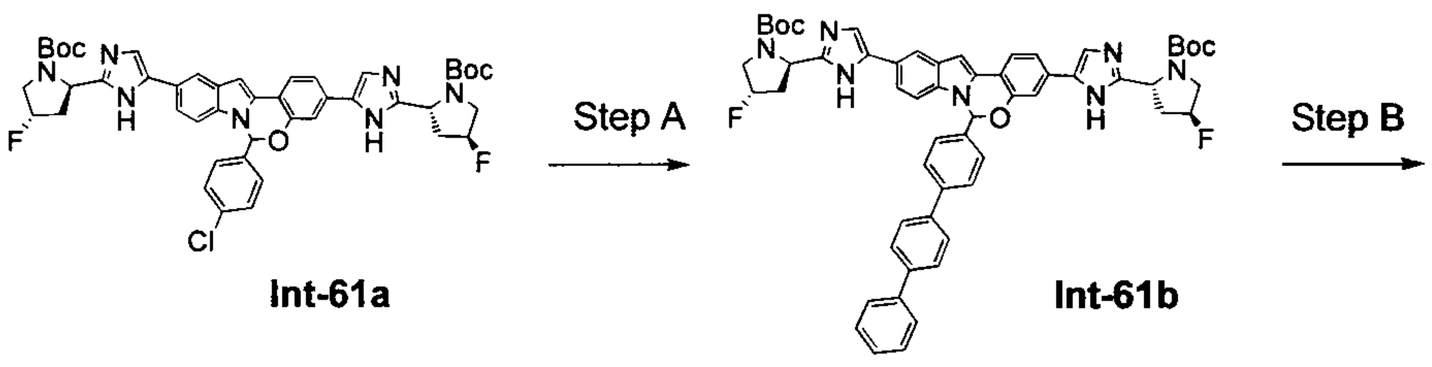
In a 125-mL round-bottom flask, **Int-60a** (100 mg, 0.118 mmol) was dissolved in methanol (1.2 mL). Hydrogen chloride solution (0.300 mL, 4 M in dioxane, 1.2 mmol) was added and the reaction mixture was allowed to stir at room temperature. After 17 hours the reaction mixture was concentrated under reduced pressure to provide a golden-brown solid, which was dried in a vacuum oven (house vacuum, ~60 °C) for 20 hours to provide **Int-60b** as a golden brown solid (99 mg, quantitative yield).

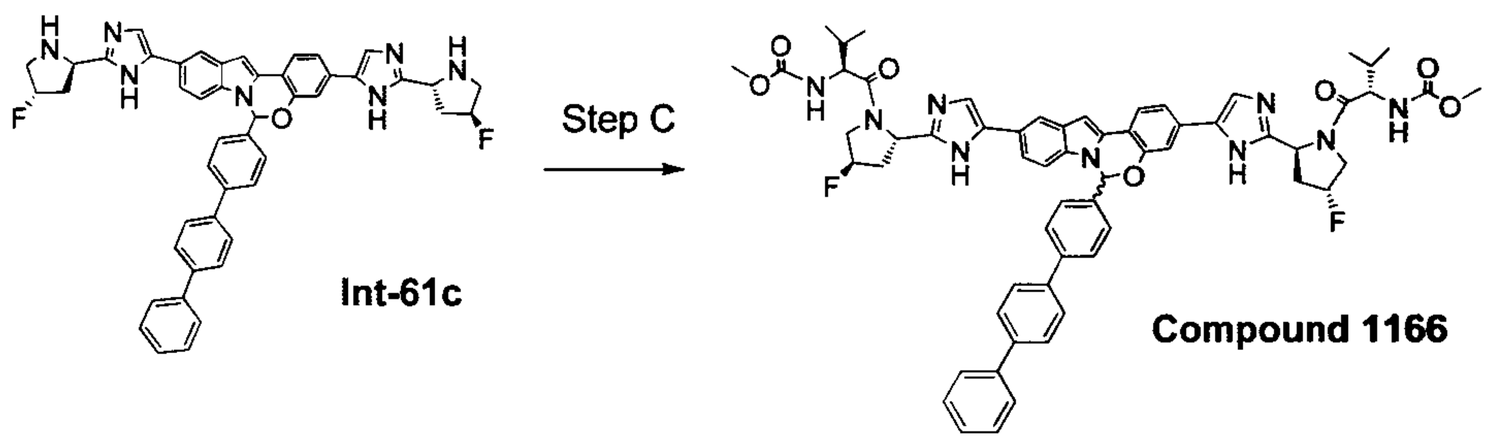
Step C

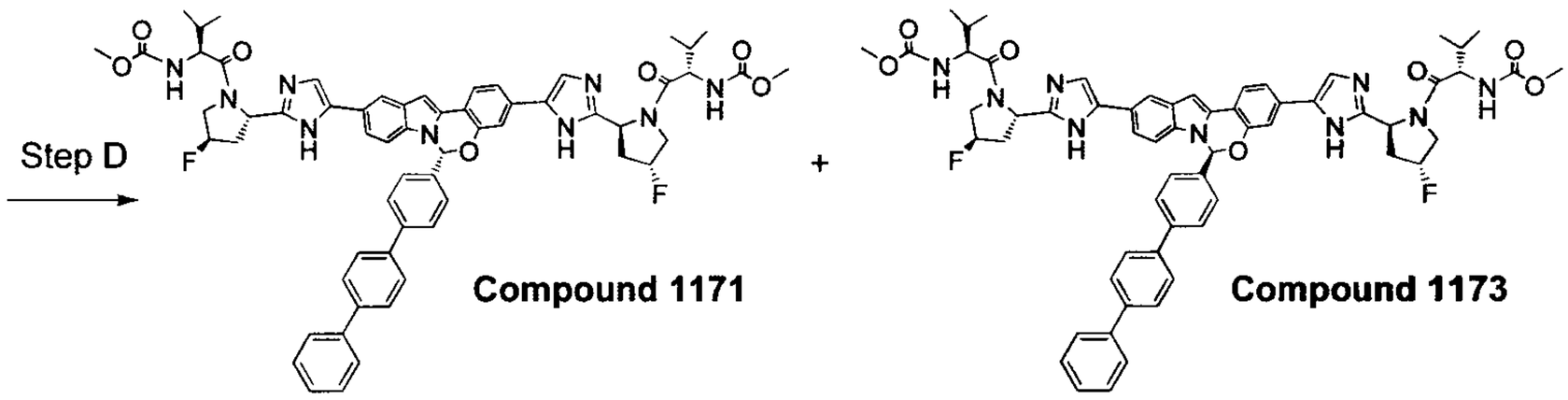
To a 50-mL flask equipped with a stir bar was added **Int-60b** (39 mg, 0.047 mmol) and **Int-1a** (17 mg, 0.094 mmol) , and dry DMF (472 µL). Diisopropylethylamine (41 µL, 31 mg, 0.236 mmol) was added and the reaction mixture was cooled to 0 °C in an ice-water bath. After ~15 minutes, solid HATU (40 mg, 0.104 mmol) was added and the reaction mixture stirred at 0 °C, After 2 hours the reaction was quenched by addition of water (20 mL), whereupon a beige solid precipitated. The solid was collected by vacuum filtration and washed further with water (~50 mL). The solid was dissolved in EtOAc (~100 mL) and the resulting solution was washed with brine (~25 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a beige crude product. Further purification by reverse phase C18 chromatography (Gilson®, Phenomenex® Gemini C18 5 µm 150 x 21.20 mm column, Eluent:10-70% MeCN/water + 0.1% TFA over 20 minutes @ 20 mL/min} afford Compound **1005** as a beige solid (28.4 mg, 63% yield).

EXAMPLE 61

Preparation of Compounds **1166, 1171 & 1173**





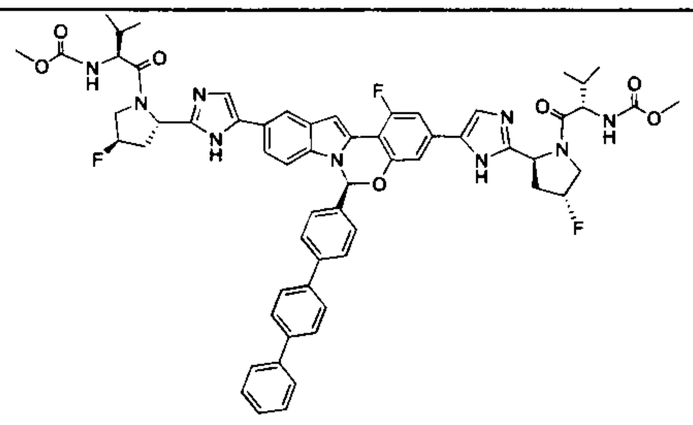


Step A

Compound **Int-61a** (150 mg, 0.179 mmol, prepared by a similar route as in example 59), biphenyl-4-ylboronic acid (35.4 mg, 0.179 mmol), $Pd_2(dba)_3$ (18.5 mg, 0.018 mmol), and dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (17 mg, 0.036 mmol) were added into a 40 mL flask. The flask was put *in vacuo* and filled with N_2. This process was repeated once. Dioxane (1.8 mL) and K_2CO_3 (1M, 0.9 mL, 0.9 mmol) were added, and the sealed flask was allowed to stir at 110 °C. After 3 hours the reaction was cooled, the aqueous layer was separated and extracted with 3 mL EtOAc. The organic layers were combined and dried over anhydrous Na_2SO_4, filtered and concentrated to provide crude product. Further purification by Silica-gel chromatography (Eluent: EtOAC (10% MeOH) in CH_2Cl_2: 0% to 80%) gave Compound **Int-61a** (137 mg, 80%).

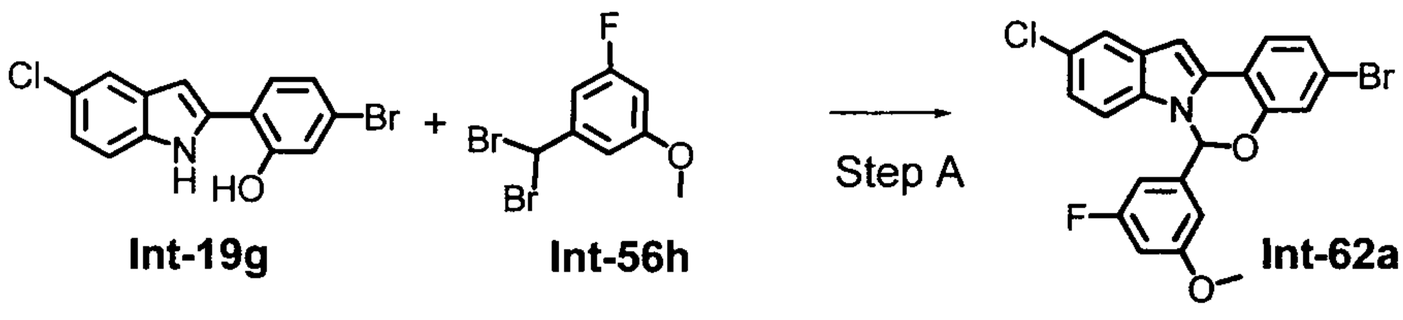
Steps B to **D** were carried out using the methods described in Example 50.

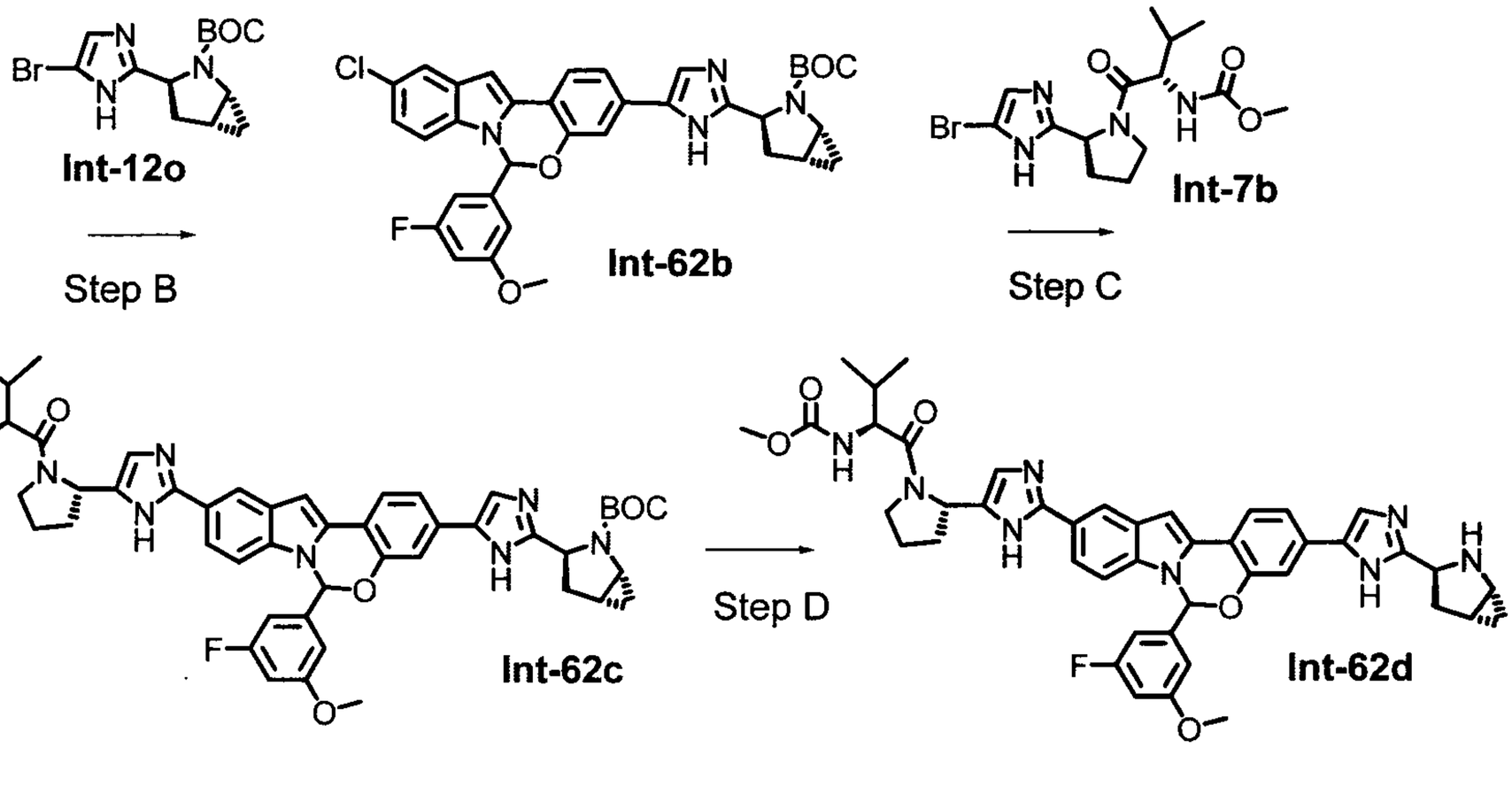
The following compound was made using the method described in the Example above:

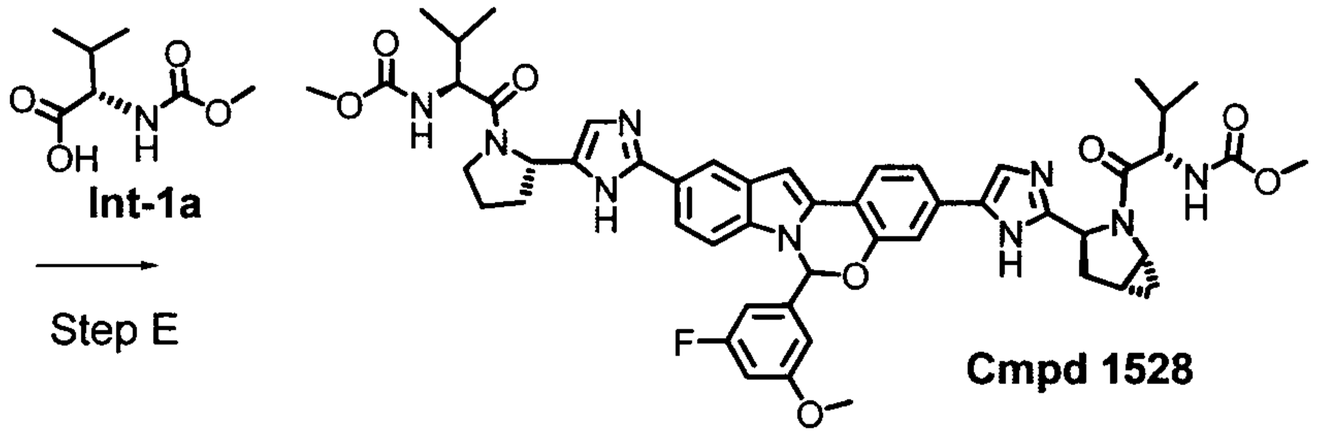
1172		single isomer

EXAMPLE 62

Preparation of Compound **1528**







Step A

To a 250 mL flask were added **Int-19g** (5.0 g, 15.5 mmol), dibromide **Int-56h** (5.8 g, 80% purity, 15.5 mmol), cesium carbonate (25.3 g, 77 mmol), and acetonitrile (50 ml) and the resulting suspension was allowed to stir at 60 °C for about 15 hours. Ethyl acetate (200 ml) was then added, and the organic layer was washed with water (2x150 ml), dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified on a 120 g silica column/ Combi-Flash Rf system(Eluent: 0-10% ethyl acetate in hexanes) to provide **Int-62a** as a white solid (3.7 g, 52%).

Step B

Intermediate **Int-62a** (500 mg, 1.09 mmol), bis(pinacolato)diboron (304 mg, 1.2 mmol), potassium acetate (535 mg, 5.45 mmol), $PdCl_2$(dppf)-CH_2Cl_2 (89 mg, 0.109 mmol), and dioxane (8 ml) were added to a 35 mL microwave reaction tube. The sealed mixture was degassed and stirred at 95 °C under nitrogen atmosphere for 4 hours and then cooled to room temperature. To this mixture were added bromide **Int-12o** (429 mg, 1.31 mmol), $PdCl_2$(dppf)-CH_2Cl_2 (89 mg, 0.109 mmol), 1.5 M aqueous solution of sodium carbonate (3.6 ml, 5.4 mmol). The resulting mixture was degassed and stirred at 95 °C under nitrogen atmosphere for 6 hours, cooled to room temperature, concentrated, to provide crude product. Further purification was accomplished on by a 40 g pre-packed silica gel column/ Combi-Flash Rf system (Eluent: 0-90% ethyl acetate in hexanes) to provide **Int-62b** as a wax (530 mg, 78%).

Step C

Int-62b (130 mg, 0.207 mmol), bis(pinacolato)diboron (58 mg, 0.23 mmol), potassium acetate (102 mg, 1.04 mmol), $Pd_2(dba)_3$-$CHCl_3$ (21.5 mg, 0.02 mmol), X-PHOS (19.8 mg, 0.04 mmol), and dioxane (2 ml) were added to a 35 mL microwave reaction tube. The sealed mixture was degassed and stirred at 110 °C under nitrogen atmosphere for 8 hours then cooled to room temperature. To this mixture were added bromide **Int-7b** (78 mg, 0.21 mmol), $PdCl_2$(dppf)-CH_2Cl_2 (14.2 mg, 0.02 mmol), 1.5 M aqueous solution of sodium carbonate (0.6 ml, 0.9 mmol). The resulting mixture was degassed and stirred at 95 °C under nitrogen atmosphere for 6 hours, cooled to room temperature, concentrated to provide crude product. Further purification on a 4 g silica gel pre-packed column/ Combi-Flash Rf system (Eluent: 0-100% ethyl acetate in hexanes) provided **Int-62c** as a solid (105 mg, 68%).

Step D

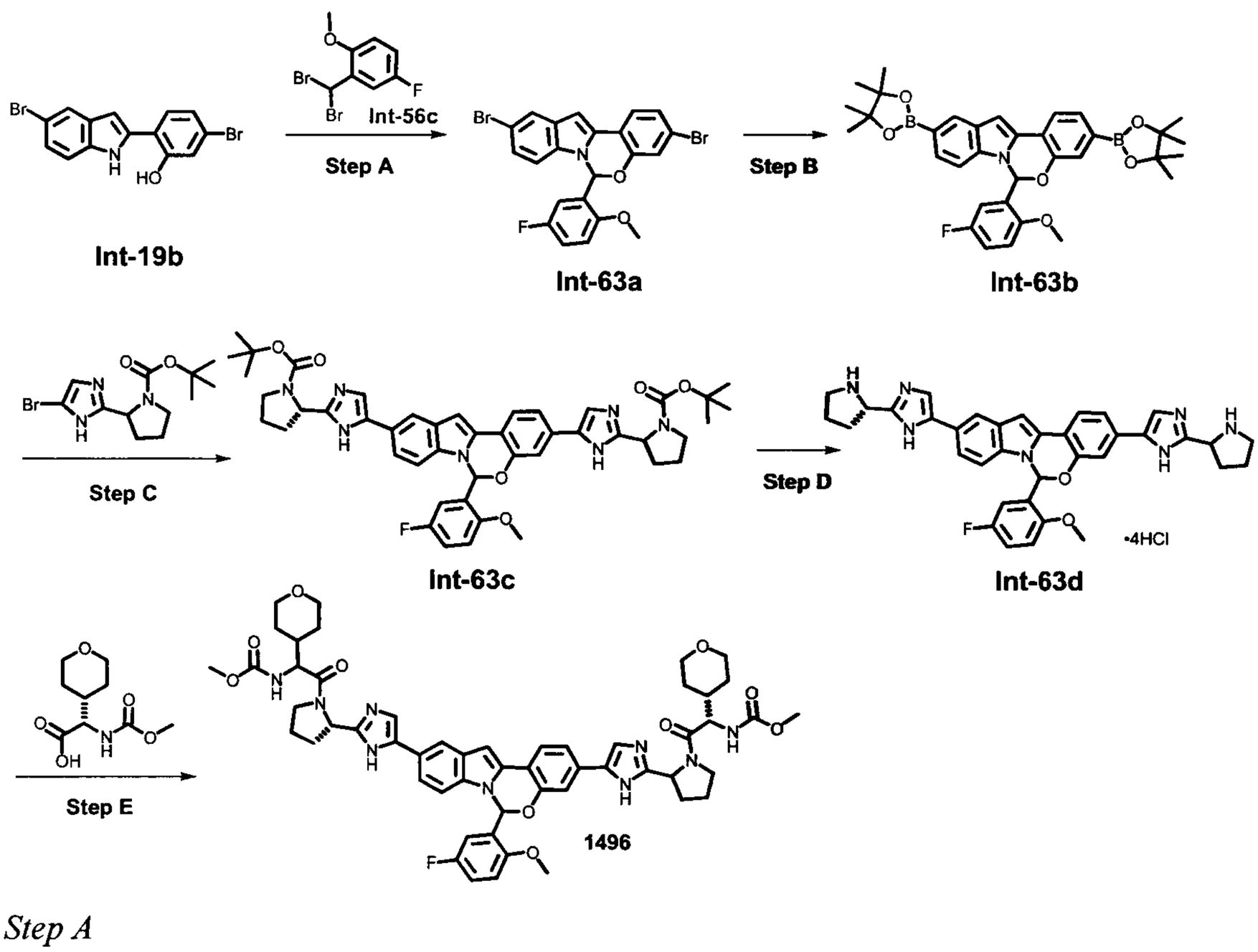
Int-62c (98 mg, 0.11 mmol), TFA (1 ml) and dichloromethane (1 ml) were added to a 25 mL flask. The resulting solution was allowed to stir at room temperature for 4 hours and concentrated *in vacuo*. The residue was dissolved in methanol (2 ml), treated with 0.1 mL of 4.0 M HCl (0.4 mmol) solution in dioxane and concentrated again *in vacuo* to provide **Int-62d** as a solid (99 mg, 100%).

Step E

Int-62d (30 mg, 0.034 mmol), acid **Int-1a** (6.5 mg, 0.04 mmol), and DMF (1 ml) were added to a 25 mL flask and the resulting solution was cooled to 0 °C. To this cooled solution was added HATU (13 mg, 0.034 mmol) and the reaction was allowed to stir at 0 °C, After 1h , water (3 drops) was added and the reaction directly purified using reverse phase chromatography (10-80% acetonitrile in water with 0.1% TFA eluent) to provide Compound **1528** as a white solid (5 mg, 13%). LC/MS anal. calcd. for: $C_{51}H_{56}FN_9O_8$ 941.4; Found: 942.5 $(M+H)^+$.

EXAMPLE 63

Preparation of Compound **1496**



Step A

Into a 250-mL round-bottom flask **equipped** with a stir bar , dibromoindole **Int-19b** (4.41 g, 12.02 mmol), **Int-56c** (**4.47** g, 14.4 mmol) were added

and dissolved in dry DMSO (50 mL). Solid cesium carbonate (20 g, 61 mmol) was added. The reaction mixture was allowed to stir at 100 °C for 14 hours. Water (~150 mL) was added to the reaction mixture, whereupon a beige solid precipitated. The suspension was extracted with EtOAc (3 x 250 mL). Combined extracts were washed with brine (~250 mL). The organic layer was dried over anhydrous MgSO4, filtered, and concentrated under reduced pressure to provide the crude product as a light orange-brown solid. The crude product was adsorbed onto silica gel (10.0 g), and then further purified using flash silica gel chromatography (Isco®; 330 g RediSep® Gold silica gel column; Eluent: 0-10% EtOAc/hexanes gradient) to provide **Int-63a** as a light brown solid (2.77 g, 46% yield).

Step B

A 125-mL round-bottom flask equipped with a stir bar was charged with **Int-63a** (1.46 g, 2.90 mmol), bis(pinacolato)diboron (1.55 g, 6.09 mmol), $(dppf)PdCl_2 \cdot CH_2Cl_2$ (106 mg, 0.145 mmol) and KOAc (854 mg, 8.71 mmol). The reaction was sealed and alternately evacuated and refilled with nitrogen (5x). Dry dioxane (19 mL) was added and the flask was immersed in a preheated 90 °C oil bath. After 1 hour the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL), filtered through a polyethylene frit and washed with brine (~50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to provide the crude product as a dark-brown semi-solid. The crude product was purified using flash silica gel chromatography (Isco®; 220 g RediSep® Gold silica gel column; Eluent: 0-30% EtOAc/hexanes gradient) to provide **Int-63b** (1.09 g, 63% yield).

Step C

A 125-mL round-bottom flask equipped with a stir bar was charged with **Int-63b** (707 mg, 1.184 mmol), bromoimidazole **Int-7d** (786 mg, 2.49 mmol), $(dppf)PdCl_2 \cdot CH_2Cl_2$ (87 mg, 0.118 mmol). The flask was alternately evacuated and refilled with nitrogen (5x). Dioxane (12 mL) was added and the reaction mixture was allowed to stir at room temperature for 5 minutes. Aqueous potassium carbonate solution (6 mL, 1 M aqueous, 6 mmol) was then added. The reaction mixture was allowed to stir

at 90 °C for 2.5 hours, cooled to room temperature and was diluted with EtOAc (~50 mL). The resulting solution was poured into a separatory funnel containing EtOAc (~50 mL) and water (~50 mL). The organic layer was washed with brine (~50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product as an orange-brown solid. The crude product was further purified using flash silica gel chromatography (Isco®; 120 g RediSep® Gold silica gel column; Eluent : 0-100% {10% MeOH/EtOAc}—hexanes gradient) to provide **Int-63c** a light brown solid (644 mg, 67% yield).

Step D

In a 50-mL round-bottom flask, **Int-63c** (633 mg, 0.776 mmol) was dissolved in methanol (8.0 mL) and hydrogen chloride solution (2.0 mL, 4 M in dioxane, (2.4 g, 8 mmol) was added. The reaction mixture was allowed to stir at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure to provide **Int-63d** as a beige solid (572 mg, 97% yield).

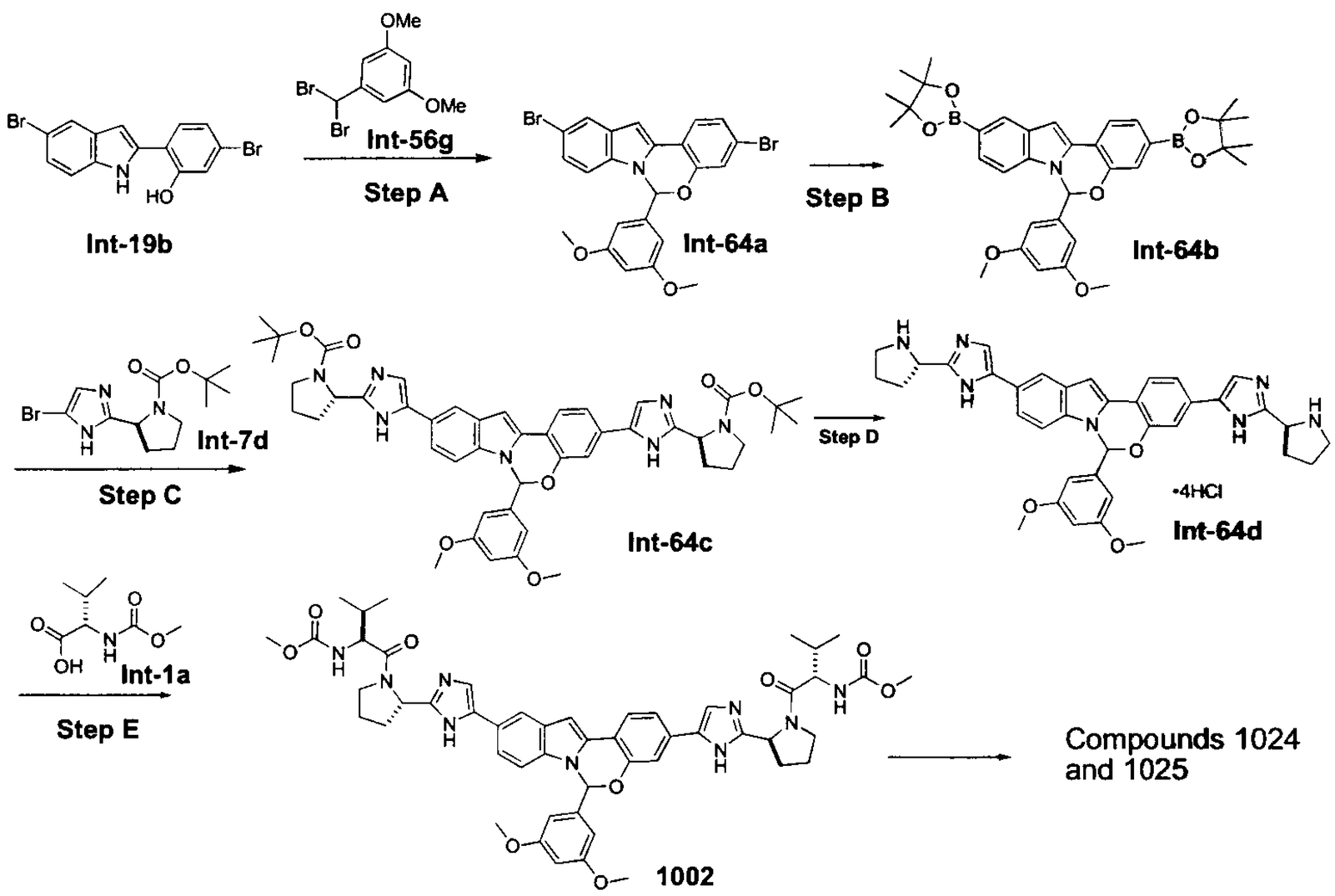
Step E

Int-4f (57 mg, 0.263 mmol) was dissolved in dry DMF (1.3 mL). The resulting solution was added to a 50-mL round-bottom flask containing solid **Int-63d** (100 mg, 0.131 mmol). *N,N*-Diisopropylethylamine (140 µL, 104 mg, 0.802 mmol) was added and the mixture agitated by sonication until no more solid adhered to the walls of the flask. The reaction mixture was allowed to stir at 0 °C (ice-water bath) for ~15 minutes. Solid HATU (110 mg, 0.289 mmol) was added and the reaction mixture was allowed to stir at 0 °C. After 1.5 hours the reaction was diluted with methanol (1 mL), and water (~0.1 mL) and solid potassium carbonate (36 mg, 0.263 mmol) were added sequentially. After 24 hours the reaction mixture was partitioned between EtOAc (~100 mL) and brine (~25 mL). The aqueous layer was extracted with a second portion of EtOAc (~25 mL). The combined extracts were washed with brine (~25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide crude product as a light brown solid.. The crude product was purified directly by reverse-phase chromatography (Gilson®; Phenomenex Gemini 150 x 21.20 mm x 5 µm column; Eluent:

0-70% MeCN/water (+0.1% TFA) gradient over 15 minutes) to provide the targeted product Compound **1496** as a white solid (84 mg, 63% yield).

EXAMPLE 64

Preparation of Compounds **1002, 1024, & 1025**



Step A

A 250-mL round-bottom flask was charged with **Int-19b** (3 g, 8.2 mmol) and DMSO (35 mL). The 1,1-dibromide **Int-56g** (2.5 g, 8.1 mmol) and cesium carbonate (8.0 g, 25 mmol) were added and the mixture was heated with stirring at 90 °C for 18 hours. The reaction mixture was poured into water (~300 mL) and extracted with EtOAc (3 x 250 mL). Combined extracts were washed with brine (~250 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product as a brown oil. The crude product was adsorbed onto 8.5 g silica gel and further purified using flash silica gel chromatography (Isco®; 300 g RediSep® Gold silica gel column; Eluent: 0-50% EtOAc/hexanes gradient) to provide **Int-64a** (751 mg, 18% yield).

Step B

In a 20-mL Biotage® microwave tube, **Int-64a** (276 mg, 0.535 mmol), bis(pinacolato)diboron (220 mg, 0.866 mmol), (dppf)$PdCl_2$•CH_2Cl_2 (34 mg, 0.042 mmol) and KOAc (122 mg, 1.24 mmol) were added. The tube was sealed and alternately evacuated and refilled with nitrogen (5x). Dry dioxane (3.5 mL) was added and the reaction mixture was allowed to stir until homogeneity was achieved (< 1 minutes). The tube was immersed in a preheated 90 °C oil bath and stirred for 45 minutes.
The reaction mixture was cooled, diluted with EtOAc (~10 mL) and filtered through a Celite® pad with washing (EtOAc). The combined filtrates were washed with brine (~25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product as an orange-brown solid. Further purification by flash silica gel chromatography (Isco®; 40 g RediSep® Gold silica gel column; Eluent: 0-30% EtOAc/hexanes gradient) to provide **Int-64b** as an off-white solid (127 mg, 39% yield).

Step C

In a 20-mL Biotage® microwave tube, **Int-64b** (122 mg, 0.200 mmol), bromoimidazole **Int-7d** (133 mg, 0.420 mmol), and (dppf)$PdCl_2$•CH_2Cl_2 (16 mg, 0.020 mmol) were mixed. The tube was sealed and alternately evacuated and back-filled with nitrogen (5x). Dioxane (2 mL) and potassium carbonate (0.60 mL, 1 M aqueous; 0.60 mmol) were added and the reaction immersed in a preheated 90 °C oil bath. After 17 hours the reaction mixture was allowed to cool, diluted with EtOAc (~100 mL) and was washed with brine (~50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide a light brown solid. The crude product was purified using flash silica gel chromatography (Isco®; 24 g RediSep Gold silica gel column; Eluent: 0-60% MeOH/CH_2Cl_2 gradient) to provide **Int-64c** as a beige solid (111 mg, 67% yield).

Step D

In a 50-mL round-bottom flask, **Int-64d** (101 mg, 0.122 mmol) was dissolved in methanol (2.0 mL) and HCl solution (300 μL, 4 M in dioxane, 1.2 mmol) was added. The pale yellow solution was allowed to stir at room temperature for 23

hours, then concentrated under reduced pressure to provide **Intermediate 900D** (100 mg, ~100% yield) as a pale yellow powder..

Step E

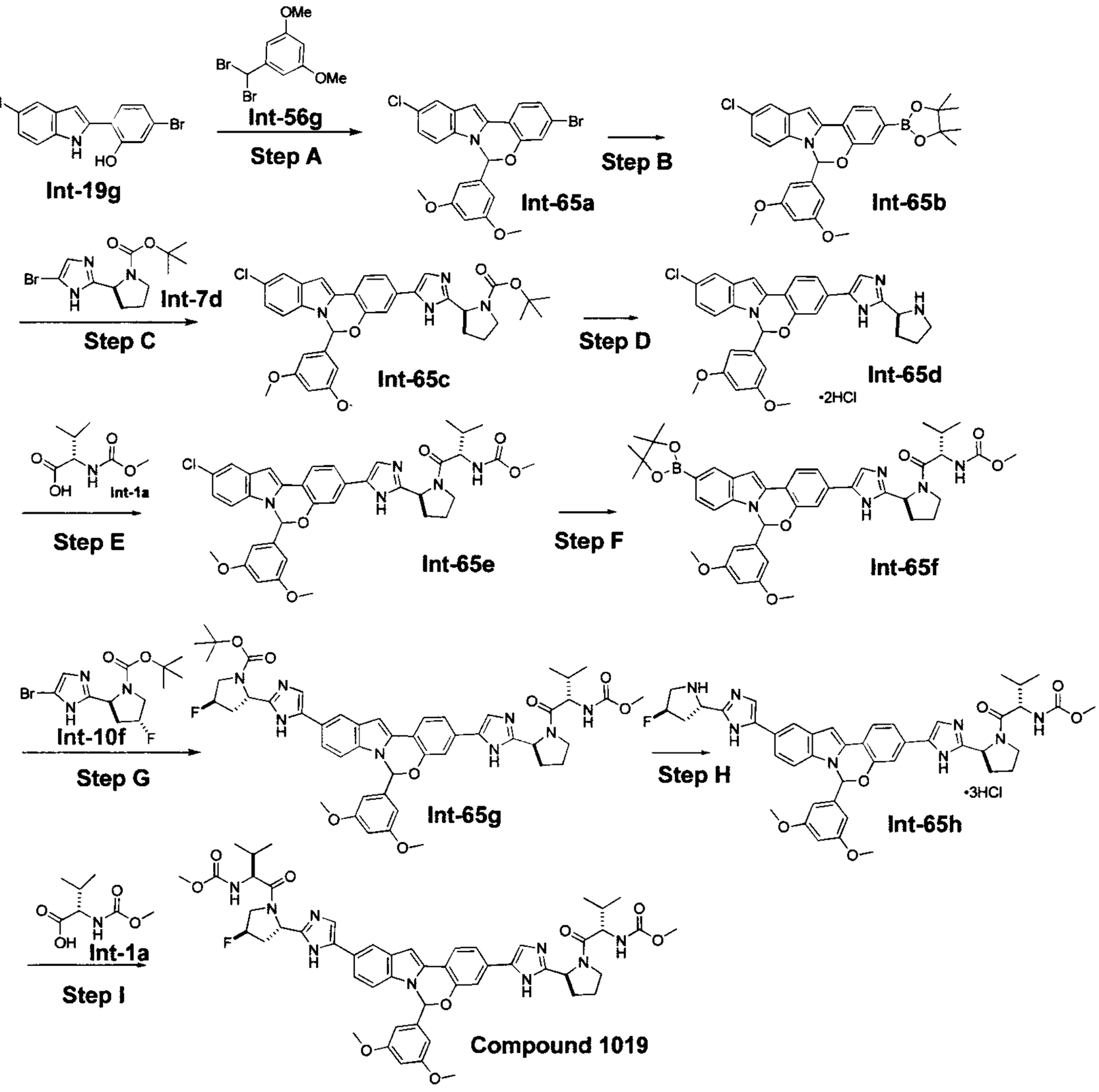
A 50-mL flask was charged with **Int-64d** (55 mg, 0.072 mmol) and **Int-1a** (25 mg, 0.143 mmol) and dissolved in dry DMF (716 µL). Diisopropylethylamine (61 µL, 46 mg, 0.358 mmol) was added and the reaction mixture was cooled to 0 °C in an ice-water bath. After ~15 minutes, solid HATU (57 mg, 0.150 mmol) was added . After 3 hours at 0 °C the reaction was quenched by addition of water (20 mL), whereupon a beige solid precipitated. The solid was collected by vacuum filtration and washed again with water (~50 mL). The solid was dissolved in EtOAc (~100 mL) and the resulting solution was washed with brine (~25 mL). The organic layer was collected, dried over MgSO4, filtered, and concentrated under reduced pressure to provide the crude product. Further purification by reverse phase C18 chromatography (Gilson®, Phenomenex Gemini C18 5 µm 150 x 21.20 mm column, Eluent: 10-70% MeCN/water + 0.1% TFA) provided Compound **1002** as a beige solid (26 mg, 39% yield).

Step F: Isomer separation by HPLC.

Compound **1002** (48.8 mg) was dissolved in abs. EtOH (1.0 mL) and the solution was filtered through a Whatman Puradisc 13 mm syringe filter. The sample was injected onto a Phenomenex Lux Cellulose-2 (5 µm, 150 x 21.20 mm) semi-preparative column; detection wavelength = 350 nm. Elution with 50% EtOH/hexane @ 10 mL/min provided the first peak (eluted between t = 0.5 minutes and t = 35 minutes) which was collected and concentrated to provide Compound **1024** (15 mg) as an off-white solid. The eluent solvent polarity was increased to 60% EtOH/hexane at t = 120 minutes while maintaining a flow rate of 10 mL. The second component, (between t = 125 minutes and t = 185 minutes), was collected and concentrated to provide Compound **1025** (15 mg) as an off-white solid.

EXAMPLE 65

Preparation of Compound **1019**



Step A

In a 250-mL round-bottom flask, the 2-(hydroxyphenyl)indole **Int-19g** (3.03 g, 9.4 mmol) and gem-dibromide **Int-56g** (8.7 g, 28 mmol) were mixed and dissolved in dry DMSO (94 mL). Solid cesium carbonate (21 g, 66 mmol) and a magnetic stir bar were added. The reaction mixture was allowed to stir at 100 °C for 21 hours. Water (~500 mL) was added to the reaction mixture, whereupon a beige solid precipitated. The suspension was extracted with EtOAc (3 x 250 mL) and the combined extracts were washed with brine (~250 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product as

a dark orange-brown solid. The crude product was adsorbed onto silica gel (10 g), and then purified using flash silica gel chromatography (Isco®; 120 g RediSep® Gold silica gel column; Eluent 0-50% EtOAc/hexanes gradient) to provide **Int-65a** as a light brown solid (1.80 g, 41% yield).

Step B

In a 125-mL round-bottom flask, **Int-65a** (2.644 g, 6.18 mmol), bis(pinacolato)diboron (1.57 g, 6.18 mmol), (dppf)$PdCl_2$•CH_2Cl_2 (138 mg, 0.168 mmol) and KOAc (1.65 g, 16.85 mmol) were mixed. The reaction was alternately evacuated and refilled with nitrogen (5x) followed by dry dioxane (38 mL). The flask was immersed in a preheated 90 °C oil bath and the reaction mixture, was allowed to stir at 90 °C for 2 hours. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (~300 mL) and washed with brine (~200 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to provide a dark yellow solid, which was purified using flash silica gel chromatography (Isco®; 120 g RediSep® Gold silica gel column; Eluent: 0-50% EtOAc/hexanes gradient) to provide **Int-65b** as yellow solid (1.99 g, 68% yield).

Step C

In a 125-mL round-bottom flask, the boronate **Int-65b** (1.14 g, 2.21 mmol), bromoimidazole **Int-7d** (750 mg, 2.37 mmol), (dppf)$PdCl_2$•CH_2Cl_2 (90 mg, 0.110 mmol) were mixed. The flask was alternately evacuated and refilled with nitrogen (5x) and dry dioxane (15 mL) was added. The reaction mixture was allowed to stir at room temperature for 5 minutes and then aqueous potassium carbonate solution (11 mL, 1 M aqueous, 11 mmol) was added. The flask was immersed into a preheated 90 °C oil bath and stirred at 90 °C for 3 hours. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (~100 mL) and the resulting solution was filtered and washed with brine (~50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated ration under reduced pressure to provide an orange-brown solid. The crude product was purified using flash silica gel chromatography (Isco®; 220 g

RediSep® Gold silica gel column; Eluent: 0-100% EtOAc/hexanes) to provide **Int-65c** as a golden yellow solid (1.06 g, 76% yield).

Step D

In a 150-mL round-bottom flask, substrate **Int-65c** (754 mg, 1.202 mmol) was dissolved in methanol (12 mL) and HCl solution (3 mL, 4 M in dioxane, 12 mmol) was added. The clear, pale yellow solution was allowed to stir at room temperature for 18 hours. The reaction mixture was concentrated by rotary evaporation under reduced pressure to provide **Intermediate Int-65d** as a pale yellow solid (728 mg, quantitative yield).

Step E

In a 50-mL round-bottom flask, **Int-65d** (719 mg, 1.20 mmol) and **Int-1a** (231 mg, 1.318 mmol) were dissolved in dry DMF (12 mL). Diisopropylethylamine (1.0 mL, 774 mg, 5.99 mmol) was added and the he reaction mixture cooled to 0 °C (ice-water bath). After 15 minutes., solid HATU (684 mg, 1.80 mmol) was added in one portion. The reaction mixture was allowed to stir at 0 °C for 1 hour. Water (~20 mL) was added and the precipitated solid was collected by vacuum filtration. The collected solid was washed with water (~5 mL) and air-dried. The crude product was subsequently purified using flash silica gel chromatography (Isco®; 40 g RediSep® Gold silica gel column; Eluent: 0-10% MeOH/CH_2Cl_2 gradient). All product-containing fractions were collected, concentrated, and re-purified using flash silica gel chromatography (Isco®; 80 g RediSep® Gold silica gel column; Eluent: 0-3.5% MeOH/CH_2Cl_2 gradient) to provide **Int-65e** (286 mg, 35% yield).

Step F

In a 50-mL round-bottom flask, **Int-65e** (285 mg, 0.417 mmol), bis(pinacolato)diboron (127 mg, 0.500 mmol), $Pd_2(dba)_3$•$CHCl_3$ (43 mg, 0.042 mmol), X-Phos (40 mg, 0.083 mmol) and KOAc (123 mg, 1.25 mmol) were mixed. The flask was alternately evacuated and refilled with nitrogen (5x). Dioxane (3 mL) was added and the reaction was allowed to stir at 120 °C for 1.5 hours. The reaction mixture was

allowed to cool slowly to room temperature for 12 hours. The reaction mixture was diluted with EtOAc (~100 mL) and washed with brine (~50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide an orange solid as crude product. The crude product was purified using flash silica gel chromatography (Isco®; 40 g RediSep® Gold silica gel column; Eluent: 0-9% MeOH/CH_2Cl_2 gradient) to provide **Int-65f** as an orange-yellow foamy solid (253 mg, 78% yield).

Step G

In a 5-mL Biotage® microwave tube, **Int-65f** (123 mg, 0.159 mmol), bromoimidazole **Int-10f** (64 mg, 0.190 mmol), (dppf)$PdCl_2$•CH_2Cl_2 (13 mg, 0.016 mmol) were mixed. The tube was alternately evacuated and refilled with nitrogen (5x), dry dioxane (1.5 mL) was added and the reaction mixture stirred at room temperature for 5 minutes. Aqueous potassium carbonate solution (0.800 mL, 1 M aqueous, 0.8 mmol) was then added. The tube was immersed into a preheated 90 °C oil bath and the reaction was allowed to stir for 16 hours. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (~50 mL), and filtered through a polyethylene filter frit. The filtrate was washed with brine (~25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide a light brown solid. The crude product was purified using flash silica gel chromatography (Isco®; 24 g RediSep® Gold silica gel column; Eluent: 0-9% MeOH/CH_2Cl_2 gradient) to provide **Int-65g** as a beige solid (92 mg, 64% yield).

Step H:

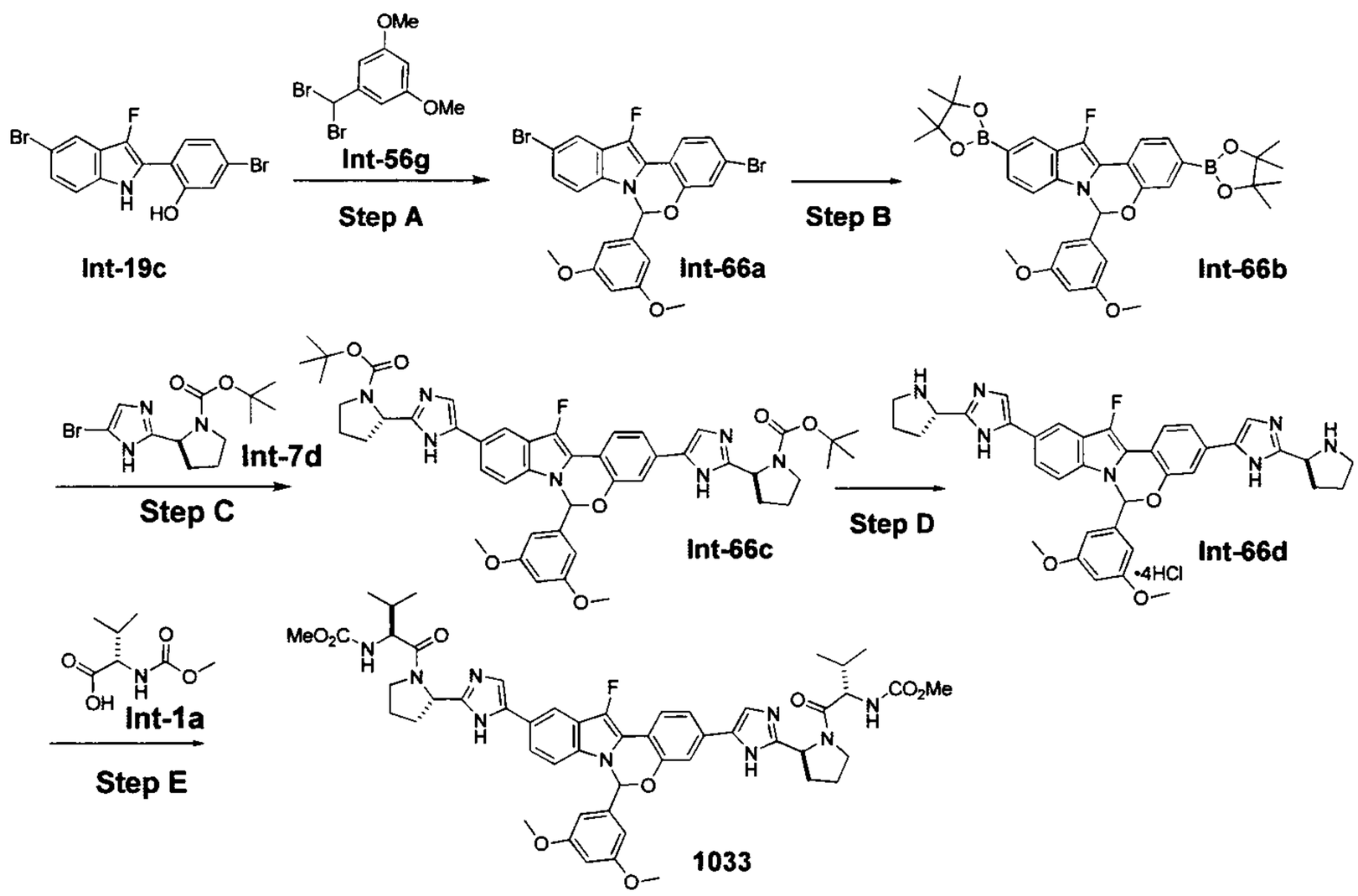
In a 50-mL round-bottom flask, the **Int-65g** (73 mg, 0.081 mmol) was dissolved in methanol (0.8 mL) and hydrogen chloride solution (200 µL, 4 M in dioxane, (240 mg, 0.800 mmol) was added. The reaction mixture was allowed to stir at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure to provide **Int-65h** as a beige solid (77 mg, quantitative yield).

Step I:

In a 50-mL round-bottom flask, **Int-65h** (73 mg, 0.080 mmol) and **Int-1a** (17 mg, 0.096 mmol) were mixed and dry DMF (1 mL) was added. Diisopropylethylamine (70 μL, 53 mg, 0.412 mmol) was added and the reaction cooled to 0 °C (ice-water bath). After 15 minutes. solid HATU (46 mg, 0.120 mmol) was added in one portion. The reaction mixture was allowed to stir at 0 °C for 1 hour. Water (~20 mL) was added and the precipitated solid was collected by vacuum filtration. The collected solid was washed with water (~5 mL), air-dried briefly, dissolved in DMF (~1 mL) and purified using reverse-phase C18 chromatography (Gilson®, Phenomenex® Gemini C18 5 μm 150 x 21.20 mm column, Eluent: 10-70% MeCN/water + 0.1% TFA) to provide Compound **1019** (21 mg, 28% yield) as a beige solid.

EXAMPLE 66

Preparation of Compound **1033**



Step A

In a 200-mL pear-shaped flask was charged with **Int-19c** (1.64 g, 4.26 mmol), **Int-56g** (2.64 g, 8.52 mmol), DMSO (17 mL) and stirred until homogeneous.

Solid cesium carbonate (10 g, 66 mmol) was added, the flask fitted with a condenser and then immersed into a preheated 100 °C oil bath. After 18 hours the reaction mixture was poured into water (~400 mL) and Extracted with EtOAc (2 x 150 mL, 1 x 300 mL). The aqueous layer was diluted with brine (~200 mL) and was extracted with EtOAc (~150 mL). The combined organic phases were washed with brine (~100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide an orange-red semi-solid. The crude product was adsorbed onto silica gel (10.0 g) and was purified using flash silica gel chromatography (Isco®; 220 g RediSep® Gold silica gel column; Eluent: 0-40% EtOAc/hexanes gradient) to provide **Int-66a** (1.09 g, 48% yield) as a beige solid.

Step B

In a 125-mL round-bottom flask, **Int-66a** (1.03 mg, 1.93 mmol), bis(pinacolato)diboron (1.08 g, 4.25 mmol), (dppf)$PdCl_2$•CH_2Cl_2 (158 mg, 0.193 mmol) and KOAc (569 mg, 5.80 mmol) were mixed. The tube was sealed and alternately evacuated and refilled with nitrogen (5x) and dry dioxane (13 mL) was added. The flask was immersed in a preheated 90 °C oil bath and the reaction mixture was allowed to stir for 1 hour. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (100 mL), filtered and washed with brine (~50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to provide a light brown solid. The crude product was purified using flash silica gel chromatography (Isco®; 120 g RediSep® Gold silica gel column; Eluent: 0-40% EtOAc/hexanes gradient) to provide **Int-66b** as a dark beige (1.00 g, 83% yield).

Step C

A 125-mL round-bottom flask was charged with intermediate **Int-66b** (992 mg, 1.58 mmol), bromoimidazole **Int-7d** (1100 mg, 3.48 mmol), and (dppf)PdCl2 CH2Cl2 (129 mg, 0.158 mmol). The flask was sealed and alternately evacuated and refilled with nitrogen (5x). Dioxane (11 mL) was added and the reaction mixture was allowed to stir at room temperature for 5 minutes. Aqueous potassium carbonate solution (5 mL, 1 M aqueous, 5 mmol) was added and the flask immersed into

a preheated 90 °C oil bath. After 22 hours the reaction was allowed to cool to room temperature, diluted with EtOAc (~100 mL) and the resulting solution washed with brine (~50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide a light brown solid. The crude product was purified using flash silica gel chromatography (Isco®; 80 g RediSep® Gold silica gel column; Eluent: 0-6% MeOH/CH_2Cl_2 gradient) to provide **Int-66c** as an orange-yellow solid (867 mg, 65% yield).

Step D

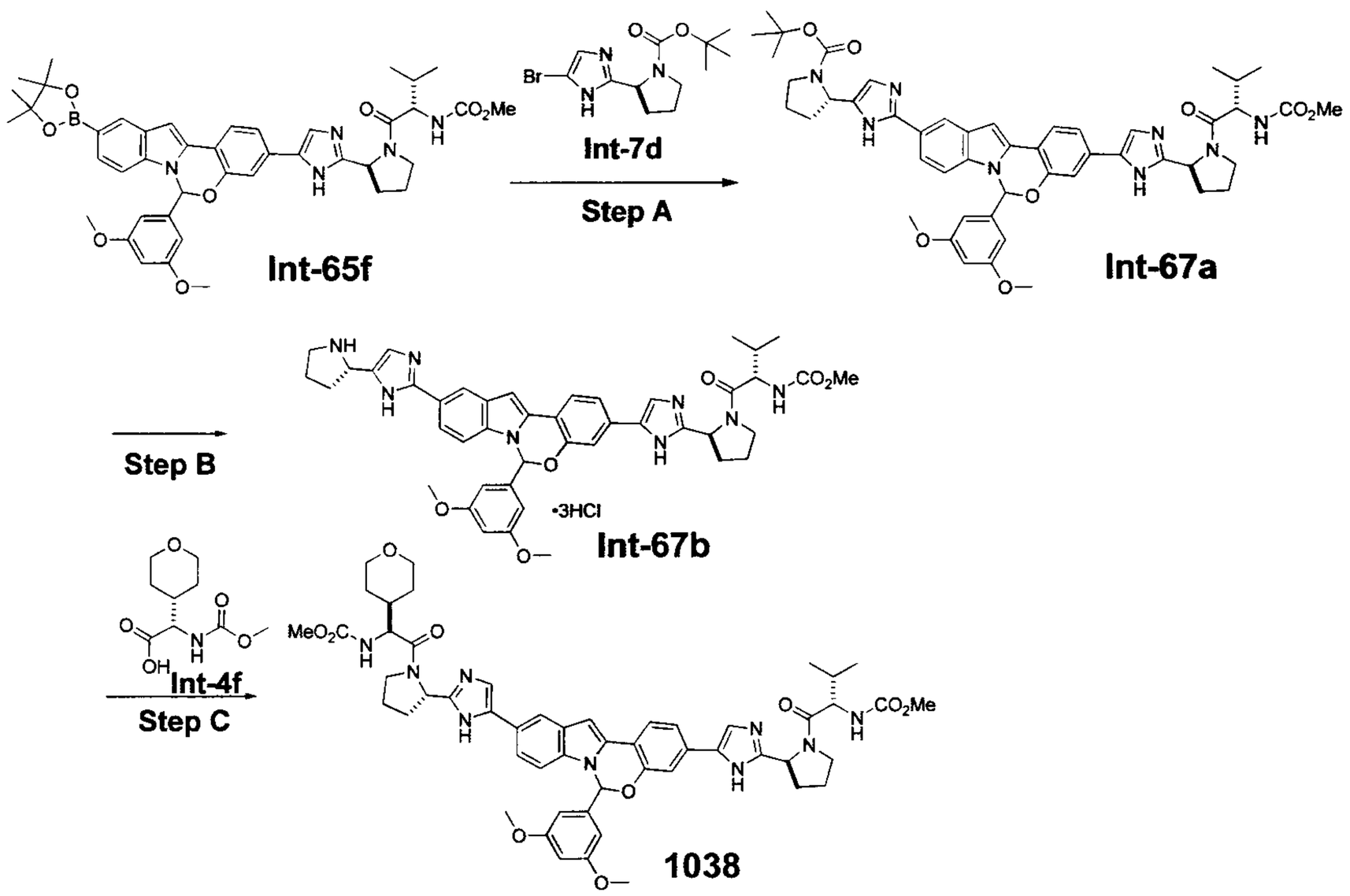
In a 100-mL round-bottom flask, **Int-66c** (690 mg, 0.816 mmol) was dissolved in methanol (8 mL) and hydrogen chloride solution (2 mL, 4 M in dioxane, (2.4 g, 8 mmol) was added. The reaction mixture was allowed to stir at room temperature for 12 hours. The reaction mixture was concentrated under reduced pressure to provide **Int-66d** as a beige solid (648 mg, quantitative yield).

Step E

In a 50-mL round-bottom flask was charged with **Int-66d** (200 mg, 0.253 mmol) and **Int-1a** (97 mg, 0.556 mmol) and dry DMF (2.5 mL). Diisopropylethylamine (265 µL, 196 mg, 1.5 mmol) was added and the reaction cooled to 0 °C (ice-water bath). After 15 minutes. solid HATU (240 mg, 0.632 mmol) was added in one portion. The reaction mixture was allowed to stir at 0 °C for 10 hours. Water (20 mL) was added to quench the reaction. The cream-colored suspension was extracted with EtOAc (2 x 50 mL) and the combined extracts were washed with brine (~25 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide a light yellow-brown solid. The crude product was purified using reverse-phase chromatography (Gilson®; Phenomenex® Gemini 150 x 21.20 mm x 5 µm column; Eluent: 10-70% MeCN/water (+0.1% TFA) gradient) to provide Compound **1033** as a beige solid (79 mg, 33% yield).

EXAMPLE 67

Preparation of Compound **1038**



Step A

In a 250-mL round-bottom flask was charged with **Int-65f** (1.51 g, 1.95 mmol), bromoimidazole **Int-7d** (739 mg, 2.34 mmol), (dppf)$PdCl_2$•CH_2Cl_2 (143 mg, 0.195 mmol). The flask was alternately evacuated and refilled with nitrogen (5x) and dry dioxane (19 mL) was added. After 5 minutes. aqueous potassium carbonate solution (10 mL, 1 M aqueous, 10 mmol) was added and the reaction immersed into a preheated 90 °C oil bath. After 10 hours, the reaction was allowed to cool to room temperature and was diluted with EtOAc (~100 mL) and water (~50 mL). The organic layer was washed with brine (~50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation under reduced pressure to provide an orange-brown solid. The crude product was purified using flash silica gel chromatography (Isco®; 220 g RediSep® Gold silica gel column; Eluent: 0-100% EtOAc/hexanes gradient) to provide **Int-67a** as a golden yellow solid (1.23 g, 71% yield).

Step B

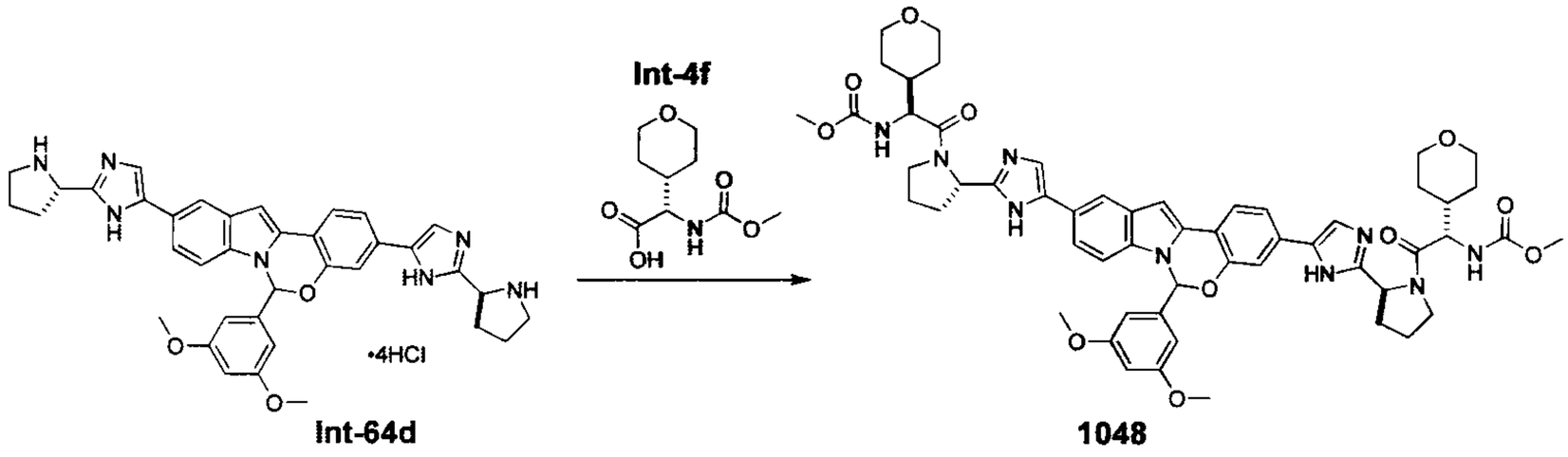
In a 50-mL round-bottom flask, **Int-67a** (1.222 g, 1.381 mmol) was dissolved in methanol (14 mL) and hydrogen chloride solution (3.5 mL, 4 M in dioxane, (4.20 g, 14 mmol) was added. The reaction mixture was allowed to stir at room temperature for 9 hours, and then concentrated under reduced pressure to provide **Int-67b** as a beige solid (1.222 g, 99% yield).

Step C

A 50-mL round-bottom flask was charged with **Int-67b** (155 mg, 0.73 mmol), **Int-4f** (45 mg, 0.208 mmol) and the solids were dissolved in a solution of diisopropylethylamine (151 µL, 112 mg, 0.867 mmol) in dry DMF (1.7 mL). The reaction mixture was cooled to 0 °C (ice-water bath) and stirred for 15 minutes. Solid HATU (99 mg, 0.260 mmol) was added in one portion. The reaction mixture was allowed to stir at 0 °C for 2 hours. Methanol (1 mL) and TFA (56 µL) were added sequentially at room temperature and the reaction mixture was allowed to stir at room temperature for an additional 2 hours. Water (20 mL) and aqueous sodium bicarbonate solution (~10 mL) were added, and the aqueous phase was extracted with EtOAc (2 x ~50 mL). The combined organic phase was washed with brine (~25 mL), dried over anhydrous MgSO4, filtered, and concentrated under reduced pressure to provide a light brown solid. The crude product was purified directly by reverse-phase chromatography (Gilson®; Phenomenex Gemini 150 x 21.20 mm x 5 µm column; Run 1: Eluent: 10-70% MeCN/water (+0.1% TFA) gradient; Run 2: 10-60% MeCN/water (+0.1% TFA) gradient) to provide Compound **1038** as a beige solid (80 mg, 47% yield).

EXAMPLE 68

Preparation of Compound **1048**

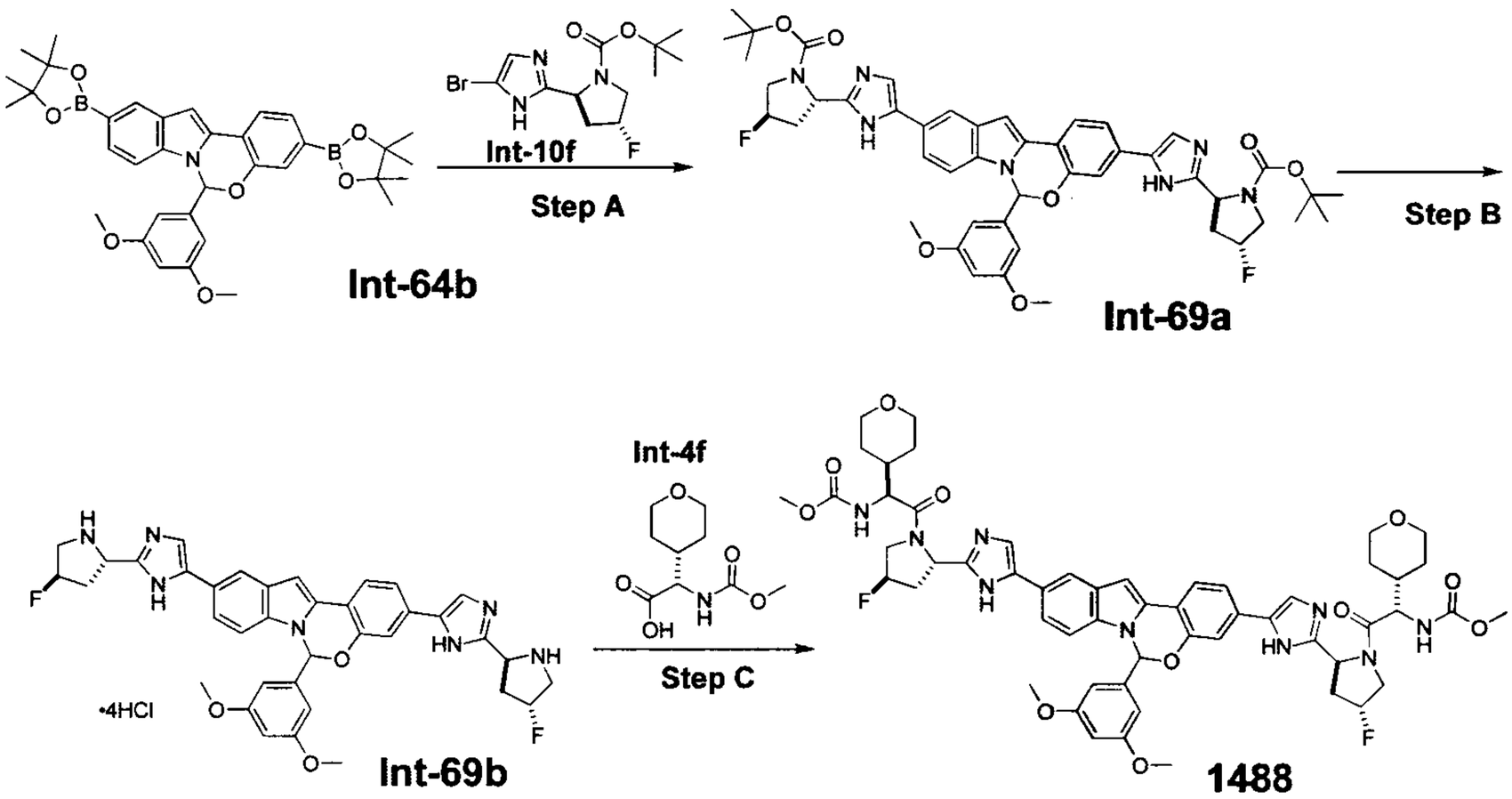


Int-64d **1048**

A 50-mL round-bottom flask was charged with **Int-64d** (167 mg, 0.216 mmol), **Int-4f** (103 mg, 0.475 mmol) and the solids were dissolved in dry DMF (2 mL). Diisopropylethylamine (226 μL, (167 mg, 1.30 mmol) was then added to the reaction at 0 °C (ice-water bath) and stirred for 15 minutes. Solid HATU (204 mg, 0.537 mmol) was then added in one portion and the reaction was allowed to stir at 0 °C for 1 hour. Methanol (1 mL) and trifluoroacetic acid (200 μL) were added and the reaction was allowed to stir at room temperature for 30 minutes. Water (20 mL) was added to quench the reaction. The reaction mixture was extracted with EtOAc (2 x 50 mL), the combined organic phase was washed with brine (~50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide a light orange-yellow solid. The crude product was purified directly by reverse-phase chromatography (Gilson®; Phenomenex Gemini 150 x 21.20 mm x 5 μm column; Eluent: 10-60% MeCN/water (+0.1% TFA)) to provide the Compound **1048** as a beige solid (135 mg, 61% yield)

EXAMPLE 69

Preparation of Compound **1488**



Step A

A 20-mL Biotage® microwave vial was charged with Int-**64b** (392 mg, 0.643 mmol), bromoimidazole **Int-10f** (451 mg, 1.35 mmol), and $(dppf)PdCl_2•CH_2Cl_2$

(47 mg, 0.064 mmol). The flask was alternately evacuated and refilled with nitrogen (5x) and dry dioxane (6.5 mL) was added and stirred vigorously. After 5 minutes aqueous potassium carbonate solution (3 mL, 1 M aqueous, 3 mmol) was added and the reaction immersed into a preheated 90 °C oil bath. After 18 hours the reaction was allowed to cool to room temperature, and diluted with EtOAc (~100 mL) and water was added. The reaction was extracted thrice with EtOAc (~50 mL), and the combined organic phase was washed with brine (~50 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide an orange-brown solid. The crude product was purified using flash silica gel chromatography (Isco®; 40 g RediSep® Gold silica gel column; Eluent: 0-100% EtOAc/hexanes gradient) to provide **Int-69a** as a golden yellow solid (409 mg, 74% yield). `

Step B

In a 50-mL round-bottom flask, the **Int-69a** (375 mg, 0.434 mmol) was dissolved in methanol (4.5 mL) and a hydrogen chloride solution (1.0 mL, 4 M in dioxane, (1.2 g, 4 mmol) was added. The reaction mixture was allowed to stir at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure to provide **Int-69b** as a beige solid (344 mg, 98% yield).

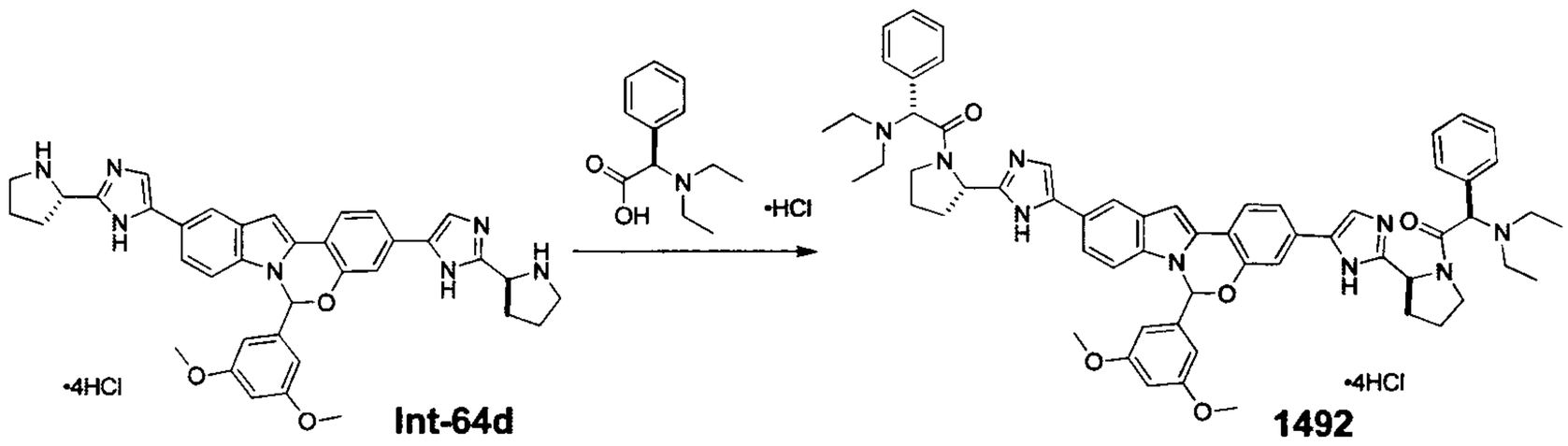
Step C

Int-4f (99 mg, 0.454 mmol) was weighed into a pre-tarred vial and transferred using DMF solvent (4 x 500 µL) to a 50-mL round-bottom flask containing **Int-69b** (167 mg, 0.206 mmol)). Diisopropylethylamine (220 µL, 163 mg, 1.26 mmol) was added by syringe. The mixture was allowed to stir at room temperature for ~1 minutes, during which time all solids dissolved. The flask was cooled in an ice-water bath for ~15 minutes and solid HATU (196 mg, 0.516 mmol) was added in one portion. After 1.5 hours at 0 °C, Methanol (1 mL) and TFA (190 µL) were added sequentially and the reaction mixture was allowed to stir for an additional 2 hours. Water (~20 mL) was added and the reaction mixture was extracted with EtOAc (2 x ~50 mL). The combined organic phases was washed with brine (~50 mL), dried over anhydrous MgSO4, filtered, and concentrated under reduced pressure to provide a light orange solid. The crude

product was purified directly by reverse-phase chromatography (Gilson®; Phenomenex Gemini 150 x 21.20 mm x 5 μm column; Eluent: 0-60% MeCN/water (+0.1% TFA) gradient over 15 minutes. Major components that eluted were Compound **1488** and a TFA adduct of same. The total yield of the final product was 146 mg, 67% yield.

EXAMPLE 70:

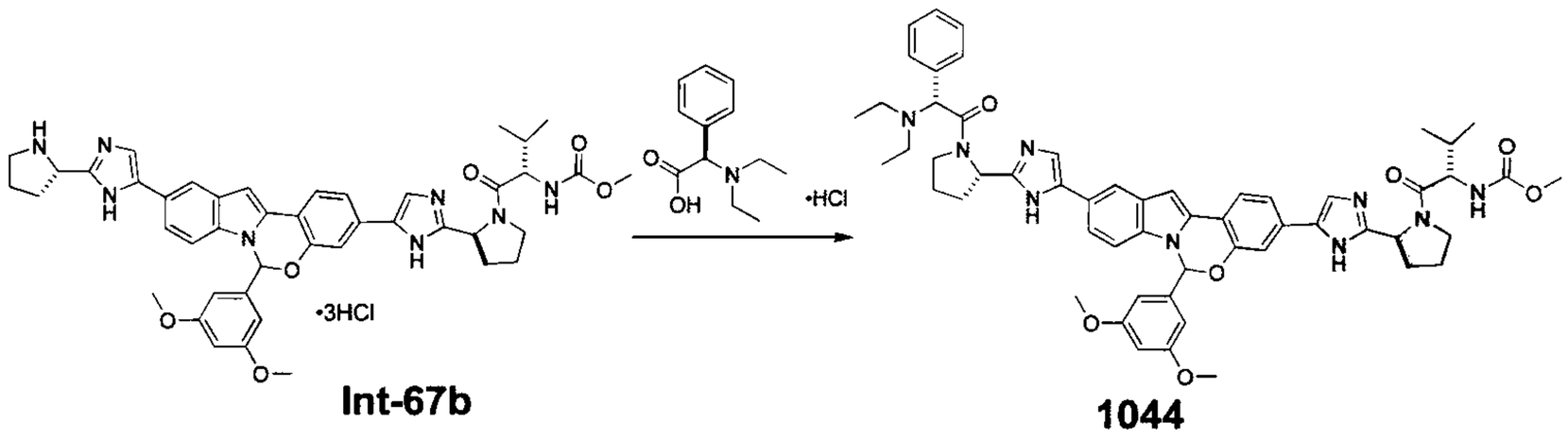
Preparation of Compound **1492**



A 50-mL round-bottom flask was charged with **Int-64d** (183 mg, 0.237 mmol) and *(R)*-*N,N*-diethylphenylglycine hydrochloride (127 mg, 0.520 mmol) and the solids were dissolved in dry DMF (2.5 mL). Diisopropylethylamine (400 μL, 296 mg, 2.29 mmol) was added, the reaction cooled to 0 °C (ice-water bath) and stirred for 15 minutes. Solid HATU (225 mg, 0.591 mmol) was added in one portion. After 1 hour methanol (1 mL) and trifluoroacetic acid (365 μL) were added and the reaction was allowed to stir at room temperature for 30 minutes. The reaction was quenched with water (20 mL) and the product was extracted into EtOAc (2 x 50 mL). The combined organic phase were washed with brine (~50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide a light orange-yellow solid. The crude product was purified directly by reverse-phase chromatography (Gilson®; Phenomenex Gemini 150 x 21.20 mm x 5 μm column; Eluent:10-60% MeCN/water (+0.1% TFA) gradient over 15 minutes) to provide fractions containing Compound **1492** and a TFA adduct of same. Retreatment of the TFA-adduct fractions with methanol as above, provided additional amounts of the desired Compound. Total yield of Compound **1492** was 201 mg, 74% yield.

EXAMPLE 71

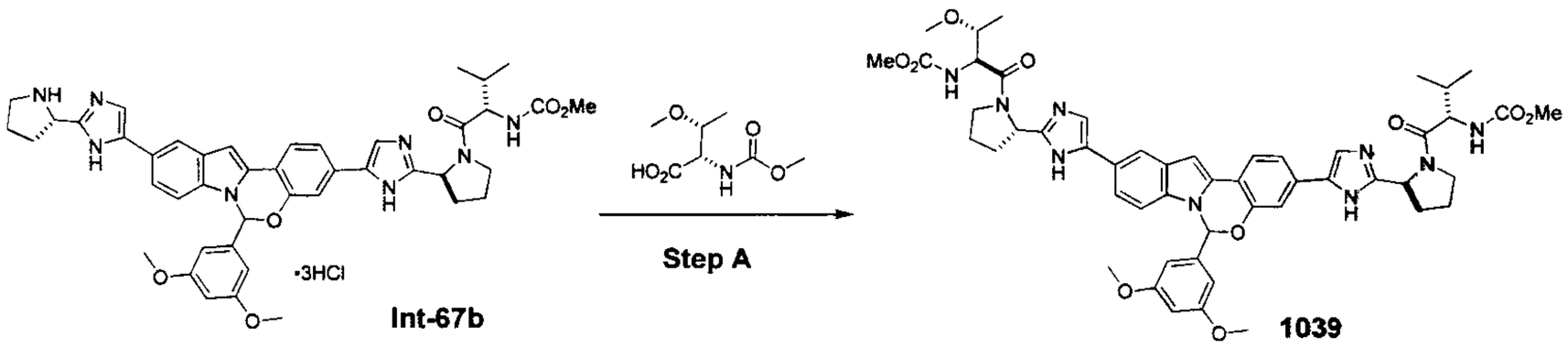
Preparation of Compound **1044**



A 50-mL round-bottom flask was charged with **Int-67b** (123 mg, 0.138 mmol) and *(R)*-*N,N*-diethylphenylglycine hydrochloride (40 mg, 0.165 mmol) and the solids were dissolved in a solution of diisopropylethylamine (240 µL, 178 mg, 1.375 mmol) in dry DMF (1.4 mL). The reaction mixture was cooled to 0 °C (ice-water bath) and stirred for 15 minutes. Solid HATU (78 mg, 0.206 mmol) was added in one portion. After 1 hour the reaction mixture was concentrated under reduced pressure to provide brown, viscous oil, which was purified using reverse-phase chromatography (**Gilson®**; Phenomenex® Gemini 150 x 21.20 mm x 5 µm C-18 column; Run 1: 450 µL injection; 10-70% MeCN/water (+0.1% TFA) gradient over 15 minutes. Run 2: 600 µL injection; 10-60% MeCN/water (+0.1% TFA) gradient over 20 minutes) to provide Compound **1044** as a beige solid (88 mg, 66% yield).

EXAMPLE 72

Preparation of Compound **1039**

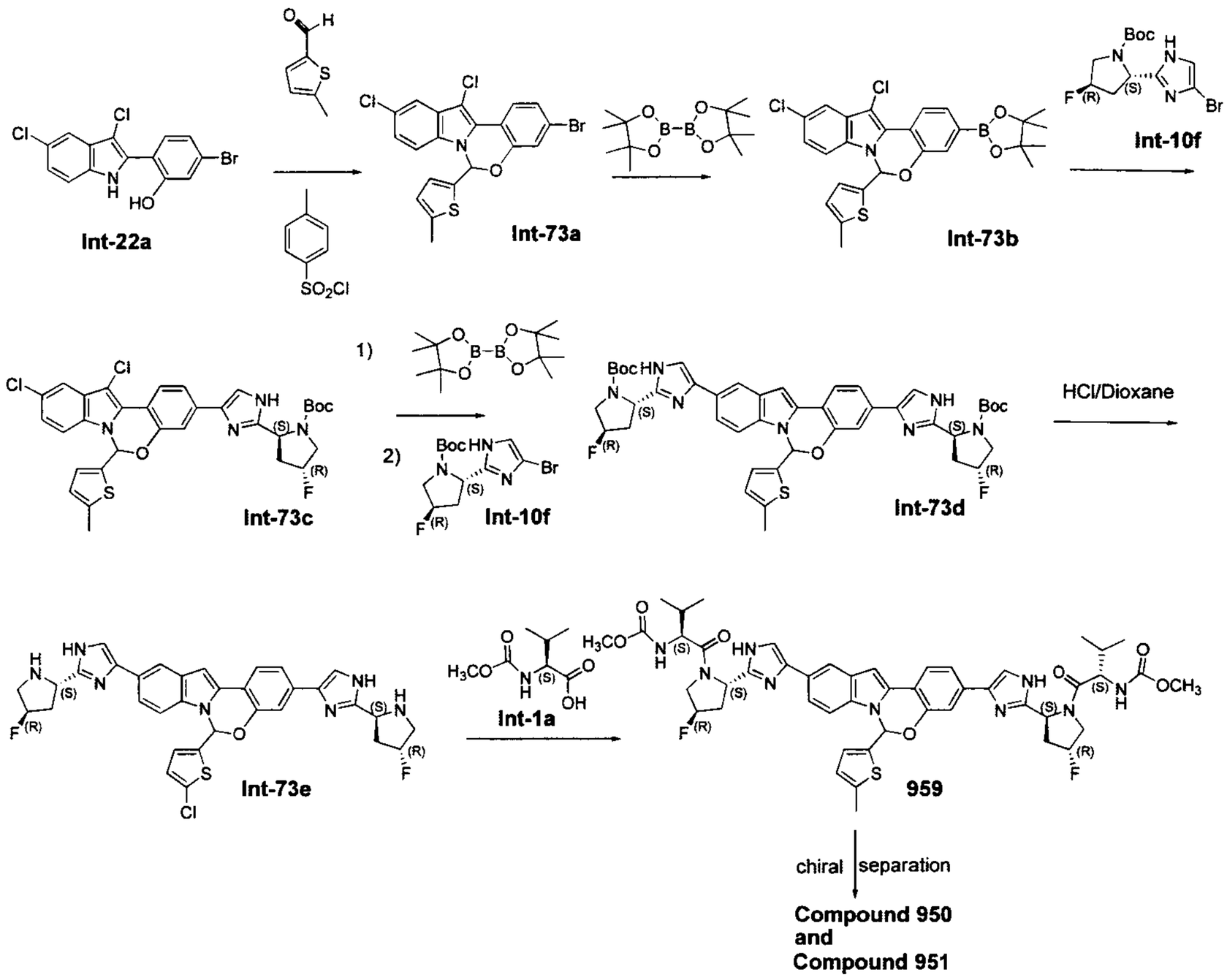


A 50-mL round-bottom flask was charged with **Inter Int-67b (104** mg, 0.116 mmol), **Int-1e** (27 mg, 0.140 mmol) and a solution of diisopropylethylamine (102

μL, 75 mg, 0.581 mmol) in dry DMF (1 mL). The reaction mixture was cooled to 0 °C (ice-water bath) and stirred for 15 minutes. Solid HATU (66 mg, 0.174 mmol) was added in one portion and the reaction mixture was allowed to stir for 2 hours and allowed to warm to room temperature. Methanol (1 mL) and TFA (56 μL) were added sequentially at room temperature and the reaction was allowed to stir at room temperature for 2 hours. Water (20 mL) followed by aqueous sodium bicarbonate solution (~10 mL) were then added. The reaction was extracted with EtOAc (2 x ~50 mL) and the combined extracts were washed with brine (~25 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide a light brown solid. The crude product was purified directly by reverse-phase chromatography (Gilson®; Phenomenex® Gemini 150 x 21.20 mm x 5 μm column; Run 1: 10-70% MeCN/water (+0.1% TFA) gradient over 20 minutes. Run 2: 10-60% MeCN/water (+0.1% TFA) gradient over 20 minutes) to provide Compound **1039** as a beige solid (65 mg, 82% yield).

EXAMPLE 73

Preparation of Compounds **959, 950, & 951**



Step A

Int-22a (1g, 2.8 mmol), 2-methyl thiophenecarboxaldehyde (1.06g, 8.4 mmol) and *p*-tosyl chloride were dissolved in toluene (10 mL) and stirred in a pressure tube at 150 °C for 6 hr. After cooling, the crude material was purified using an ISCO silica gel column (pre-packed, 80 g) eluted with EtOAc : Hex (0% to 5%) to yield **Int-73a** (500 mg, 38%).

Step B

Int-73a (0.5 g, 1.08 mmol), bis(pinacolato)diboron (0.3 g, 1.2 mmol), KOAc (316 mg, 3.2 mmol) and $PdCl_2(dppf)_2$ (88 mg g, 0.11 mmol) were added into a microwave tube. After the flask was flashed with N_2, and dioxane (3 mL) was added. The mixture was allowed to stir at 110 °C for 1 hour. The crude reaction containing **Int-73b** was used without further purification.

Step C

To the reaction flask charged with **Int-73b** was added **Int-10f** (430 mg, 1.3 mmol), $PdCl_2(dppf)_2$ (88 mg, 0.11 mmol) and K_2CO_3 (1 N aq., 3.23 ml). The tube was sealed, degassed and stirred at 90 °C for about 15 hours. After cooling, EtOAc (100mL) was added , the layers separated and the organic phase washed with brine (100 mL). The organic phase dried and concentrated to provide a semi-solid. The crude product was purified on a ISCO column (pre-packed silica gel, 40 g) and eluted with Hex:EtOAc 0% to 70% gradient to provide product **Int-73c** 650 mg (94%).

Step D

Int-73c (640 mg, 1.0 mmol), bis(pinacolato)diboron (508 mg, 2 mmol), Pd_2dba_3 (155 mg, 0.15 mmol), X-Phos (143 mg, 0.3 mmol) and KOAc (491 mg, 5 mmol) were added to a 20 mL microwave tube. The tube was sealed, degassed and the reaction was allowed to stir at 117 °C for 8 hr. To this reaction mixture was added **Int-10f** (259 mg, 0.78 mmol), $PdCl_2(dppf)_2$ (106 mg, 0.13 mmol) and K_2CO_3 (1 N aq., 1.9 ml) The tube was sealed and degassed and heated to 100 °C for an additional 24 hr. After cooling, EtOAc (100mL) was added, the layers separated, and the organic phase washed with Brine (100 mL). The organic phase was dried and concentrated to provide a solid. The crude material was purified on an ISCO column (pre-packed silica gel, 24 g) and eluted with DCM: DCM/MeOH/NH_3.MeOH (90:10:1) 0% to 80% to provide the product **Int-73d** 130 mg (24%).

Step E

Int-73d (145 mg, 0.18 mmol) was dissolved in dioxane (2 mL) and HCl (4N in dioxane, 0.9 mL) was added at room temperature. After 1.5 hours, the reaction was concentrated *in vacuo in vacuo*. The product **Int-73e** was isolated without further purification (123 mg, 100%).

Step F

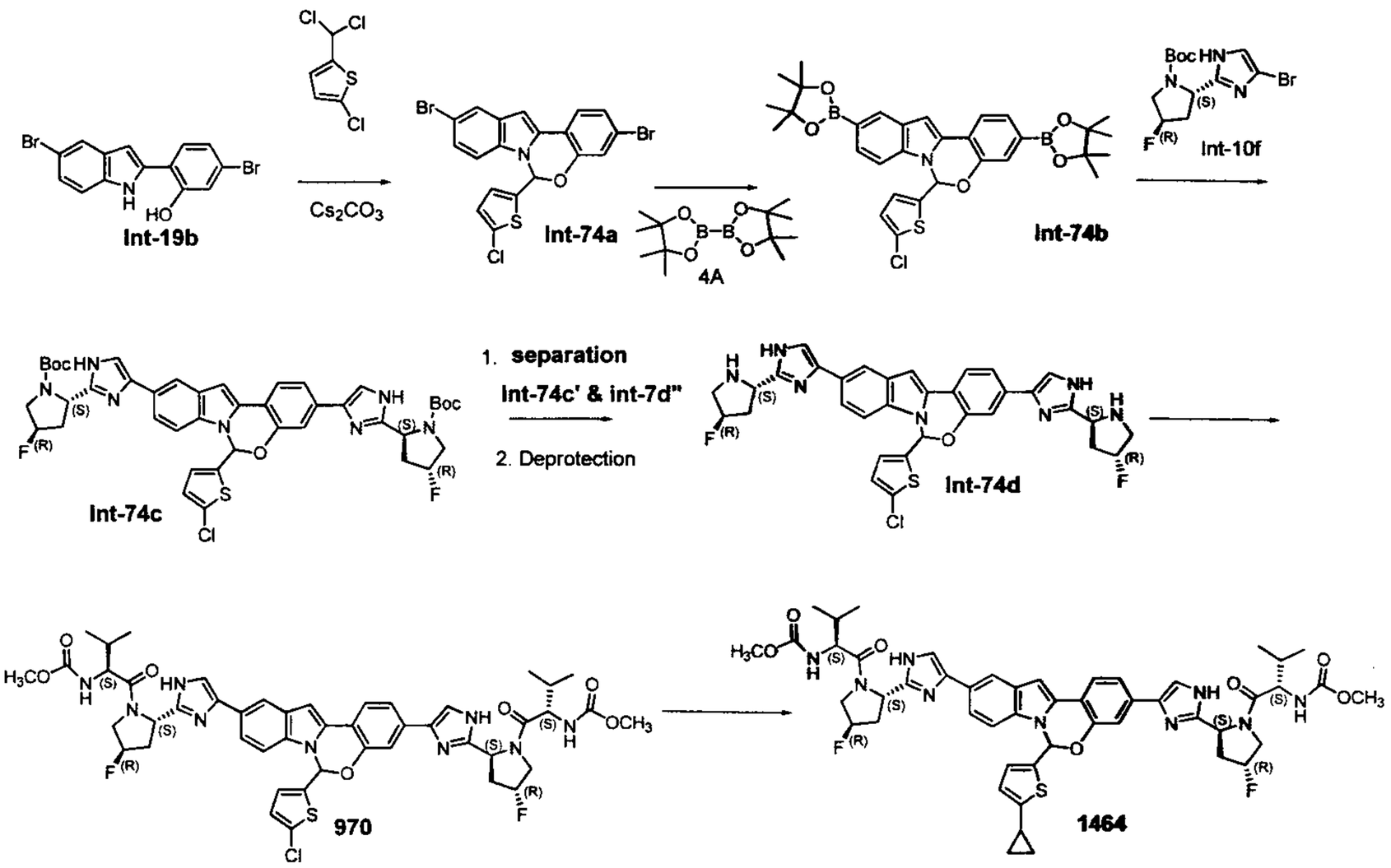
Int-73e (123 mg, 0.18 mmol) was dissolved in DMF (5 mL) and cooled to 0 °C. HATU(154 mg, 0.41 mmol), **Int-1a** (71.1 mg, 0.41 mmol) were added followed by addition of Hunig's base (0.19 mL, 1.06 mmol). After 1.5 hours at 0°C, water was added to quench the reaction. The mixture was diluted with EtOAc and extracted with NaClaq. The organic pahse was dried and concentrated to affors a solid. Further purification with by silica- gel chromatography (pre-packed column, 23 g) eluted with DCM and EtOAC/MeOH/$NH_3.H_2O$ (90:10:1) 0% to 80% to gave Compound **959** 103 mg (62%).

Compounds **950 & 951**

The diastereomers of Compound 959 (103 mg) were separated by chiral SFC separation on a AS-H column (50% MeOH (0.2% DEA)/CO2, 50 ml/min, 100 bar), to provide isomer A Compound **950** (27 mg, 35%) and isomer B Compound **951** (28 mg).

EXAMPLE 74

Preparation of Compound **1464**



Step A

2-Chloro-5-dichloromethylthiophene prepared from 2-chlorothiophene-aldehyde (5 g, 13.62 mmol) and Cs_2CO_3 (19.97 g, 61.3 mmol) was charged in a flask and dissolved in DMSO (50 mL). **Int-19b** (5.49 g, 27.2 mmol) was added and the reaction was heated to 100 °C. After 1 hour, the reaction was filtered and the filtrated was extracted with NaCl aq. The organic phase was dried and concentrated *in vacuo* to a semi-solid. The crude material was purified using flash column chromatography on silica gel (220 g column) eluted with EtOAc in Hex 0% to 5% to provide **Int-74a** (1.35g, 20%).

Step B

Int-74a (1.53 g, 3.09 mmol), dipinacolatoborane (1.8 g, 7.1 mmol), KOAc(1.52 g, 15.44 mmol) and $PdCl_2(dppf)_2$ (0.504 g, 0.62 mmol) were charged into a microwave tube. After the flask was flashed with N_2, dioxane (20 mL) was added. The mixture was allowed to stir at 95 °C for 4 hours. The crude reaction was diluted with EtOAc (100 mL) and it was extracted with NaCl aq. The organic phase was dried and concentrated *in vacuo*. The crude material was purified using flash column chromatography on silica gel with EtOAc in Hex (0% to 20%) eluent to provide **Int-74b** (990 mg, 54%).

Step C

Int-74b (990 mg, 1.68 mmol), **Int-10f** (1.35 g, 4.03 mmol), $PdCl_2(dppf)_2$ (0.274 g, 0.342 mmol) and K_2CO_3 (1 N aq., 8.4 ml) were added to a 20 mL microwave tube. The tube was sealed, degassed with nitrogen and stirred at 100 °C for about 15 hours. After cooling, EtOAc (100mL) was added and the reaction was extracted with brine (100 mL). The organic phase was separated, dried and concentrated *in vacuo*. The crude material was purified on a ISCO silica-gel column (40 g) and with EtOAc/Hex (0% to 70%) eluent to provide product **Int-74c** 500 mg (33%).

Int-74c (504 mg) was subjected to SFC chiral separation on OD-H column (IPA (0.05% DEA)/CO_2) to provide isomers **Int-74c'** and **Int-74c"** (176 mg, 35%).

Step D

Int-74c" ((176 mg) was dissolved in dioxane (10 mL) and HCl (4N in dioxane, 0.53 mL) was added and stirred at room temperature. After 1.5 hr. the solvent was removed *in vacuo*. **Int-74d** was isolated without further purification (167 mg, 100%).

Step E

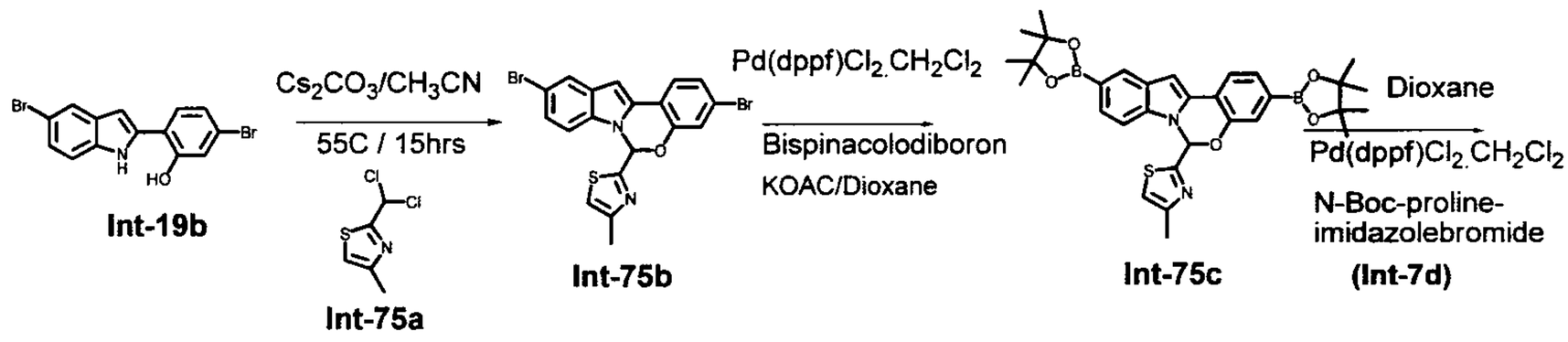
Int-74d (diastereomer B, 167 mg, 0.21 mmol) was dissolved in DMF (3 mL) and cooled to 0 °C. HATU(169 mg, 0.44 mmol), **Int-10f** (74.1 mg, 0.423 mmol were added followed by addition of Hunig's base (0.22 mL, 1.27 mmol) and the reaction was allowed to stir at 0°C. After 1.5 hours, water was added and the reaction diluted with EtOAc and extracted with NaClaq. The organic phase was dried and concentrated *in vacuo* to provide a solid.. Purification by silica gel chromatography (23 g) with DCM and EtOAC/MeOH/NH3 (90:10:1 - 0% to 100%) eluent provided the title Compound **970** (140 mg, 69.1%).

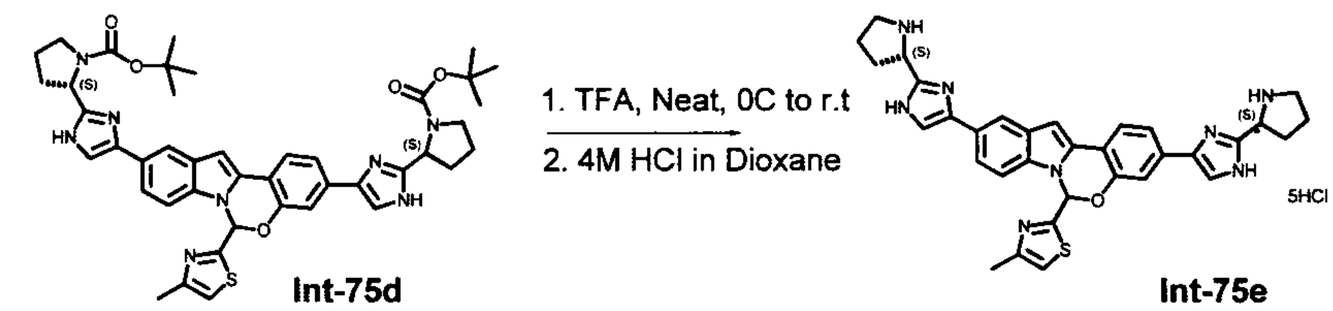
Compound 1464 (diastereomer B).

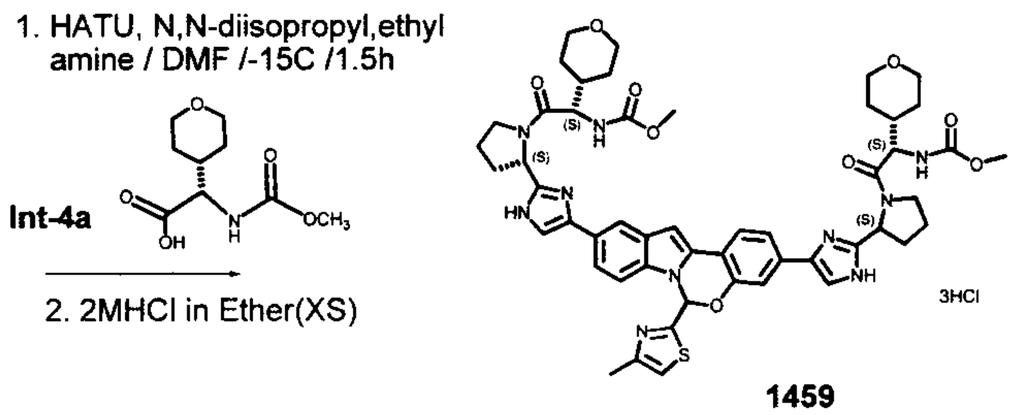
Compound **970** (60 mg, 0.063 mmol), cyclopropylboronic acid (81 mg, 0.94 mmol), Pd_2dba_3 (6.5 mg, 6.26 µmol), X-Phos (5.97 mg, 0.013 mmol) and K_2CO_3 (1 N aq., 188 µl) were added to a 20 mL microwave tube. The tube was sealed and degassed with nitrogen. The reaction was allowed to stir at 110 °C for 5 hr. The crude material was purified on silica gel using DCM to EtOAc/MeOH/NH3.H_2O (100:10:1- 0% to 90%) eluent to provide Compound **1464** (40 mg, 62%).

EXAMPLE 75

Preparation of Compound **1459**







Step A

To a solution of 4-Methyl-2-thiazole-2-carboxaldehyde (2.0g, 15.73mmol) in CH_2Cl_2 (40 mL) at -20^{0}C, added pyridine(0.254ml, 3.15mmol) followed by addition of PCl_5(6.55g, 31.5mmol) . The mixture was allowed to stir at -20 °C for 30 minutes. $NaHCO_3$ (13.2g, 10eq.) was added as solid to the reaction mixture. After stirring for additional 30 minutes the reaction was filtered through celite and washed with 2 X 25 mL CH2Cl2. The filtrate was concentrated under reduced pressure to provide the crude. It was re-dissolved in CH_2Cl_2 and filtered through a pad of silica-gel. Filtrate on concentration and drying gave **Int-75a** as brown oil. (32%)

Step B

The dibromo indole (**Int-19b,** 0.5g, 1.362mmol), 2-(dichloromethyl)-4-methylthiazole(**Int-75a,** 0.496g, 2.72mmol) and Cesium carbonate (0.976g, 3.00mmol) were combined in acetonitrile (10ml) in a 50mL round bottomed flask equipped with condenser and heated at 55°C for 15 hrs. TLC analysis showed consumption of starting

material. The reaction was diluted with EtOAc, washed with water(3X20ml), brine (1x20ml), dried(Na2SO4), filtered and concentrated under reduced pressure to provide brown semi-solid crude. It was allowed to stir with ether and filtered to provide **Int-75b** as yellow solid. The filterate was concentrated and purified using ISCO silica-gel column. The combined yield of 4 was 0.32g (49%).

Step C

Intermediate **Int-75b** (0.095g, 0.2mmol), bis(pinacolato)diboron (0.106g, 0.419mmol), potassium acetate(0.117g, 1.197mmol) and PdCl2(dppf).CH2Cl2 (0.065g, 0.08mmol) and Dioxane (2.0ml) were combined in a microwave tube and sealed and purged with nitrogen (3 x). The reaction was heated at 90°C for 2hrs. TLC showed complete reaction. The reaction mixture containing **Int-75c** was used without additional workup.

Step D

To the above reaction mixture (Intermediate **Int-75c** (0.114g, 0.2mmol) in the microwave tube, was added N-Bocproline imidazole bromide(**Int-7d**, 0.139g, 0.44mmol), PdCl2(dppf).CH2Cl2 (0.033g, 0.04mmol) and Potassium carbonate (1.199ml of 1M aqueous solution, 1.199mmol) . Sealed and purged with nitrogen (3 x). The reaction was heated at 90^0C for 4hrs. Reaction was worked up by diluting with EtOAc (25ml) and water (20ml). The resulting mixture was vigorously stirred for 10 minutes and then filtered through Celite. Filtrate was partitioned. The organics were washed with water (3x15ml) and brine(1x15ml), dried(Na_2SO_4), filtered and concentrated *in vacuo*. The resulting crude was purified using preparatory silica gel column chromatography, using 5%MeOH/CH2Cl2 to provide desired product **Int-75d** (79%).

Step E

Trifluoroacetic acid (0.25ml, 3.24mmol) was added to Intermediate **Int-75d** at ^{0}C. The mixture was allowed to warm room temperature and stirred for additional 1 hour. The solvent was removed under reduced pressure. The product was treated with

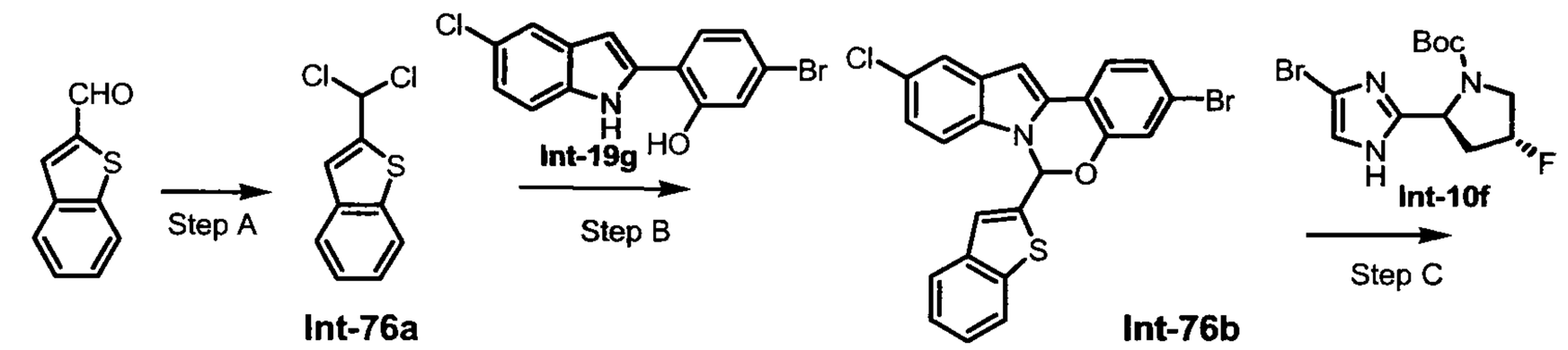
0.36ml of 4MHCl in dioxane (1.44mmol). After 10 minutes of stirring, excess acid and solvent removed and the product **Int-75e** was dried for about 15 hours.

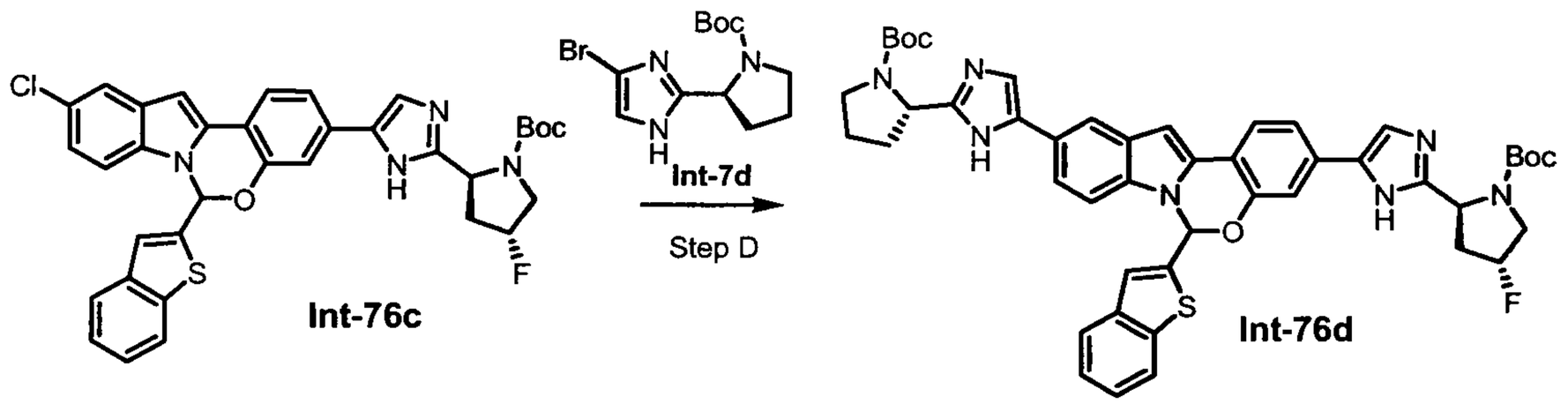
Preparation of Compound **1459**

To a solution of Intermediate **Int-75e** (0.035g, 0.045mmol) in DMF (1.4ml) was added (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl) acetic acid (0.022g, 0.1mmol), HATU(0.038g, 0.1mmol). The reaction was cooled to -15^{0}C and Hunig's base (0.051ml, 0.363mmol) was added drop-wise. The resulting mixture was allowed to stir for 1.5 hrs at -15^{0}C. The reaction was quenched with water (20ml). The product was extracted with EtOAC (3x20ml). The organics were washed with water (3x20ml), brine (1x20ml), dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide crude which was purified using Gilson reverse phase chromatography using gradient elution of 0% to90% CH_3CN with 0.1%TFA and water with 0.1% TFA. The desired fractions were collected and concentrated under reduced pressure and then treated with 0.3ml of 2MHCl in ether. The solvent was removed and the sample was dried for about 15 hours to provide Compound **1459** as an orange brown solid. (32%).

EXAMPLE 76

Preparation of Intermediate Compound **Int-76d**





*Step A – Preparation of Int-**76a***

To a cooled mixture of thionyl chloride (20 ml, 274 mmol) and DMF (0.7 ml) at 0 °C, benzothiophene 2-carboxaldehyde (4.7 g, 29.0 mmol) was added in 3 portionas, and stirred at 0 °C for 30 minutes and then a;lowed to warm for about 15 hours. The mixture was poured into ice and aqueous 1N sodium hydrogen carbonate and then extracted with EtOAc. The combined organic solution was washed with brine and dried (Na_2SO_4) and concentrated *in vacuo* to provide **Int-76a** (6.1 g, 28.1 mmol, 97 % yield).

Step B – Preparation of Compound **Int-76b**

Int-19g (4.5 g, 13.95 mmol), **Int-76a** (6.06 g, 27.9 mmol) , and cesium carbonate (18.18 g, 55.8 mmol) in DMSO (22 ml) was allowed to stir at 80 °C for 2 hours. The mixture was then added to cold water and the resulting solid was filtered off and washed with water to provide a 1.55 g of a solid . The filtrate was concentrated and the residue was allowed to stir with 1:1 MeOH-MC to provide crude solid material which was further purified using silica-gel Chromatography (Pre-packed Biotage column, 80g solid loading, Eluent: 1000% Hex to 15% EtOAc/Hex) to provide the desired product **Int-76b** (650 mg, Yield 33.8%).

*Step C – Preparation of **Int-76c***

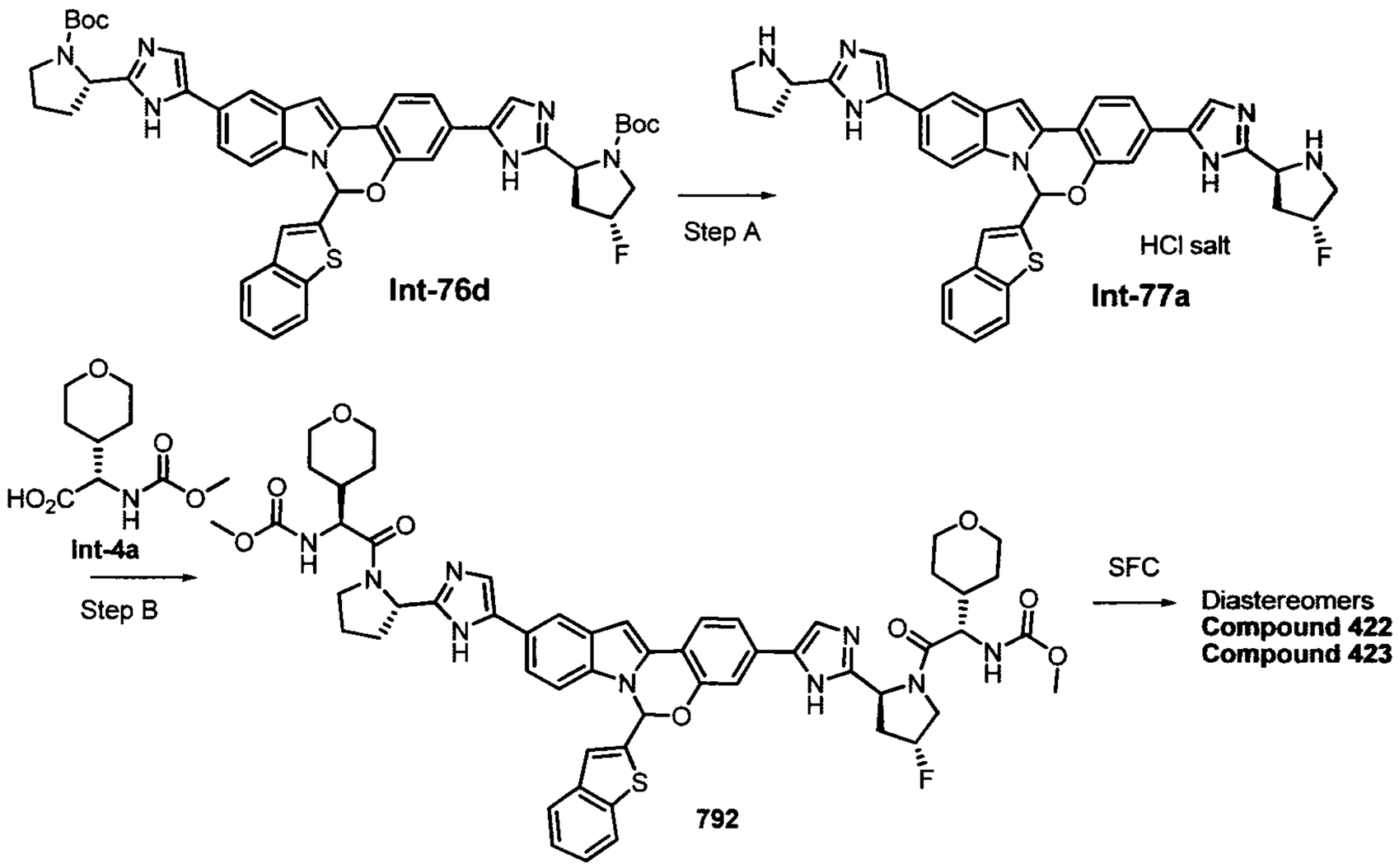
A mixture of **Int76b**(0.418 g, 0.90 mmol), bis(pinacolato)diboron (0.25 g, 0.99 mmol), KOAc (0.176 g, 1.80 mmol), and Pd(dppf)Cl_2 (0.066 g, 0.09 mmol) in 1,4-Dioxane (3 ml) was degassed (by N_2 flush) and heated to 100 °C. After 4h , the reaction was cooled to room temperature, and **Int-10f** (329 mg, 0.99 mmol), Pd(dppf)Cl_2 (66 mg, 0.09 mmol) and 1N K_2CO_3 (1.8 ml, 1.8 mmol) were added. The mixture was degassed and heated at 100 °C for 2 hours. The mixture was cooled to room temperature, diluted in EtOAc, and filtered through celite pad. The filtrate was concentrated *in vacuo* and the residue was purified on an ISCO 80 g gold column (Eluent: CH_2Cl_2-5%MeOH/ CH_2Cl_2) to provide **Int-76c** (503 mg, 0.785 mmol, **88 % yield)** as a pale yellow solid.
LC/MS (M+H) = 641.2.

Step D – Preparation of **Int-76d**

A mixture of **Int-76c** (0.292 g, **0.455** mmol), bis(pinacolato)diboron (0.127 g, 0.50 mmol), KOAc (0.089 g, 0.91 mmol), X-Phos (0.043 g, 0.091 mmol), and Pd_2dba_3 (0.047 g, 0.046 mmol) in 1,4-Dioxane (3.5 ml) was degassed (by N_2 flush) and heated to 100 °C. After 18 hours, the reaction was cooled to room temperature, the crude mixture was treated with **Int-7d** (160 mg, 0.51 mmol), Pd(dppf)Cl_2 (34 mg, 0.046 mmol) and 1N K_2CO_3 (0.92 ml, 0.92 mmol). The mixture was degassed and stirred at 100 °C for 6 hours, cooled to room temperature, diluted in EtOAc, and filtered through celite pad. The filtrate was concentrated *in vacuo* and the residue was purified on an ISCO 40 g gold column (Eluent: Hex-EtOAc 100:1 to 85:15 gradient) to provide **Int-76d** (225 mg, 58 % yield) as a pale yellow solid. LC/MS (M+H) = 842.3.

EXAMPLE 77

Preparation of Compounds **792, 422 & 423**



Step A

Trifluoroacetic acid (1 ml, 12.98 mmol) was added to a stirred, cooled 0 °C solution of **Int-76d** (0.171 g, 0.203 mmol) in CH_2Cl_2 (3 ml). After 5 minutes the reaction was allowed to warm to room temperature and stir an additional 90 minutes.. The mixture was concentrated *in vacuo* and the residue was dissolved in MeOH followed by treatment with 2N HCl in ether. The methanol solution was then concentrated to dryness providing **Int-77a** (0.145 g, 0.203 mmol, 100 % yield) which was used without further purification.

LC/MS (M+H) = 642.3.

Step B

A round flask was charged with **Int-77a** (145 mg, 0.203 mmol), DMF (1.5 ml) and **Int-4a** (88 mg, 0.406 mmol) and cooled to -15 °C. To the reaction mixture were added N,N-diisopropylethylamine (0.248 ml, 1.42 mmol) and HATU (154 mg, 0.406 mmol). After 10 minutes and the reaction was allowed to warm to 0 °C. After 3 hours, the reaction was quenched by 0.5 mL of water and the mixture was filtered and purified

on a Gilson HPLC (Eluent: Acetonitrile/Water + 0.1% TFA) to provide Compound **792** (106 mg, 41 % yield) as a diastereomeric mixture (~1:1).

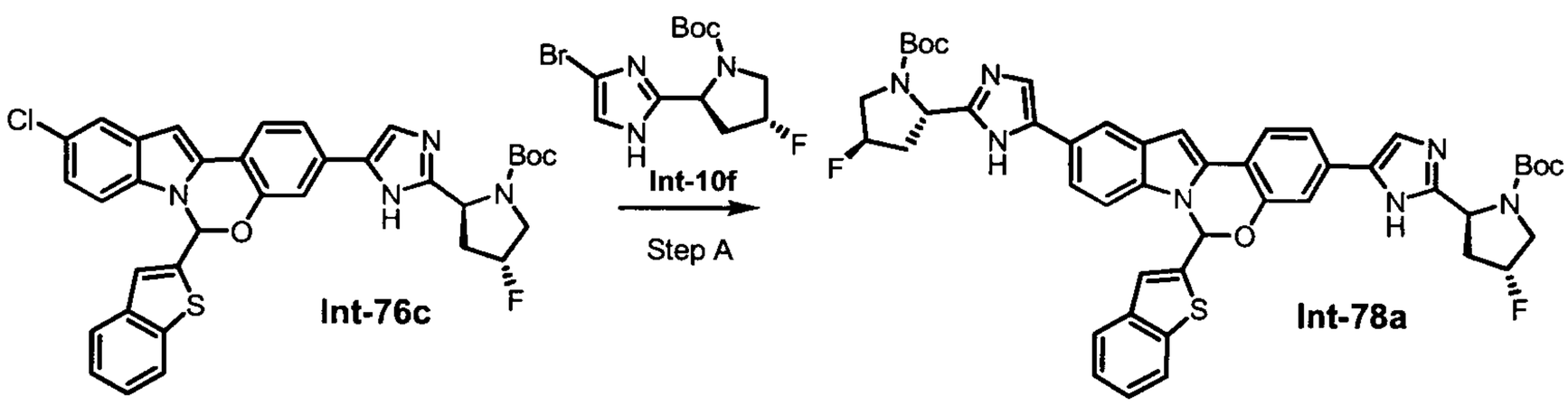
The diastereomers of Compound **792** were separated by SFC to provide pure diastereomers Compound **422** and Compound **423**.

LC/MS (M+H) = 1041.4. SFC separation condition:

Instrument: Thar 80 SFC ; Column: Chiral Cel OJ, 20μm ,Daicel Chemical Industries, Ltd 250×30mmI.D. Mobile phase: A: Supercritical CO_2, B:ETOH(contained 0.2% DEA) , A:B =45:55 at 80ml/min; Column Temp: 38 ℃

EXAMPLE 78

Preparation of Intermediate Compound **Int-78a**

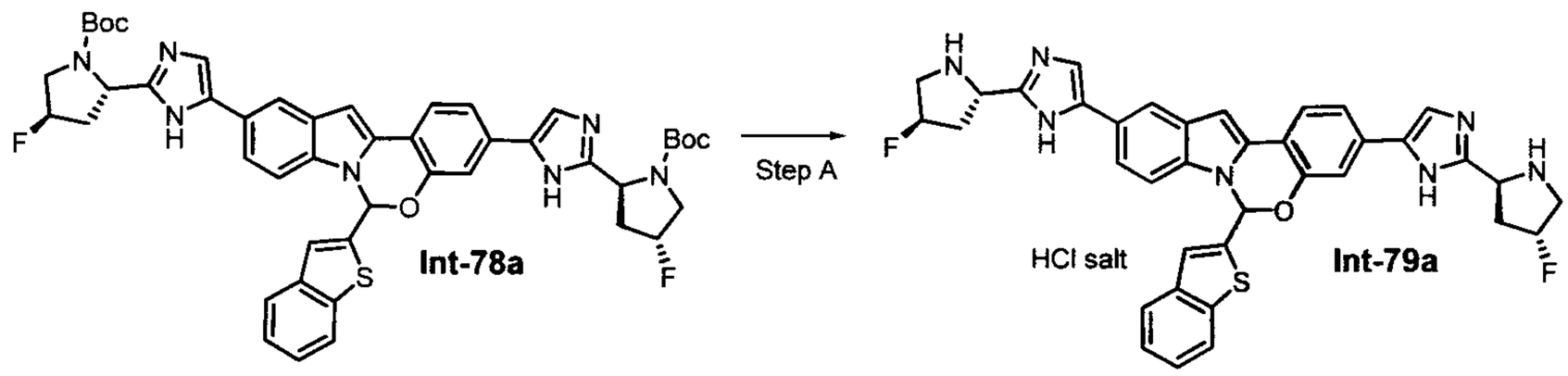


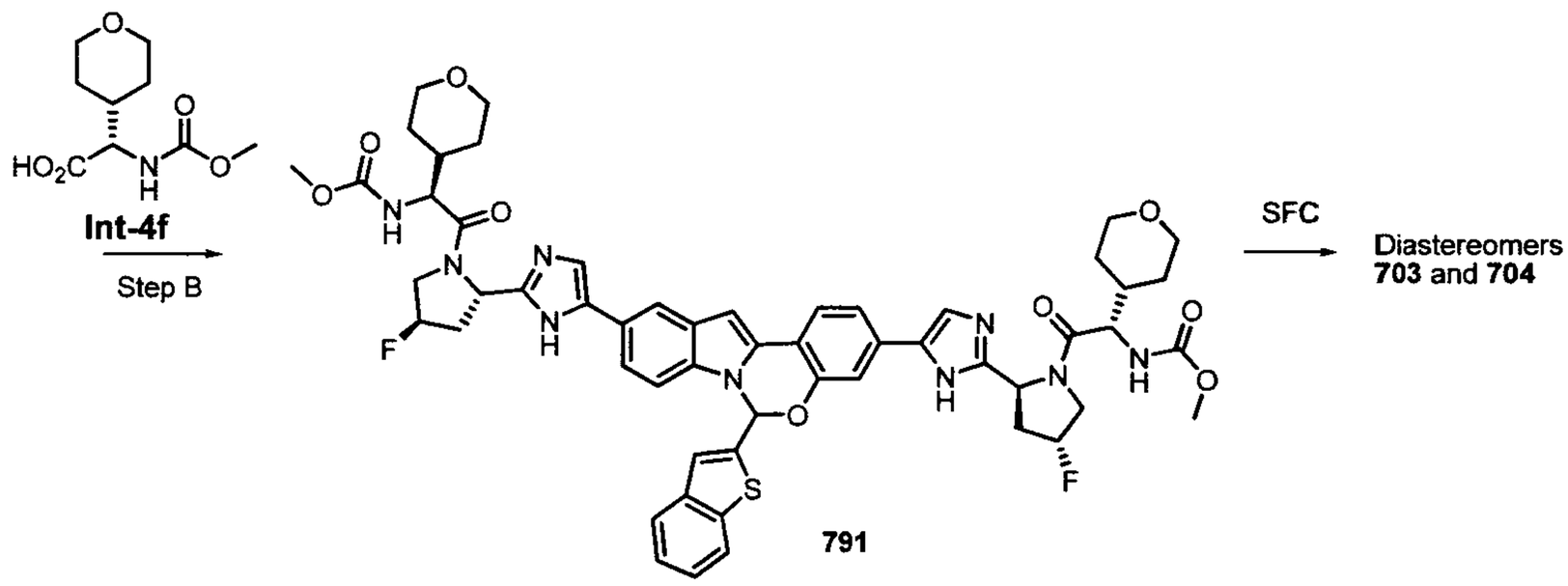
Int-78a (248 mg, 0.288 mmol, 62 % yield) was prepared from **Int-76c** (343 mg, 0.47 mmol) using the method described in Example 50..

LC/MS (M+H) = 860.3.

EXAMPLE 79

Preparation of Compounds **791, 703 & 704**





Step A

Compound **Int-79a** (211 mg, 0.29 mmol, 100% crude yield).was prepared from **Int-78a** (248 mg, 0.29 mmol) following the method described in Example 77 Step A LC/MS (M+H) = 660.3.

Step B

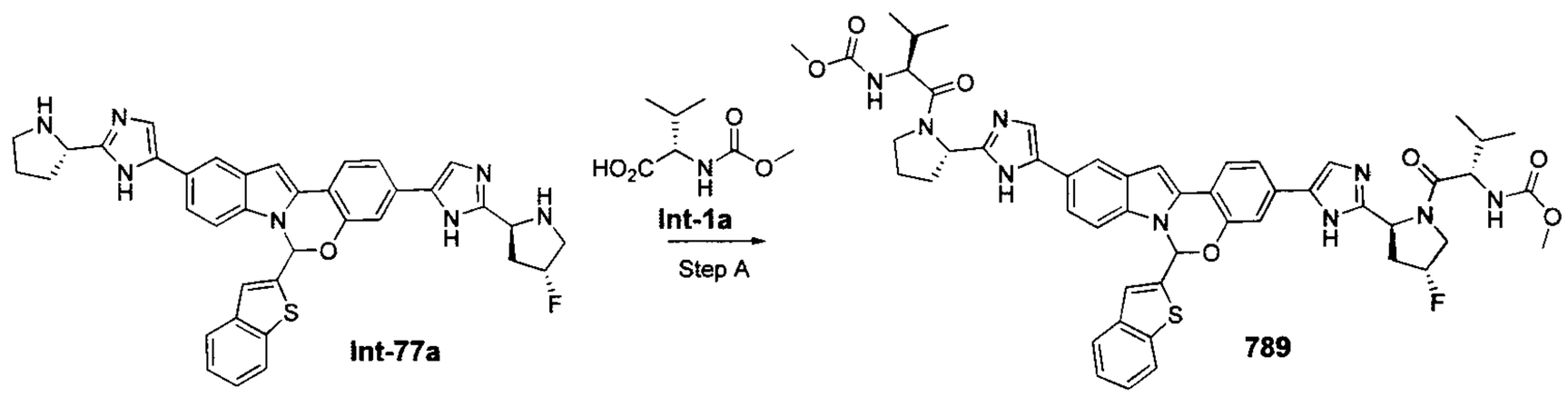
Compound **791** (112 mg, 0.087 mmol, 44% yield) was prepared from **Int-79a** (147 mg, 0.20 mmol) using the method described in **Example 77**, Step B SFC separation provided the pure diastereomers Compound **703** and Compound **704** LC/MS (M+H) = 1058.2.

SFC Separation condition: (Thar 80 SFC , Chiral Pak AS, 20μm, Daicel Chemical Industries, Ltd 250×30mmI.D.

Mobile phase: A: Supercritical CO_2 , B:ETOH(contained 0.2% DEA) , A:B =60:40at 80ml/min

EXAMPLE 80

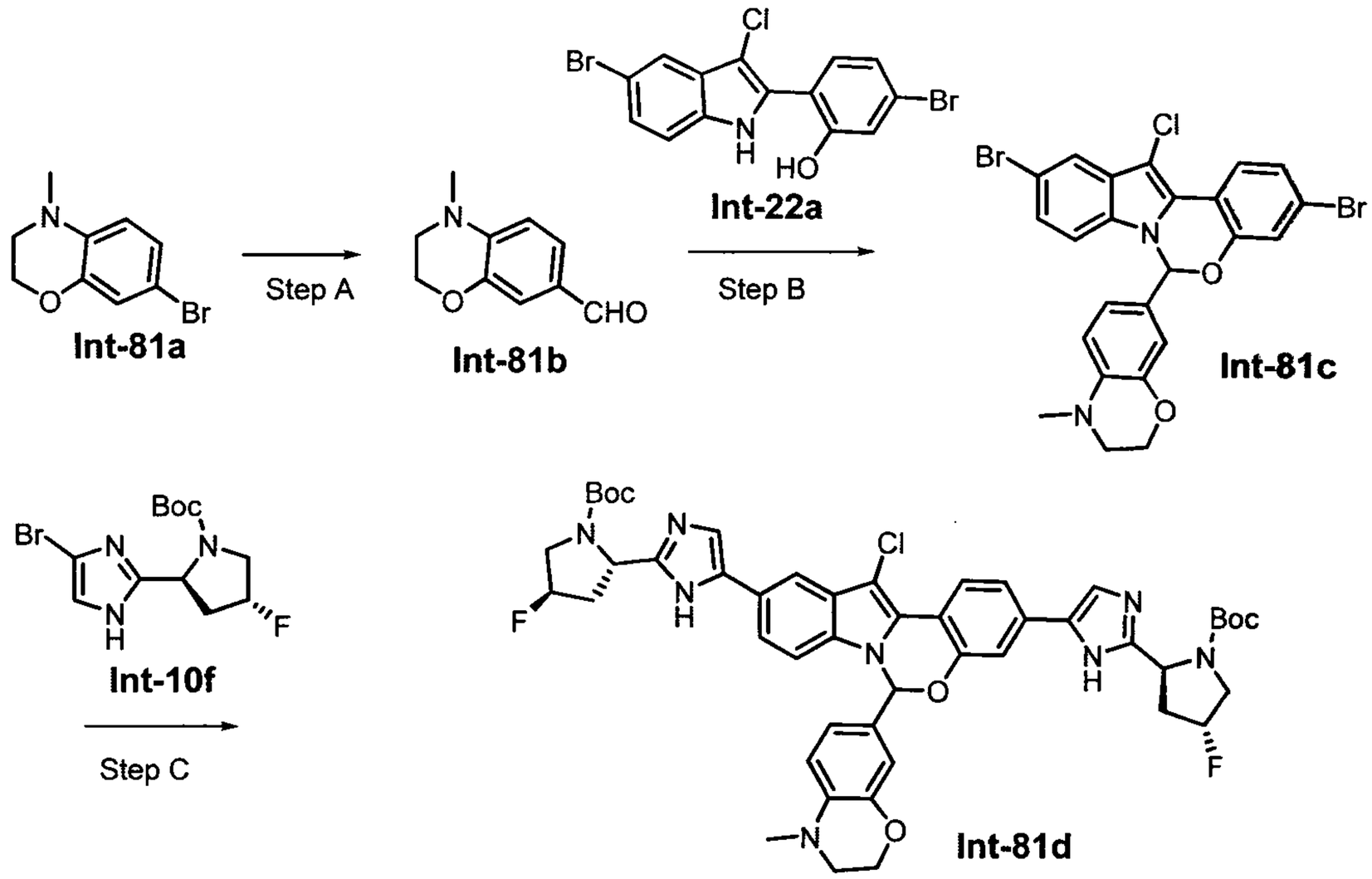
Preparation of Compound **789**



Compound **789** (106 mg, 0.084 mmol, 41% yield) was prepared from **Int-77a** (145 mg, 0.203 mmol) using **Int-1a** using the method described in Example 77, Step B LC/MS (M+H) = 1041.4.

EXAMPLE 81

Preparation of Intermediate Compound **Int-81d**



Step A

n-BuLi (5.79 ml, 14.47 mmol) was added to a stirred, cooled -78 °C solution of 7-bromo-4-methyl-3,4-dihydro-2H-1,4-benzoxazine (**Int-81a,** 3 g, 13.15 mmol) in THF (24 ml). After stirring 1h at -78 °C for 1 hour., DMF (2.037 ml, 26.3

mmol) was added dropwise and the mixture allowed to warm slowly over 2 hours to room temperature. The reaction was quenched with aqueous ammonium chloride, and the product extracted into ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), filtered and under reduced pressure to provide **Int-81b** (2.32 g, 13.09 mmol, 100 % yield) as a green solid.

Step B

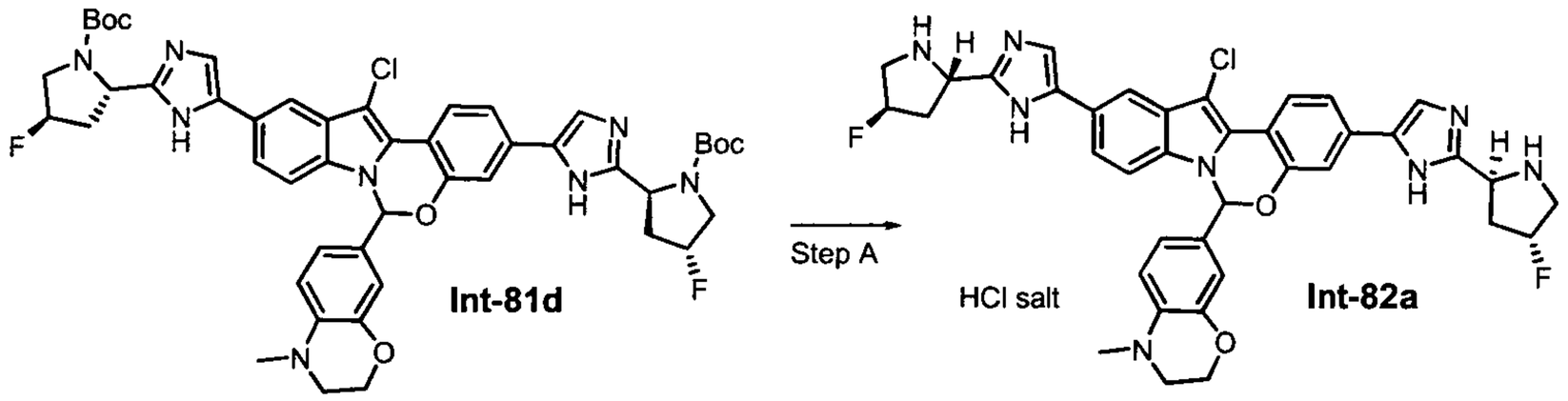
A 0.2-0.5 mL microwave tube was charged with **Int-22a** (1g, 2.491 mmol), **Int-81b** (1.12 g, 6.32 mmol), p-TsCl (0.142 g, 0.747 mmol) and Toluene (8 ml). The reaction was heated in the microwave reactor at 170 °C for 6 hours. The mixture was cooled, concentrated *in vacuo* and the residue was purified on an ISCO 24 g gold column (Eluent: 100% Hex to 50% EA/Hex gradient) to provide **Int-81c** (190 mg, 0.339 mmol, 13.61 % yield).

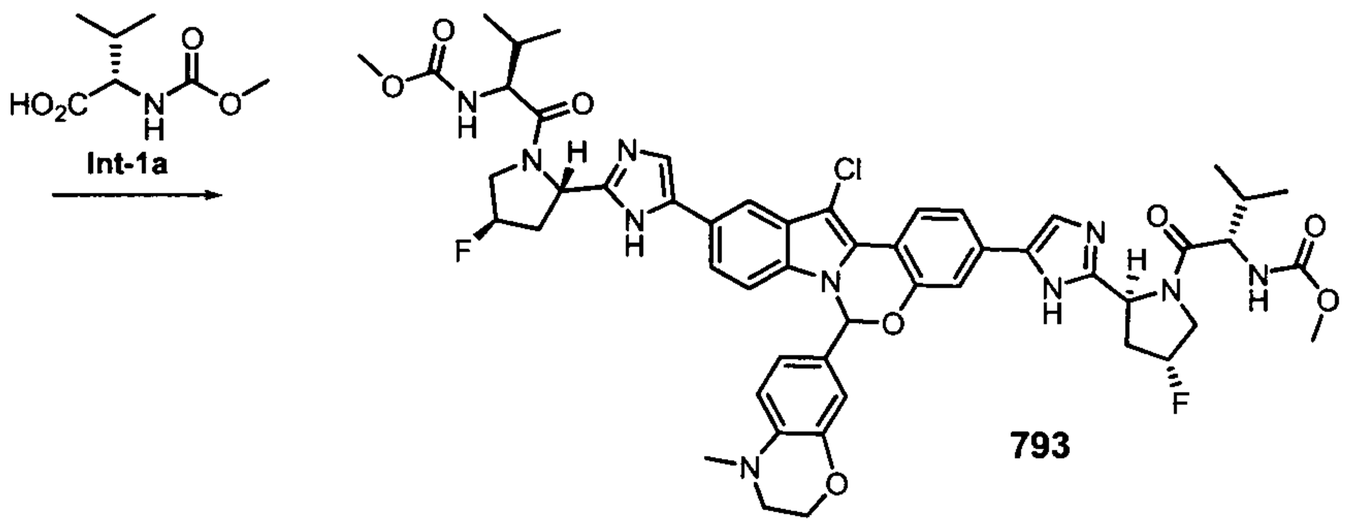
Step C

A mixture of **Int-81c** (350 mg, 0.624 mmol), bis(pinacolato)diboron (349 mg, 1.373 mmol), KOAc (245 mg, 2.497 mmol), and Pd(dppf)Cl_2 (45.7 mg, 0.062 mmol) in 1,4-Dioxane (5 ml) was degassed (by N_2 flush) and heated to 100 °C. After 18h, the reaction wascooled to room temperature, the mixture was treated with **Int-10f** (438 mg, 1.310 mmol), 1N K_2CO_3 (2.5 ml, 2.5 mmol) and Pd(dppf)Cl_2 (45.7 mg, 0.062 mmol). The mixture was degassed and heated to 100 °C for 18 hours. The mixture was cooled, diluted in EtOAc and filtered through celite pad, and the filtrate was concentrated *in vacuo* to provide a solid. The crude product was purified using flash column chromatography on silica gel on (ISCO 40g gold, Eluent:Hex-EtOAc 100:0 to 85:15) to provide **Int-81d** (233 mg, 0.256 mmol, 41.1 % yield) as a pale yellow solid. LC/MS (M+H) = 909.4.

EXAMPLE 82

Preparation of Compound **793**





Step A

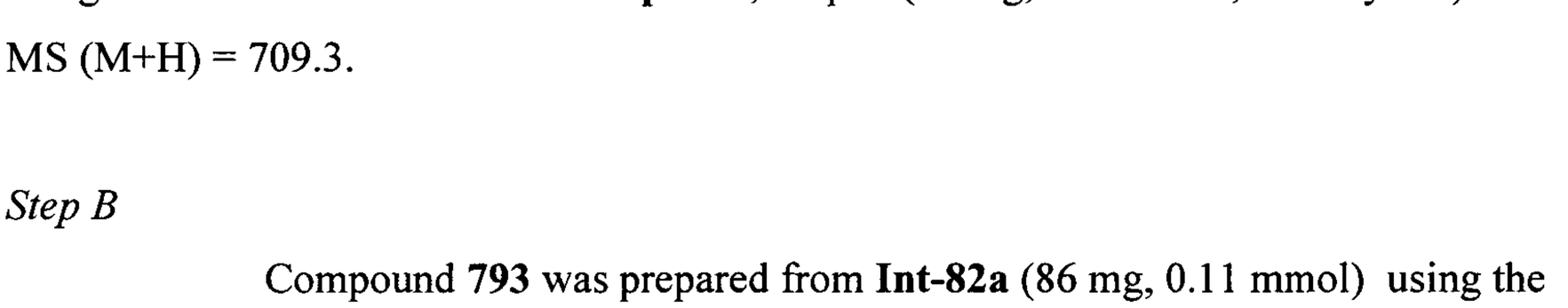
Compound **Int-82a** was prepared from **Int-81d** (100 mg, 0.11 mmol) using the method described in **Example 77**, Step A (86 mg, 0.11 mmol, 100% yield). LC/MS (M+H) = 709.3.

Step B

Compound **793** was prepared from **Int-82a** (86 mg, 0.11 mmol) using the method described in **Example 77**, Step B (63 mg, 0.050 mmol, 46% yield). LC/MS (M+H) = 1024.4.

EXAMPLE 83

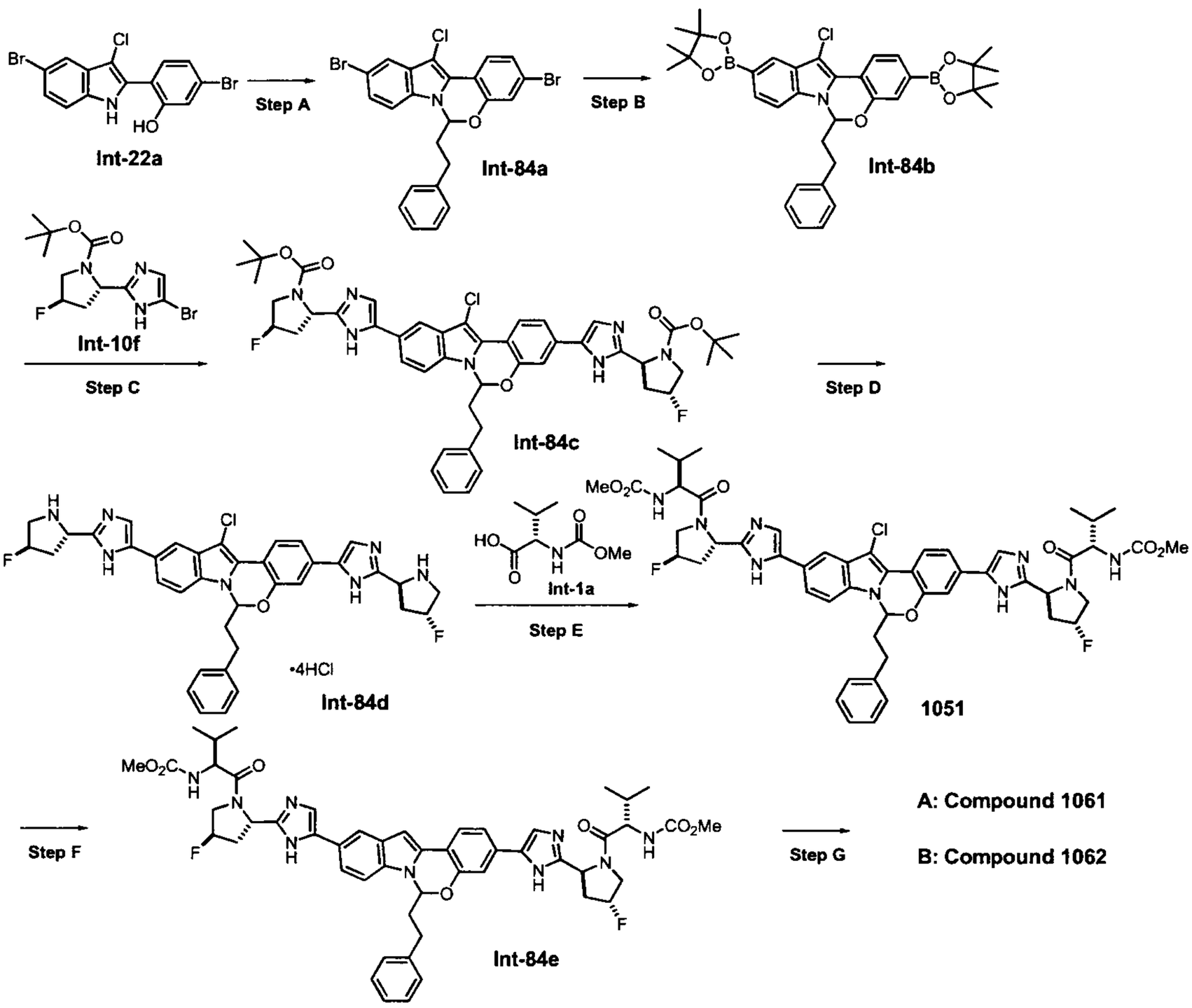
Preparation of Compound **794**



A mixture of X-Phos (4.27 mg, 8.95 μmol), Compound **793** (56 mg, 0.045 mmol), Pd_2dba_3 (4.63 mg, 4.47 μmol), KOAc (10.98 mg, 0.112 mmol) and bis(pinacolato)diboron (17.04 mg, 0.067 mmol) in 1,4-Dioxane (1 ml) was degassed and heated to 100 °C for about 15 hours. The mixture was the then cooled to room temperature, filtered and the crude reaction mixture purified on a Gilson HPLC (Eluent: Acetonitrile/Water + 0.1% TFA) to provide Compound **794** (30.5 mg, 0.025 mmol, 56% yield). LC/MS (M+H) = 989.5.

EXAMPLE 84

Preparation of Compounds **1051**, **1061** & **1062**



Step A

A 20-mL microwave tube was charged with **Int-22a** (1.0 g, 2.5 mmol), 3-phenylpropanal (3.3 mL, 3.3 g, 25 mmol) and *p*-toluenesulfonyl chloride (48 mg, 0.25

mmol) and toluene (8 mL). The reaction mixture was heated and stirred at 170 °C in a microwave for 12 hours. The reaction mixture was concentrated *in vacuo in vacuo*, and the residue adsorbed onto silica gel. Purification by by silica gel chromatography (Eluent:0-15% EtOAc/hexanes) provided **Int-84a** as a yellow oil (901 mg, 70% yield)

Step B

A 20-mL microwave tube was charged with **Int-84a** (901 mg, 1.74 mmol), bis(pinacolato)diboron (1.1 g, 4.4 mmol), (dppf)$PdCl_2$•CH_2Cl_2 (142 mg, 0.17 mmol) and KOAc (512 mg, 5.22 mmol). Dioxane (10 mL) was added, and the sealed reaction degassed with dry nitrogen. The reaction was allowed to stir at 90 °C for 2 hours, then allowed to cool to room temperature, and diluted with EtOAc (100 mL). The organic phase was washed sequentially with water (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide a solid. The crude product was purified using flash column chromatography on silica gel (Eluent: 0-20% EtOAc/hexanes) to provide **Int-84b** (1.3 g).

Step C

A 20-mL microwave tube was charged with **Int-84b** (572 mg, 0.93 mmol), **Int-10f** (687 mg, 2.05 mmol), and (dppf)$PdCl_2$•CH_2Cl_2 (38 mg, 0.047 mmol). The tube was sealed, dioxane (8 mL) was added , degassed with nitrogen. and aqueous potassium carbonate (6 mL, 1 M, 6 mmol) added. The reaction mixture was heated at 90 °C for 16 hours, cooled to room temperature and diluted with EtOAc (100 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL), and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified using flash column chromatography on silica gel (Eluent: EtOAc (containing 10% MeOH): hexanes of 10:90 to 90:10) to provide **Int-84c** (580 mg, 72% yield).

Step D

A 125-mL round-bottom flask was charged with **Int-84c** (411 mg, 0.47 mmol) and methanol (9 mL). HCl (9.4 mL, 2 M in diethyl ether, 19 mmol) was added

and the reaction mixture was allowed to stir for about 15 hours at room temperature. The reaction mixture was concentrated *in vacuo* to provide **Int-84d** (384 mg, quantitative yield).

Step E

In a 125-mL round-bottom flask, **Int-84d** (382 mg, 0.52 mmol) and **Int-1a** (228 mg, 1.3 mmol) were dissolved in DMF (7.5 mL) and diisopropylethylamine (0.63 mL, 0.47 g, 3.6 mmol) was added. The reaction mixture was cooled to 0 °C and was allowed to stir for 15 minutes. HATU (395 mg, 1.04 mmol) was added and the reaction mixture was allowed to stir at 0 °C for 30 minutes, and then at room temperature for 2.5 hours. The reaction mixture was poured into water (30 mL). The precipitate was collected by filtration, then dissolved in methylene chloride (200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude product was purified using reverse-phase C18 chromatography (Gilson, 0-90% CH_3CN (+ 0.1% TFA)—water (+ 0.1% TFA) over 15 minutes) to provide Compound **1051** as a yellow foam (199 mg, 39% yield).

Step F

Compound **1051** (247 mg, 0.251 mmol) was dissolved in methanol (13 mL) and palladium (268 mg, 10 wt% on carbon, containing 50 wt% water) was added. The reaction mixture was hydrogenated for 71 hours, at which point LC/MS analysis showed a 4:1 mixture of desired product and starting mixture. The hydrogenation was continued for a further 92 hours. The reaction mixture was filtered and the catalyst was rinsd with methanol (~100 mL). The filtrate was concentrated, adsorbed onto silica gel (15 mL), then purified using flash column chromatography on silica gel (0-10% MeOH (+1% NH_4OH)/CH_2Cl_2) to provide **Int-85e** (164 mg, 69% yield).

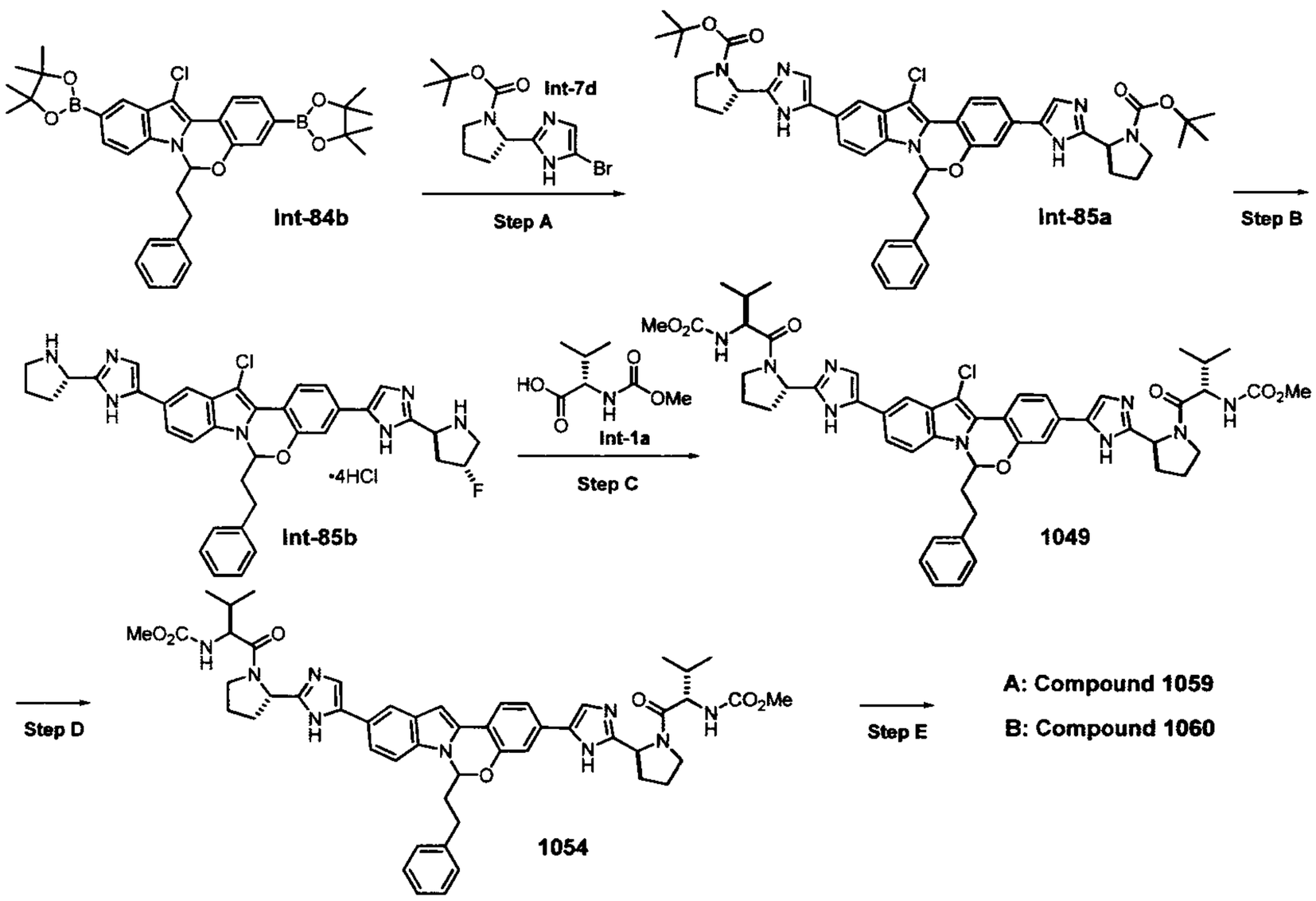
Step G

The isomers of **Int-85e** were separated by HPLC. **Int-85e** (164 mg) was dissolved in abs. EtOH (6.0 mL) and the solution was filtered. The sample was divided into four equal portions, each of which was injected onto a Phenomenex Lux Cellulose-2

(5 μm, 150 x 21.20 mm) semi-preparative column; detection wavelength = 350 nm. Initial elution with 25% EtOH/hexane @ 10 mL/min for 159 minutes gave Compound **1061** (t_R = 83 minutes; 62 mg). The solvent polarity was increased to 35% EtOH/hexane, and further elution at 10 mL/min gave Compound **1062** (t_R = 163 minutes; 72 mg).

EXAMPLE 85

Preparation of Compounds **1049, 1054, 1059 & 1060**



Step A

In a 20-mL microwave tube, **Int-84b** (229 mg, 0.37 mmol), **Int-7d** (261 mg, 0.82 mmol), and (dppf)$PdCl_2$•CH_2Cl_2 (15 mg, 0.019 mmol) were combined. The tube was sealed, evacuated, and placed under nitrogen atmosphere. Dioxane (4 mL) and aqueous potassium carbonate (3 mL, 1 M, 3 mmol) was added. The reaction mixture was allowed to stir for about 15 hours at 90 °C, then allowed to cool to room temperature. The reaction mixture was diluted with EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified

using flash column chromatography on silica gel (0-100% EtOAc(containing 10% MeOH)—hexanes) to provide **Int-85a** (212 mg, 69% yield).

Step B

In a 125-mL round-bottom flask, **Int-85a** (456 mg, 0.55 mmol) was dissolved in methanol (11 mL). HCl (5.5 mL, 2 M in diethyl ether, 11 mmol) was added and the reaction mixture was allowed to stir for about 15 hours at room temperature. The reaction mixture was concentrated *in vacuo* to provide **Int-85b** (425 mg, quantitative yield).

Step C

In a 125-mL round-bottom flask, **Int-85b** (439 mg, 0.62 mmol) and **Int-1a** (274 mg, 1.56 mmol) were dissolved in DMF (8 mL) and diisopropylethylamine (0.76 mL, 0.56 g, 4.3 mmol) was added. The reaction mixture was cooled to 0 °C and was allowed to stir for 15 minutes. HATU (475 mg, 1.24 mmol) was added and the reaction mixture was allowed to stir at 0 °C for 30 minutes, and then at room temperature for 2 hours. The reaction mixture was poured into water (30 mL). The precipitate was collected by filtration, then dissolved in EtOAc (200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude product was purified using reverse-phase C18 chromatography (Gilson, 0-90% CH_3CN (+ 0.1% TFA)—water (+ 0.1% TFA) over 15 minutes) to provide Compound **1049** as a yellow foam (362 mg, 62% yield).

Step D

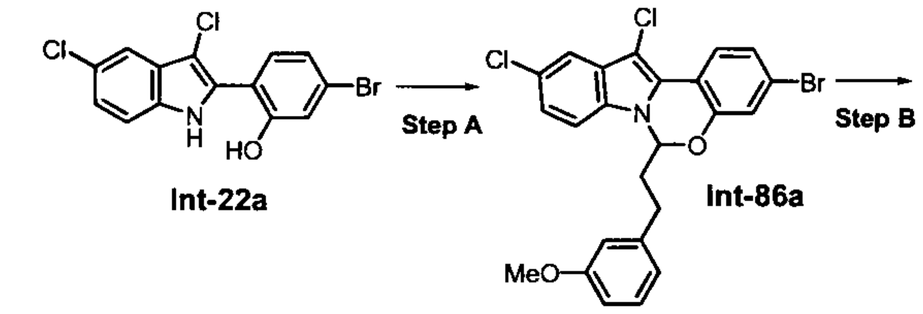
Compound **1049** (362 mg, 0.383 mmol) was dissolved in methanol (20 mL) and palladium (163 mg, 10 wt% on carbon, containing 50 wt% water) was added. The reaction mixture was hydrogenated for 71 hours, at which point LCMS analysis showed only a trace amount of remaining starting material. The reaction mixture was filtered and the catalyst was rinsed with methanol (~100 mL). The filtrate was concentrated, adsorbed onto silica gel (15 mL), then purified using flash column chromatography on silica gel (0-10% MeOH (+1% NH_4OH)/CH_2Cl_2) to provide Compound **1054** (231 mg, 66% yield).

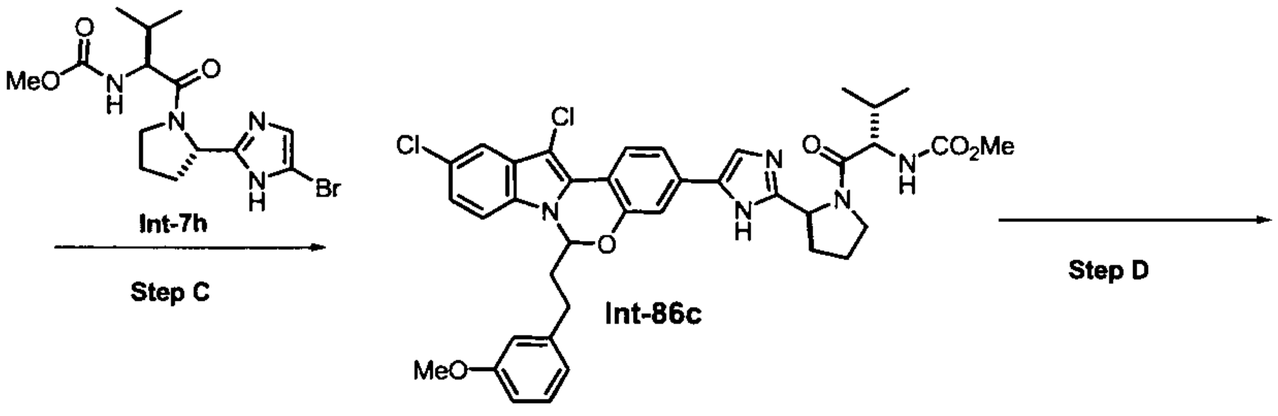
Step E

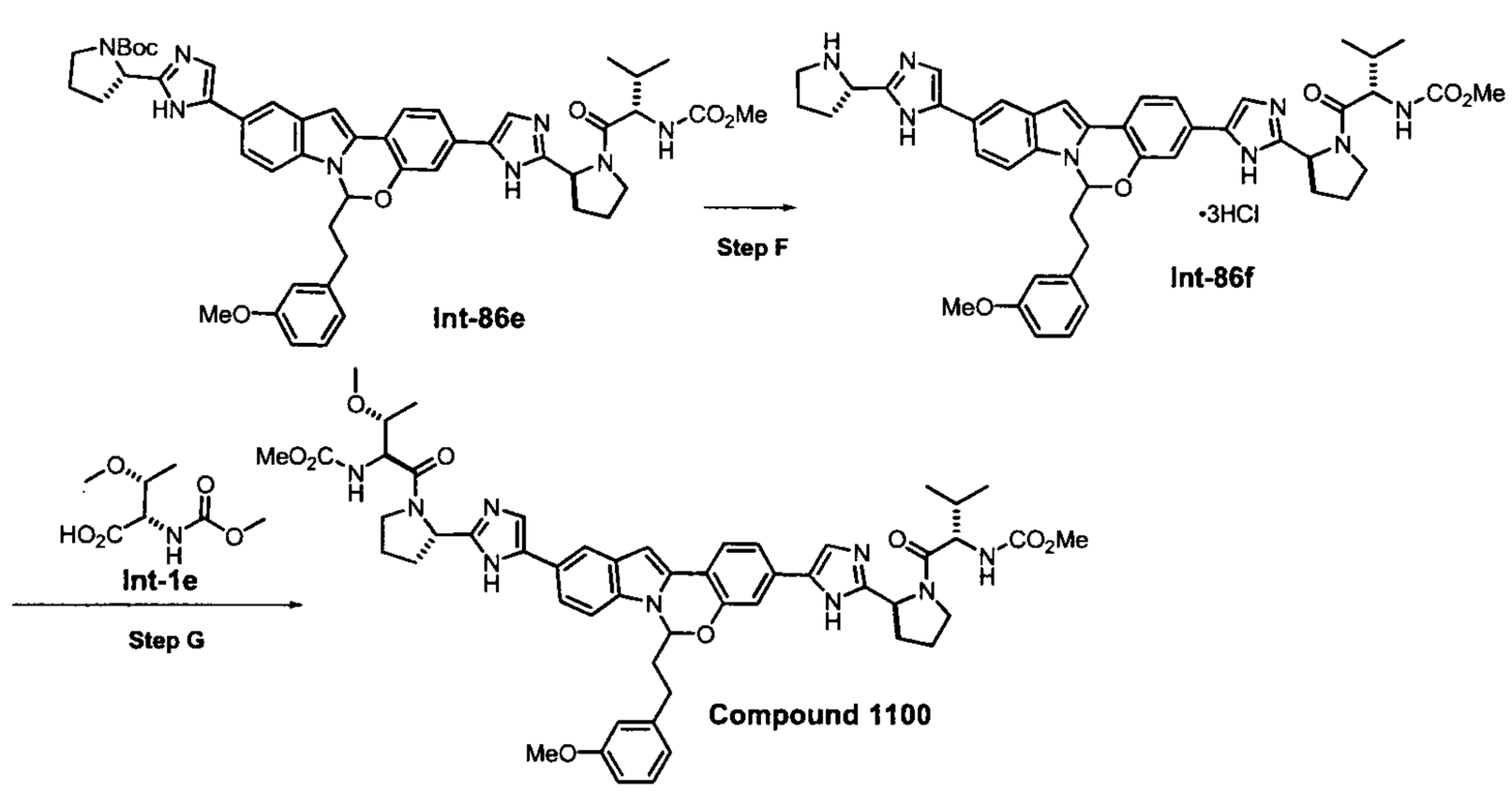
The isomers comprising Compound **1054** were separated by HPLC. Compound **1054** (222 mg) was dissolved in abs. EtOH (6.0 mL) and the solution was filtered. The sample was divided into two equal portions, each of which was injected onto a Phenomenex Lux Cellulose-2 (5 μm, 150 x 21.20 mm) semi-preparative column; detection wavelength = 350 nm. Elution with 45% EtOH/hexane (+ 0.1% diethylamine) @ 10 mL/min gave Fraction A: Compound **1059** (t_R = 32 minutes, 91 mg) and Fraction B: Compound **1060** (t_R = 97 minutes, 68 mg).

EXAMPLE 86

Preparation of Compound **1100**







Step A

A 20-mL microwave tube was charged with **Int-22a** (1.0 g, 2.8 mmol), 3-(3'-methoxyphenyl)propanal (2.3 g, 14 mmol), *p*-toluenesulfonyl chloride (53 mg, 0.280 mmol) and dissolved in toluene (9 mL). The tube was sealed and heated in a microwave with stirring at 170 °C. After 12 hours the reaction was concentrated partially *in vacuo*,

and the residue was adsorbed onto silica gel (20 mL). The crude product was purified using flash column chromatography on silica gel (Eluent: 0-10% EtOAc: hexanes) to provide **Int-86a** (1.39 g, 99% yield)

Step B

A20-mL microwave tube was charged with, **Int-86a** (1.39 g, 2.76 mmol), bis(pinacolato)diboron (772 mg, 3.04 mmol), (dppf)$PdCl_2$•CH_2Cl_2 (202 mg, 0.276 mmol) and KOAc (813 mg, 8.29 mmol). The tube was sealed, evacuated, and placed under nitrogen atmosphere. Dioxane (11 mL) was added, the reaction was allowed to stir at 90 °C for 2 hours, and then allowed to cool to room temperature. EtOAc (40 mL) and water (40 mL) were added . The aqueous layer was extracted with EtOAc (2 x 40 mL). Combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified using flash column chromatography on silica gel (Eluent 0-30% EtOAc/hexanes) to provide **Int-86b** (1.07 g, 70% yield).

Step C

A 20-mL microwave tube was charged with **Int-86b** (500 mg, 0.91 mmol), **Int-7h** (373 mg, 0.999 mmol), and (dppf)$PdCl_2$•CH_2Cl_2 (67 mg, 0.091 mmol). The tube was sealed, evacuated, and placed under nitrogen atmosphere. Dioxane (9 mL) and aqueous potassium carbonate (2.7 mL, 1 M, 2.7 mmol) was added and the reaction was allowed to stir for about 15 hours at 80 °C. After cooling to room temperature, EtOAc (50 mL) and water (50 mL) were added. and the layers separated. The aqueous layer was extracted with EtOAc (2 x 10 mL), and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified using flash column chromatography on silica gel (Eluent: 0-100% EtOAc/hexanes) to provide **Int-86c** (385 mg, 59% yield).

Step D

In a 20-mL microwave tube, **Int-86c** (380 mg, 0.530 mmol), bis(pinacolato)diboron (336 mg, 1.3 mmol), $(dba)_3Pd_2$•$CHCl_3$ (55 mg, 0.053 mmol), X-

Phos (51 mg, 0.106 mmol) and KOAc (156 mg, 1.61 mmol) were combined. The tube was sealed, evacuated, and placed under nitrogen atmosphere. Dioxane (5.3 mL) was added and the reaction was allowed to stir at 120 °C for 1 hour, then allowed to cool to room temperature. The reaction mixture was diluted with EtOAc (20 mL) and washed sequentially with water (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified using flash column chromatography on silica gel (Eluent: 0-100% EtOAc/hexanes) to provide **Int-86d** (382 mg, 93% yield).

Step E

In a 20-mL microwave tube, **Int-86d** (302 mg, 0.391 mmol), **Int-7d** (124 mg, 0.391 mmol), and (dppf)$PdCl_2$•CH_2Cl_2 (32 mg, 0.039 mmol) were combined. The tube was sealed, evacuated, and placed under nitrogen atmosphere. Dioxane (8 mL) and aqueous potassium carbonate (1.2 mL, 1 M, 1.2 mmol) was added. The reaction was allowed to stir for about 15 hours at 80 °C, then allowed to cool to room temperature. The reaction mixture was diluted with EtOAc (200 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified using flash column chromatography on silica gel (Eluent: 0-100% EtOAc (containing 10% MeOH)—hexanes) to provide **Int-86e** (78 mg, 22% yield).

Step F

A 125-mL round-bottom flask was charged with **Int-86e** (81 mg, 0.092 mmol) and methanol (2 mL). HCl (0.84 mL, 2 M in diethyl ether, 1.7 mmol) was added and the reaction was allowed to stir for about 15 hours at room temperature. The reaction mixture was concentrated *in vacuo* to provide **Int-86f** (109 mg, quantitative yield).

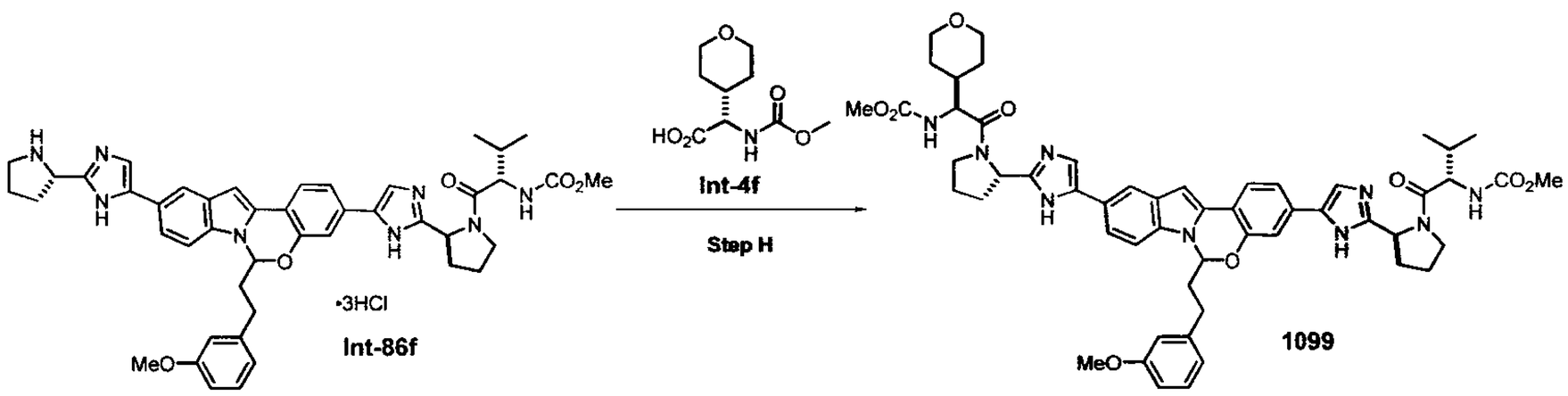
Step G

A 25-mL round-bottom flask was charged with **Int-1e** (53 mg, 0.067 mmol), **Int-86f** (15.5 mg, 0.081 mmol) and DMF (1 mL). Diisopropylethylamine (82 uL, 61 mg, 0.472 mmol) was added to the solution. The reaction mixture was cooled to 0 °C,

stirred for 15 minutes and HATU (395 mg, 1.04 mmol) was added. The reaction mixture was allowed to stir at 0 °C for 30 minutes, and then at room temperature for 2 hours. Additional diisopropylethylamine (20 uL, 2 eq) was added and the reaction was allowed to proceed for an additional 1 hour. The reaction mixture was diluted with EtOAc (30 mL) and poured into water (30 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic phase were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude product was purified using reverse-phase C18 chromatography (Gilson, 0-90% CH_3CN (+ 0.1% TFA)—water (+ 0.1% TFA) over 15 minutes) to provide Compound **1100** as a yellow solid (31 mg, 48% yield).

EXAMPLE 87

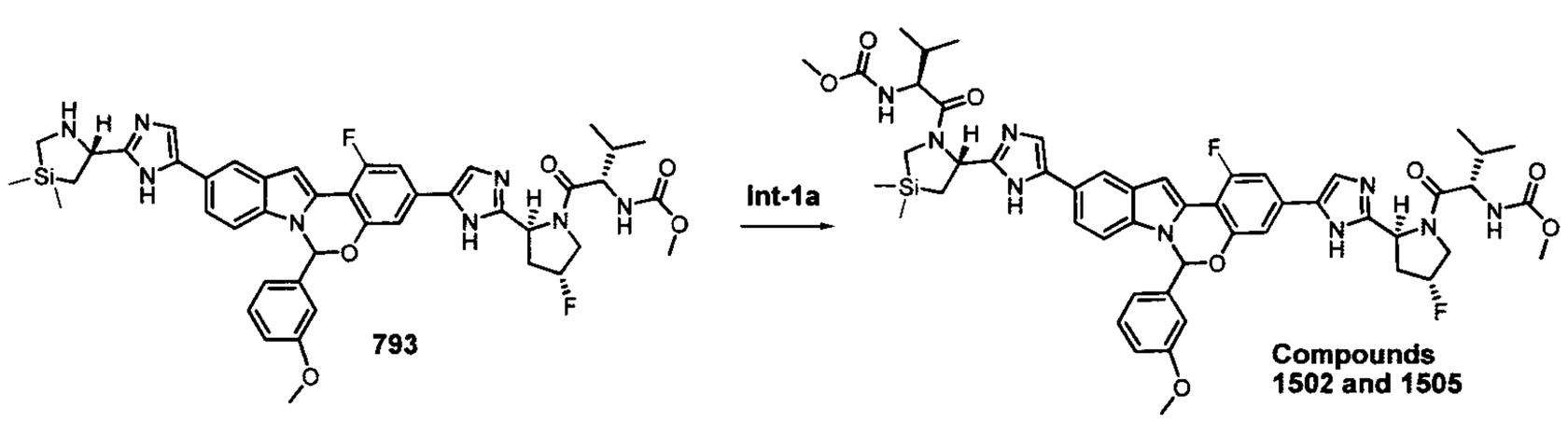
Preparation of Compound **1099**



A 25-mL round-bottom flask was charged with **Int-86f** (53 mg, 0.067 mmol), **Int-4f** (18 mg, 0.081 mmol), DMF (1 mL) and diisopropylethylamine (82 uL, 61 mg, 0.47 mmol). The reaction mixture was cooled to 0 °C and was allowed to stir for 15 minutes. HATU (26 mg, 0.067 mmol) was added and the reaction mixture was allowed to stir at 0 °C for 30 minutes, and then at allowed to warm to room temperature over 2 hours. Additional **Int-4f** (8.8 mg, 0.6 eq), HATU (5 mg, 0.2 eq) and diisopropylethylamine (20 uL, 2 eq) were added and the reaction was allowed to proceed for an additional 1 hour. The reaction was diluted with EtOAc (30 mL) and poured into water (30 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organic phase were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified using reverse-phase C18 chromatography (Gilson, 0-90% CH_3CN (+ 0.1% TFA)—water (+ 0.1% TFA) over 15 minutes) to provide Compound **1099** as a yellow solid (28 mg, 43% yield).

EXAMPLE 88

Preparation of Compounds **1502 and 1505**



Compound **793** (prepared as above in example 57 from **Int-14d** and **Int-19j)** (38 mg, 0.039 mmol) and **Int-1a** (7.5 mg, 0.04 mmol) using the method described in Example 57, step E to provide Isomeric Compounds **1502** and **1505** (19 mg, 46% yield).

EXAMPLE 89

Cell-Based HCV Replicon Assay

To measure cell-based anti-HCV activity of selected Compounds of the present invention, replicon cells were seeded at 5000 cells/well in 96-well collagen I-coated Nunc plates in the presence of the test Compound. Various concentrations of test Compound, typically in 10 serial 2-fold dilutions, were added to the assay mixture, with the starting concentration ranging from 250 μM to 1 μM. The final concentration of DMSO was 0.5%, fetal bovine serum was 5%, in the assay media. Cells were harvested on day 3 by the addition of 1x cell lysis buffer (Ambion cat #8721). The replicon RNA level was measured using real time PCR (Taqman assay). The amplicon was located in 5B. The PCR primers were: 5B.2F, ATGGACAGGCGCCCTGA (SEQ ID NO. 1); 5B.2R, TTGATGGGCAGCTTGGTTTC (SEQ ID NO. 2); the probe sequence was FAM-labeled CACGCCATGCGCTGCGG (SEQ ID NO. 3). GAPDH RNA was used as endogenous control and was amplified in the same reaction as NS5B (multiplex PCR) using primers and VIC-labeled probe recommended by the manufacturer (PE Applied Biosystem). The real-time RT-PCR reactions were run on ABI PRISM 7900HT Sequence Detection System using the following program: 48°C for 30 minutes, 95°C for 10 minutes, 40 cycles of 95°C for 15 sec, 60°C for 1 minutes. The ΔCT values (CT_{5B}-CT_{GAPDH}) were

plotted against the concentration of test Compound and fitted to the sigmoid dose-response model using XLfit4 (MDL). EC_{50} was defined as the concentration of inhibitor necessary to achieve ΔCT=1 over the projected baseline; EC_{90} the concentration necessary to achieve ΔCT=3.2 over the baseline. Alternatively, to quantitate the absolute amount of replicon RNA, a standard curve was established by including serially diluted T7 transcripts of replicon RNA in the Taqman assay. All Taqman reagents were from PE Applied Biosystems. Such an assay procedure was described in detail in *e.g.* Malcolm *et al., Antimicrobial Agents and Chemotherapy* 50: 1013-1020 (2006).

HCV replicon assay EC_{90} data was calculated for selected Compounds of the present invention using this method and is provided in the table immediately below and in Table 2 in Example 89.

Compound No.	1a WT (nM)	1b WT (nM)	1a Y93H (nM)	2a WT (nM)	3a WT (nM)
31	0.004	0.003	15	0.05	1.2
32	0.002	0.002	3	0.007	0.3
61	0.036	0.011	14.6	0.27	2.7
62	0.011	0.006	8.4	0.12	3
63	0.005	0.003	1.8	0.045	2.7
64	0.013	0.008	6.2	0.083	4.8
66	0.006	0.004	27	0.06	2.7
67	0.005	0.008	29	0.1	2.5
68	0.002	0.002	0.02	0.21	1.0
69	0.001	0.001	0.6	0.11	1.8
75	0.005	0.006	28.937	0.006	0.465
76	0.010	0.005	68.123	0.018	5.367
79	0.004	0.004	28.273	0.010	1.357
84	0.012	0.007	6.086	NA	1.239
86	0.004	0.004	1.619	0.298	0.402
87	0.007	0.006	13	0.22	1.7

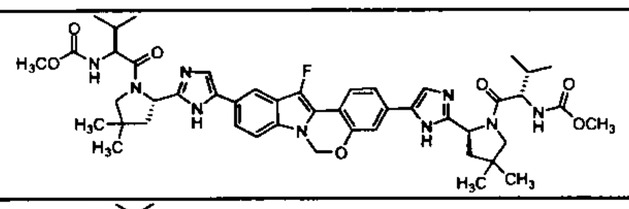
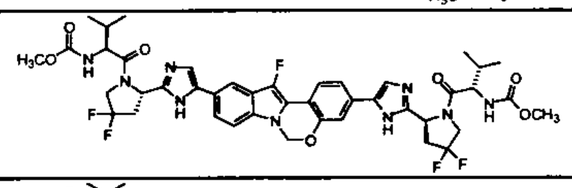
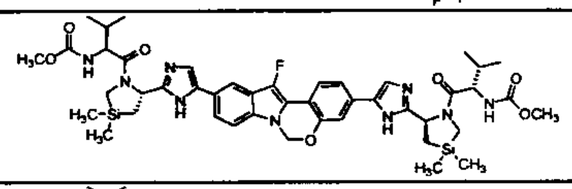
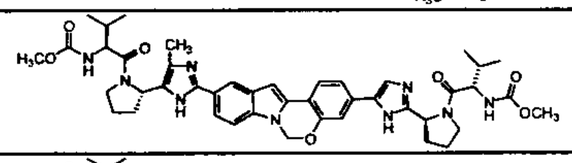
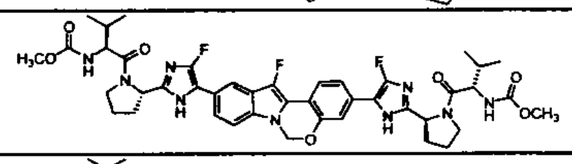
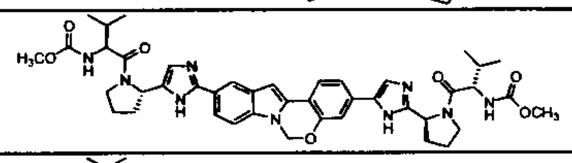
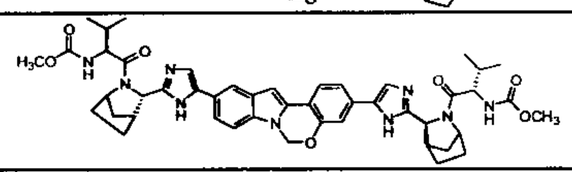
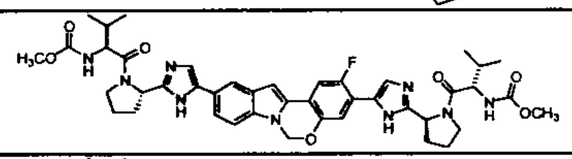
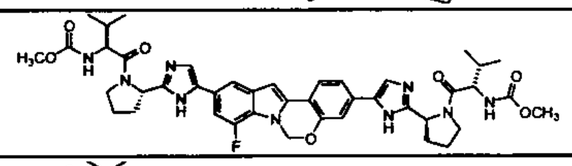
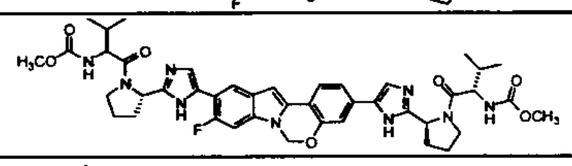
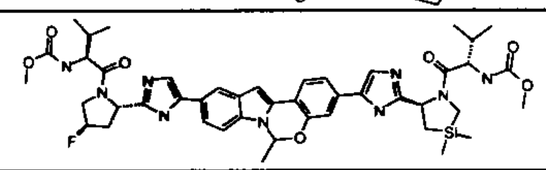
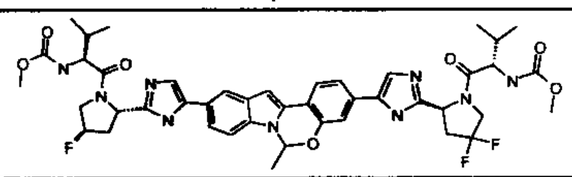
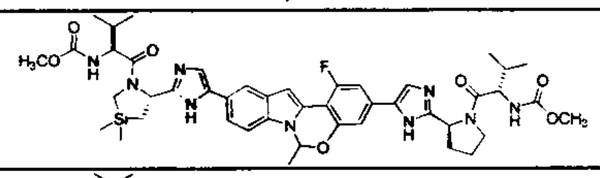
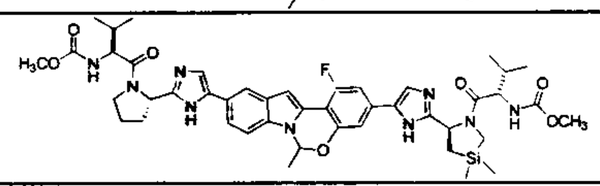
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89	0.014	0.022	77.94	0.682	3.921
90	0.012	0.004	2.840	NA	2.301
91	0.003	0.004	0.401	0.306	0.354
92	0.011	0.007	6	0.46	1.2
93	0.026	0.009	14.7	0.36	3
94	0.003	0.004	0.06	0.3	0.35
95	0.02	0.01	100	0.11	0.98
99	0.004	0.007	39	0.022	0.17
103	0.015	0.016	38	0.032	0.16
104	0.005	0.003	14	0.023	0.09
108	0.014	0.015	68	0.13	5.4
109	0.015	0.016	139	0.13	0.4
110	0.006	0.006	68	0.02	0.25
117	0.004	0.003	44	0.063	0.08
121	0.027	0.021	256	0.15	3.5
125	0.020	0.016	18	0.04	0.14
126	0.003	0.005	20	0.066	>10
129	0.016	0.009	80	0.047	0.65
130	0.03	0.006	211	0.3	5.8
133	0.002	0.002	32	0.15	0.58
136	0.006	0.006	78	0.07	0.31
143	0.020	0.013	26	0.23	0.31
145	0.004	0.005	8	0.007	0.1
149	0.004	0.004	29	0.04	0.4
150	0.001	0.003	7	0.11	0.21
153	0.003	0.003	12	0.008	0.074

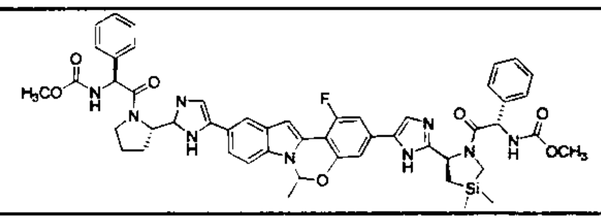
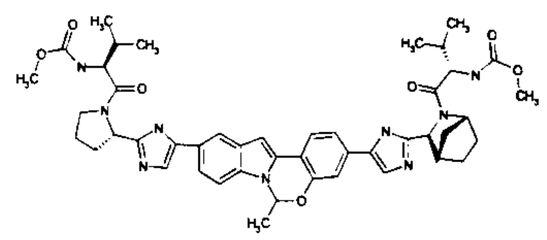
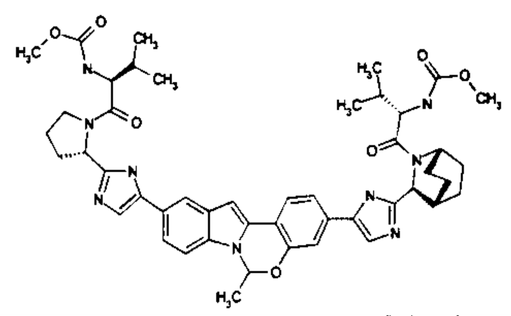
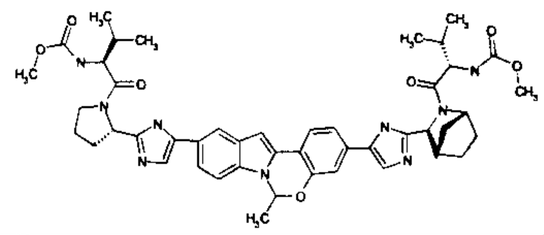
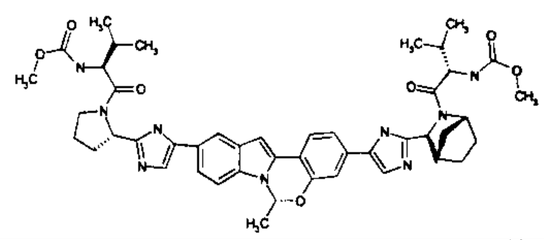
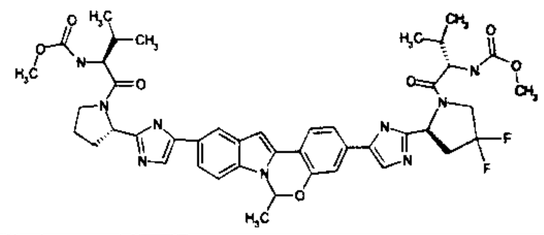
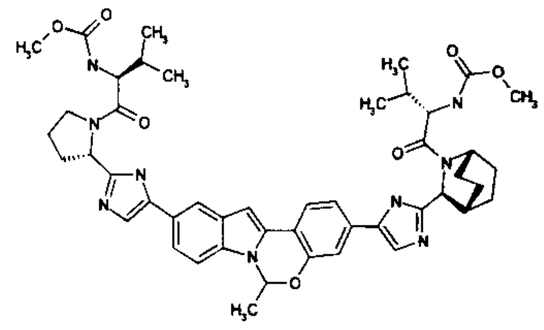
EXAMPLE 90

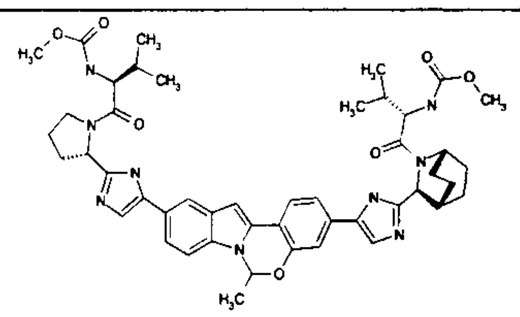
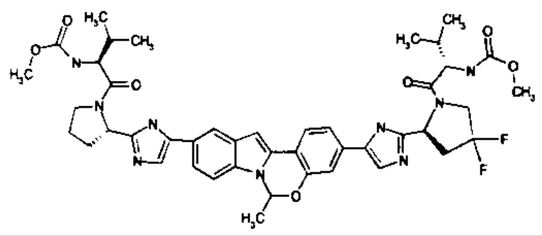
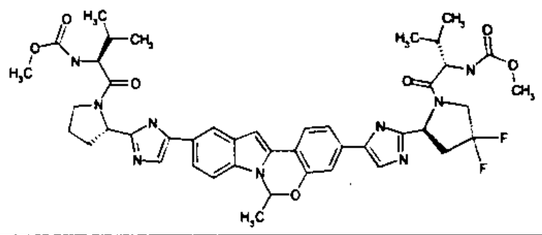
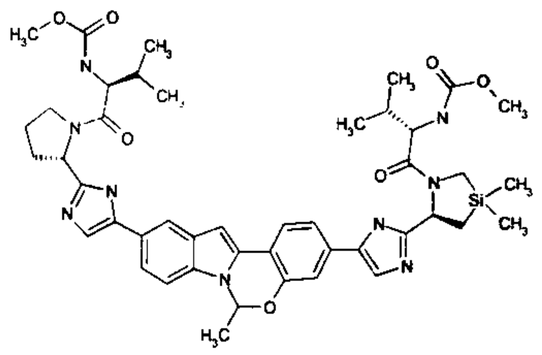
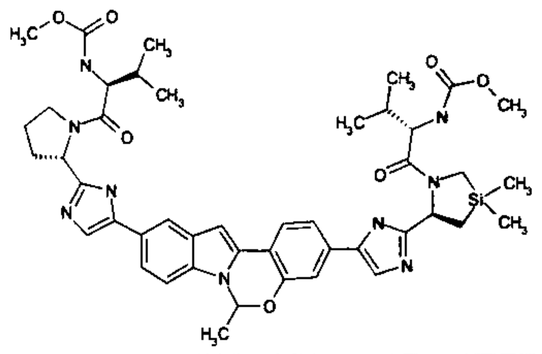
Additional Compounds of the Invention

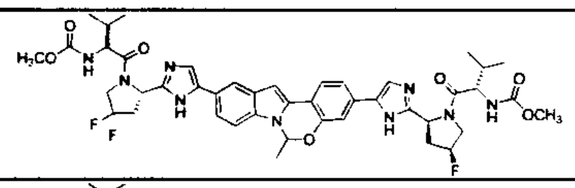
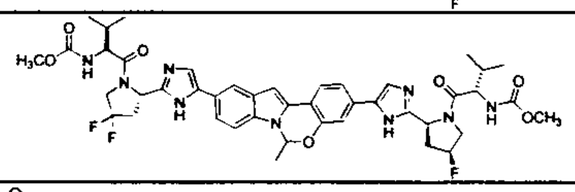
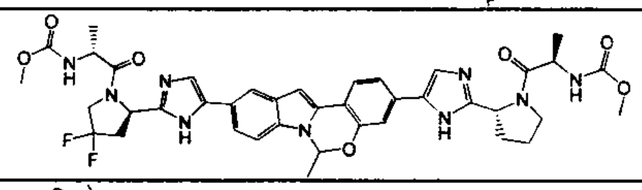
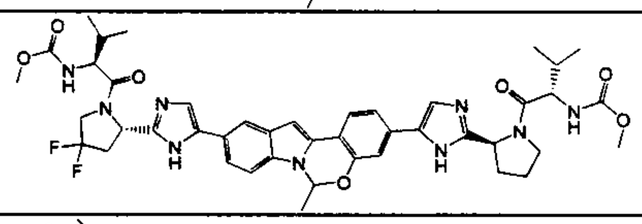
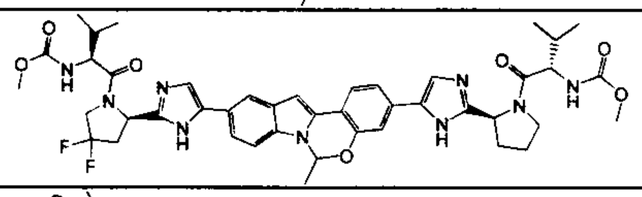
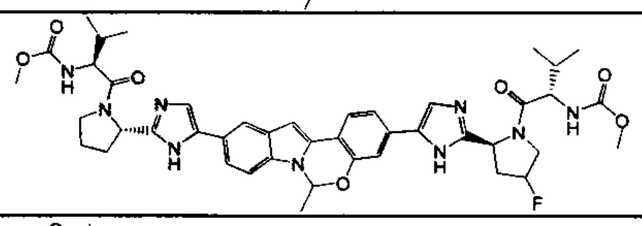
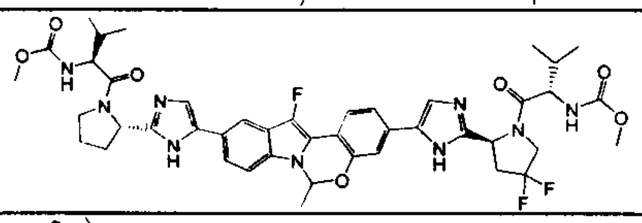
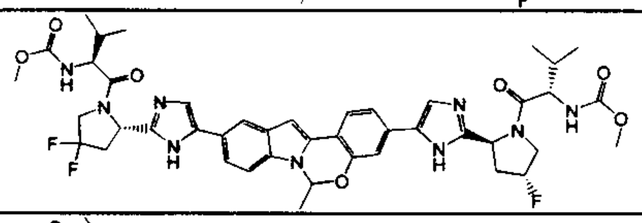
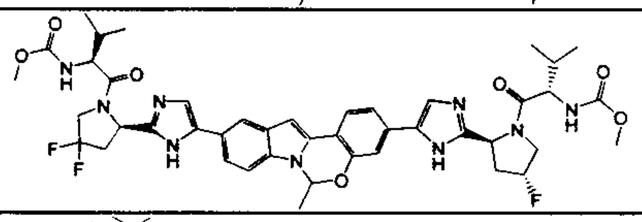
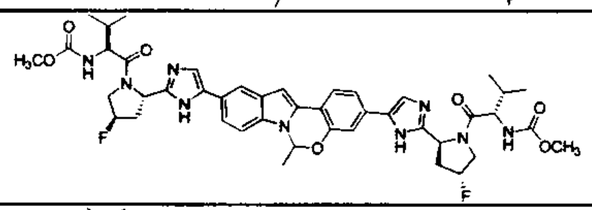
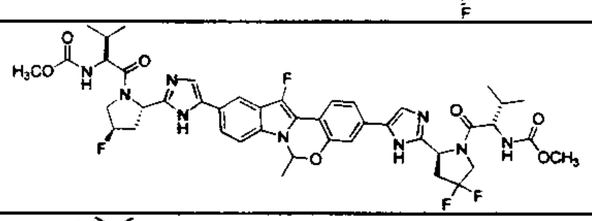
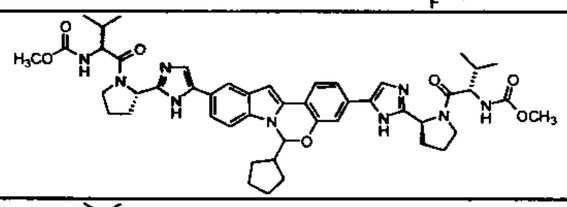
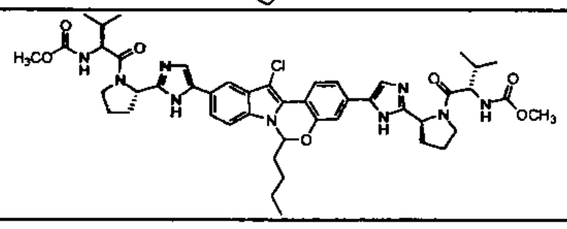
Additional illustrative compounds of the present invention are set forth below in Table 2. The Replicon data provided for selected compounds depicted in Table 2 was generated using the method described in Example 89.

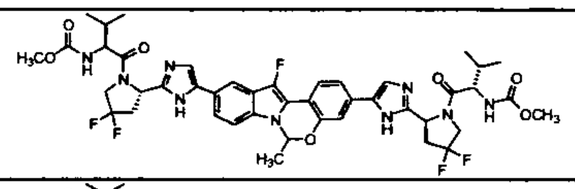
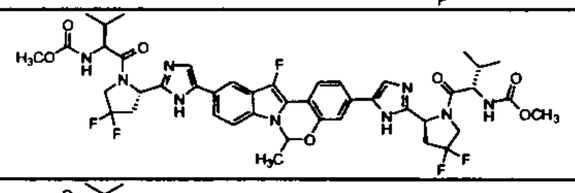
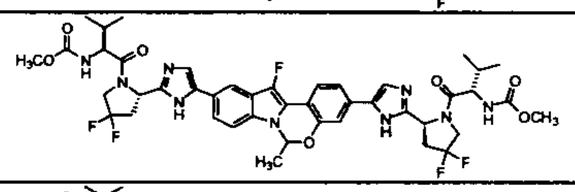
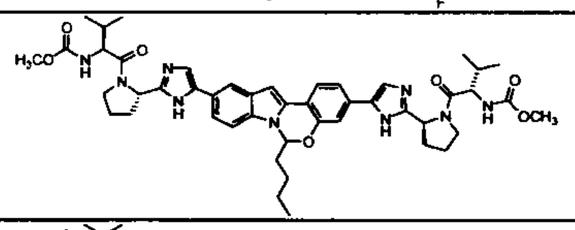
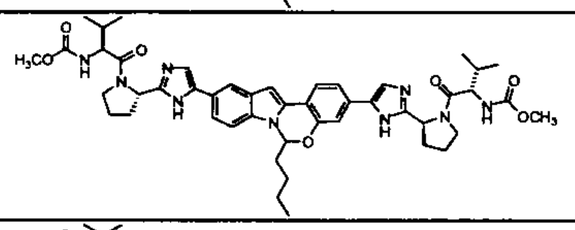
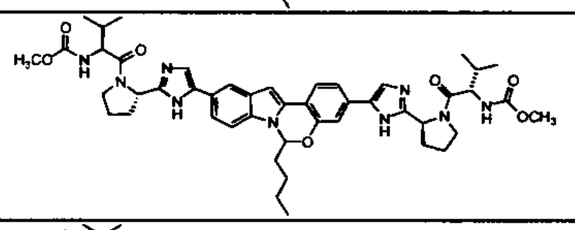
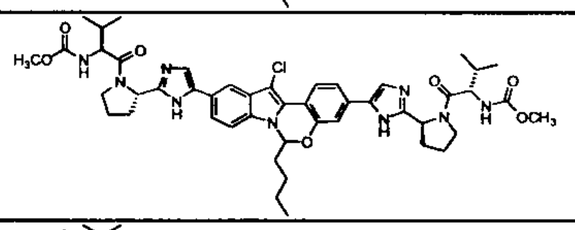
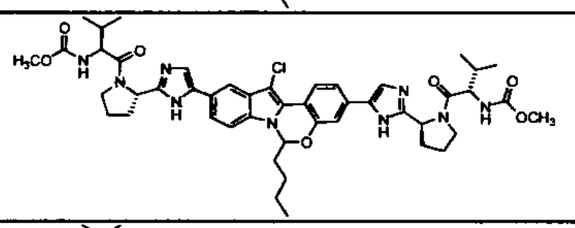
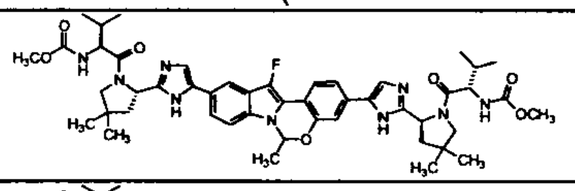
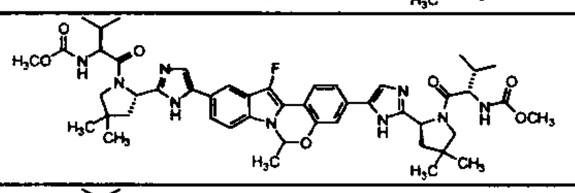
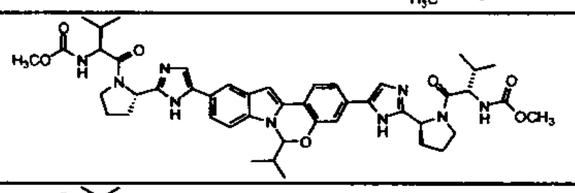
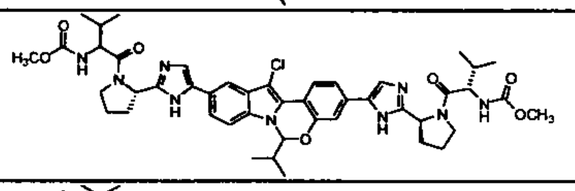
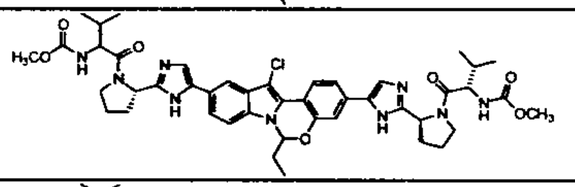
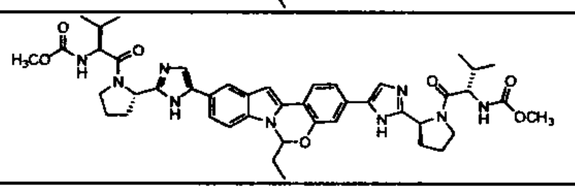
Table 1

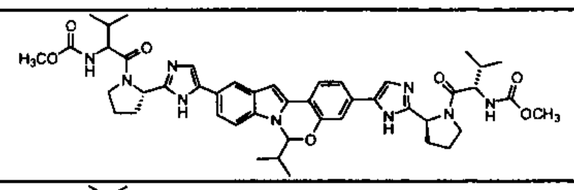
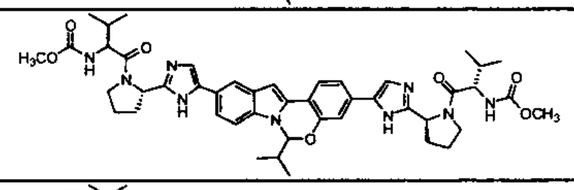
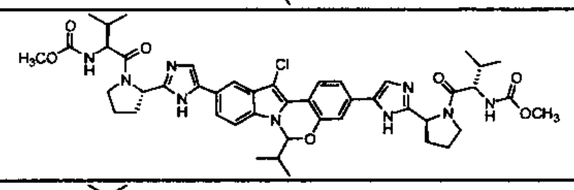
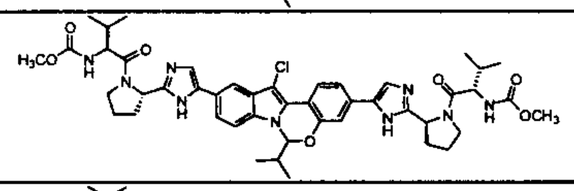
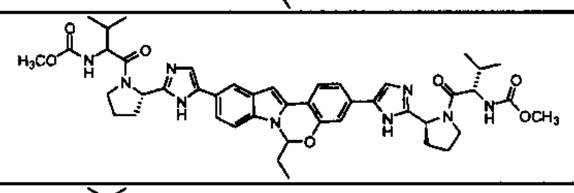
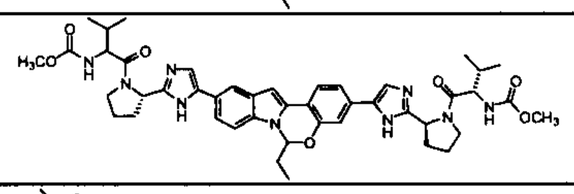
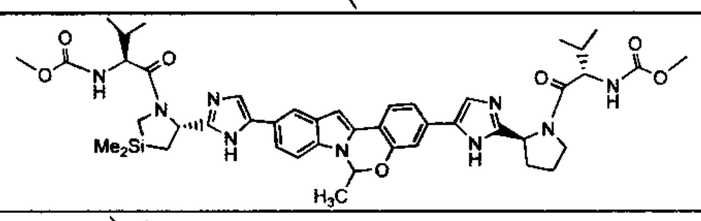
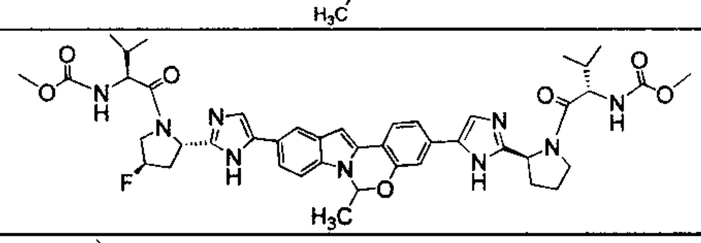
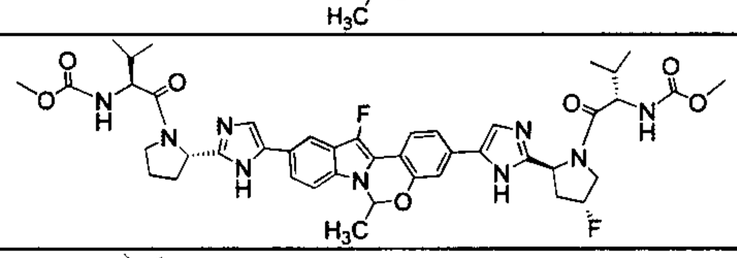
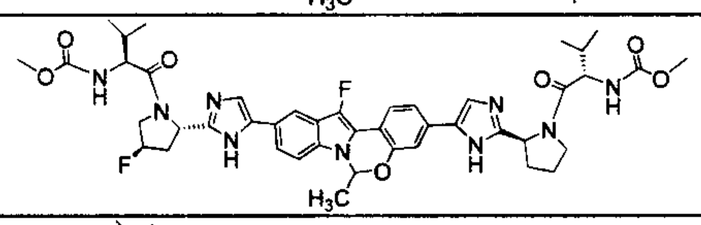
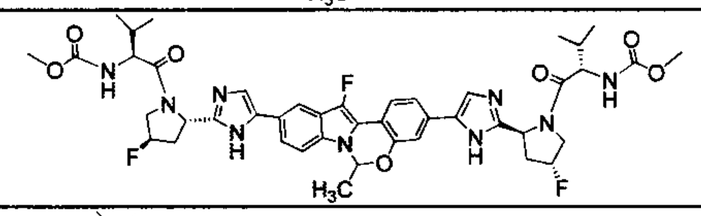
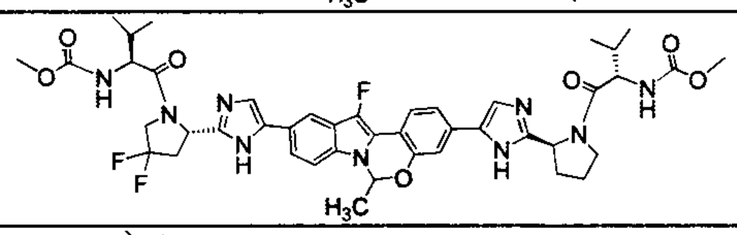
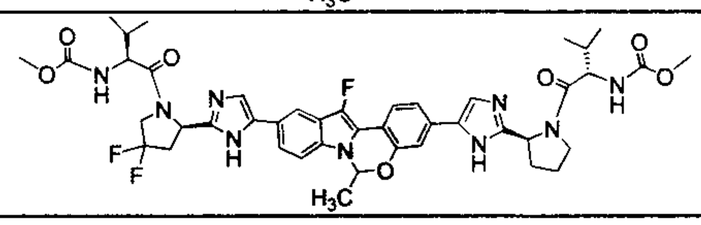
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2		897
3		912
4		820
5		861
6		806
7		877
8		825
9		825
10		825
11		882.5 (M+1)
12		874.5 (M+1)
13		883
14		883

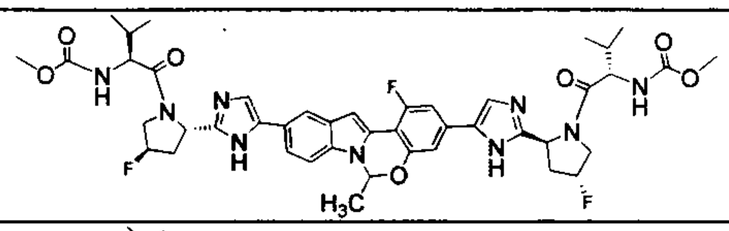
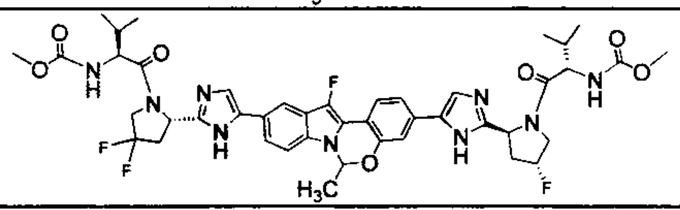
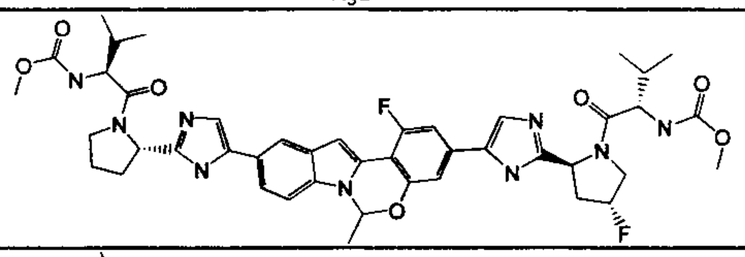
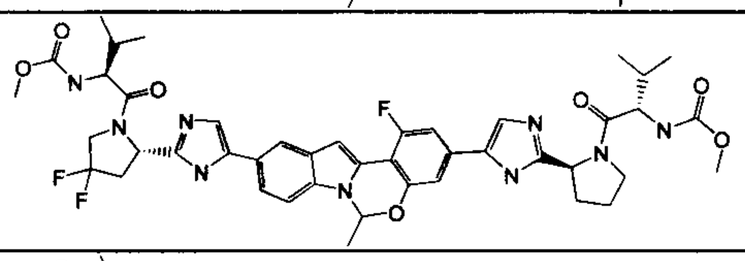
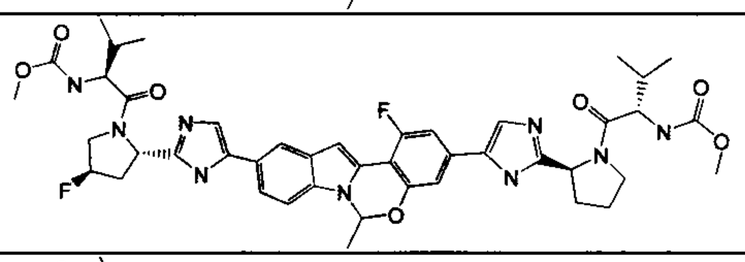
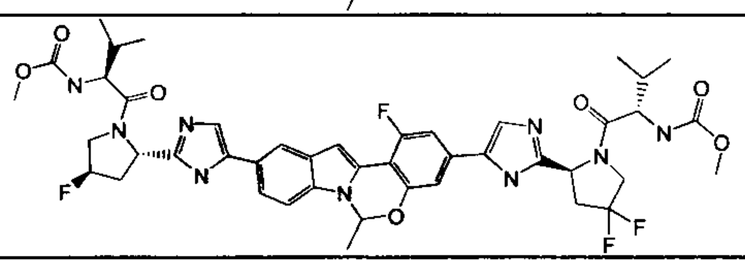
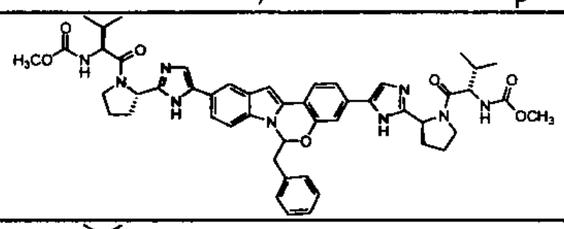
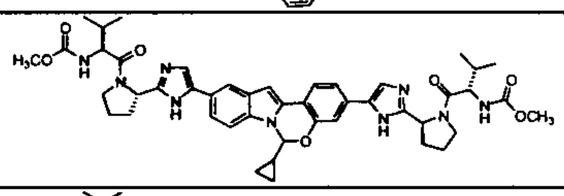
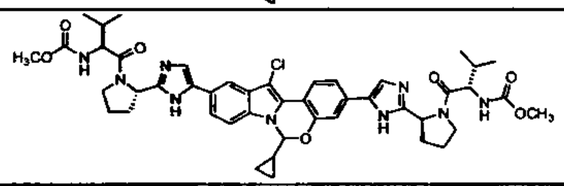
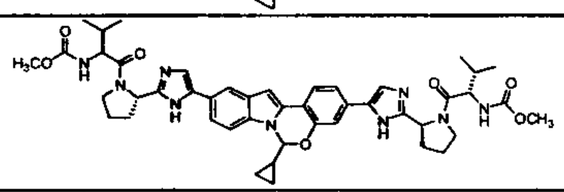
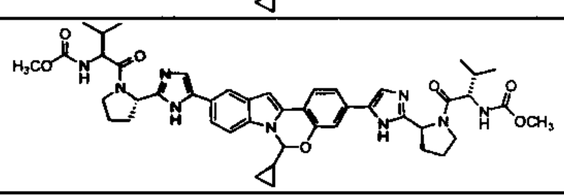
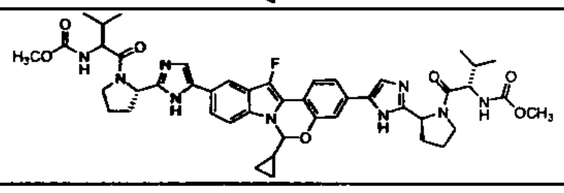
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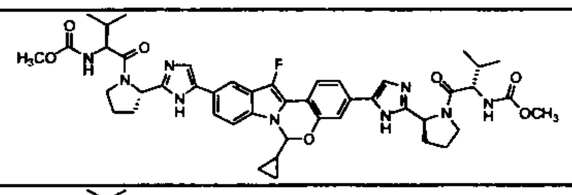
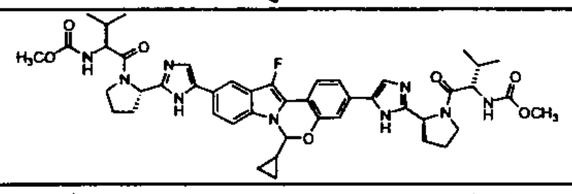
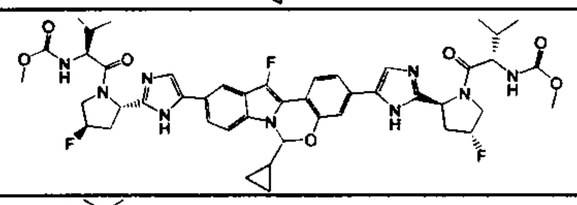
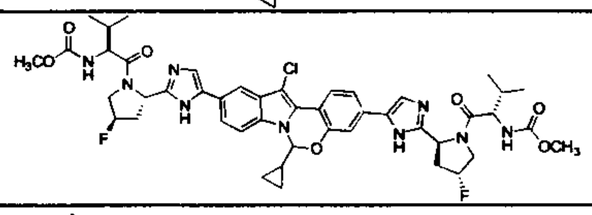
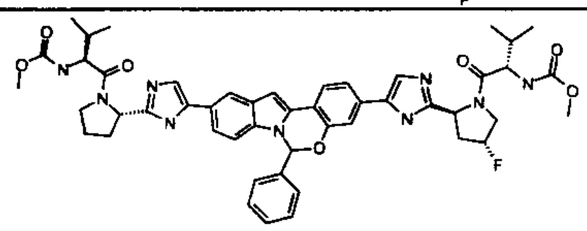
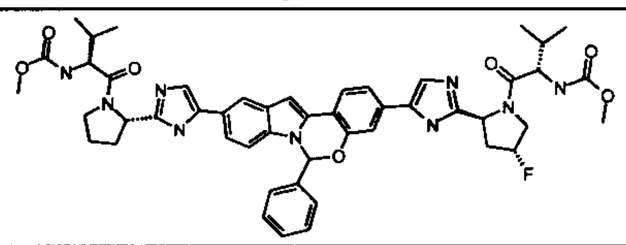
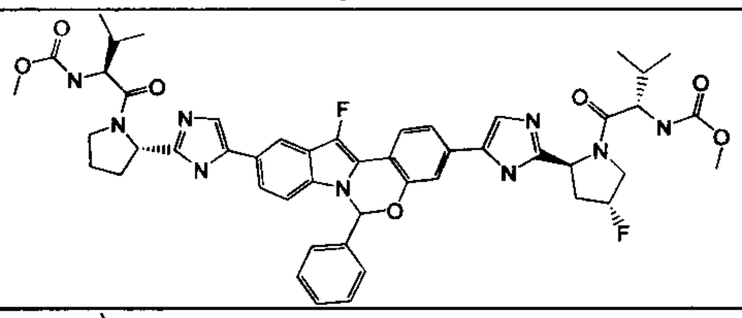
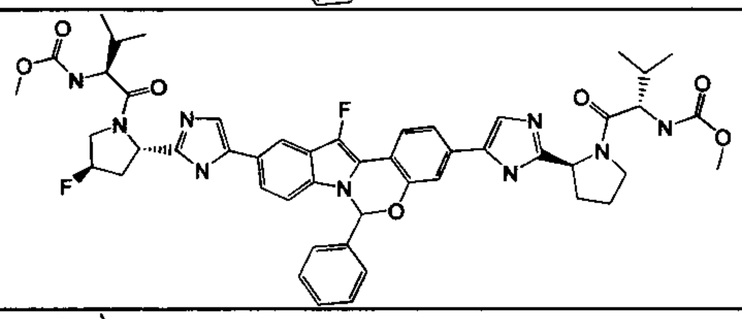
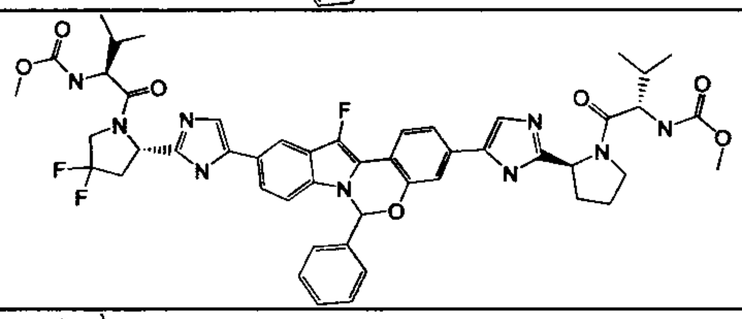
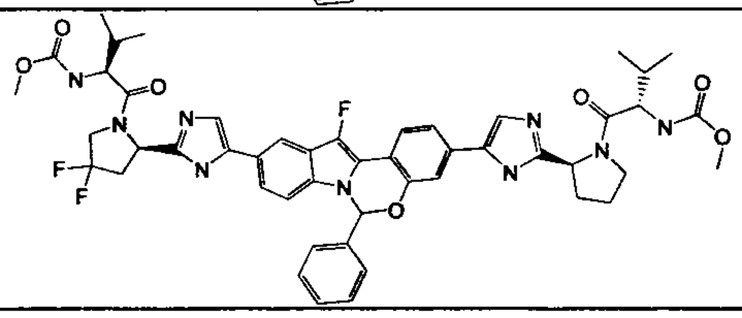
		
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24		856.5
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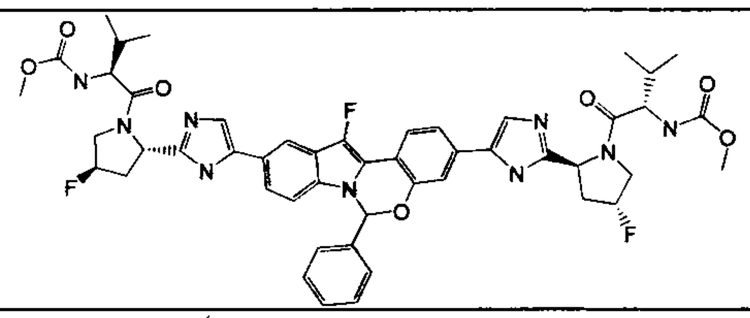
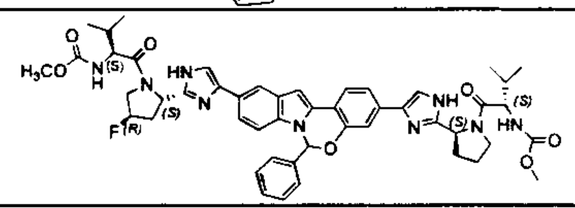
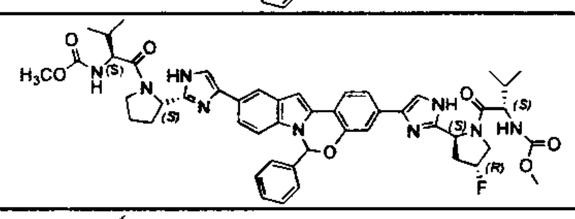
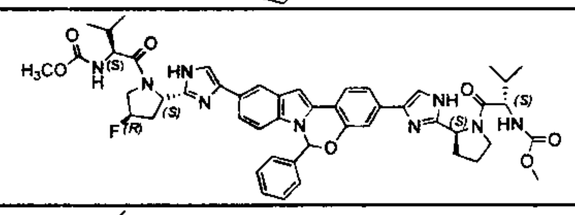
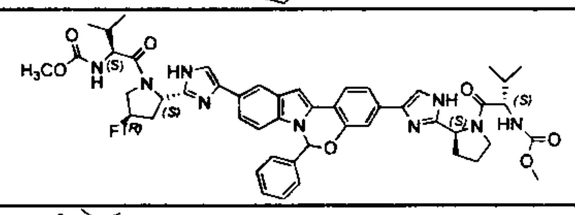
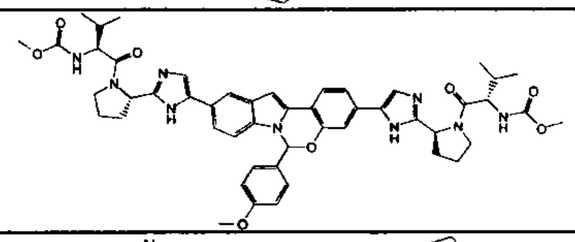
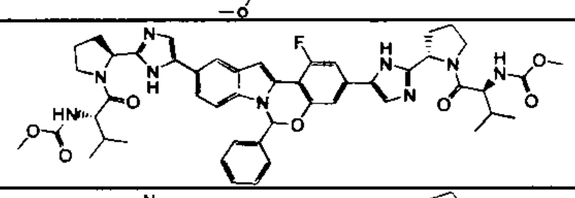
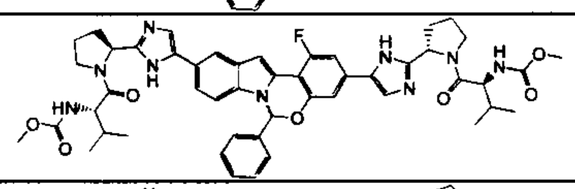
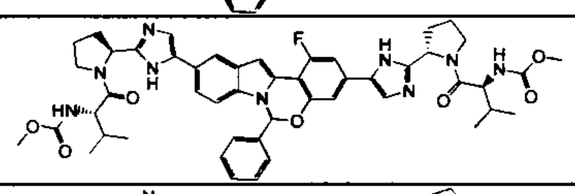
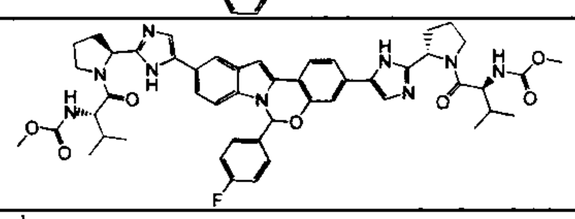
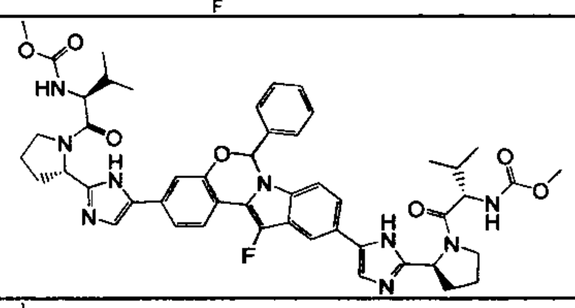
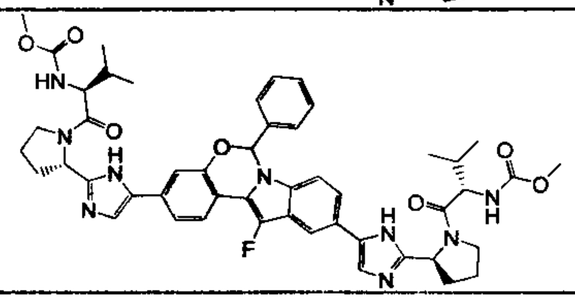
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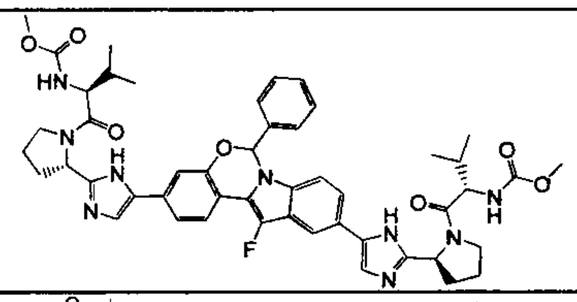
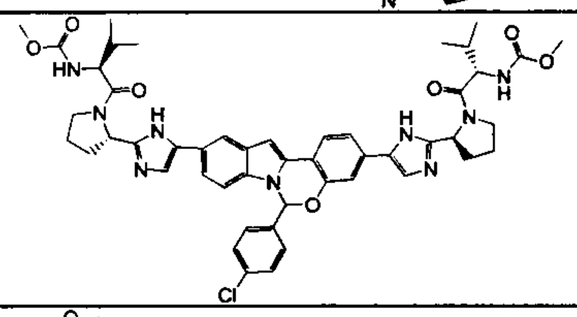
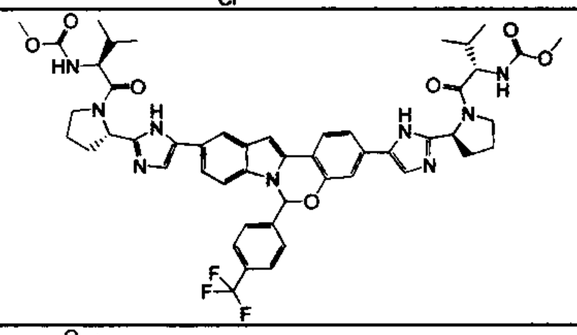
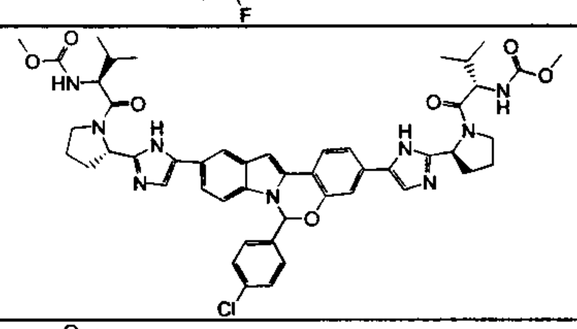
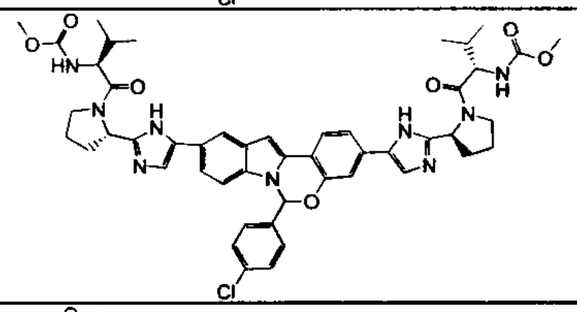
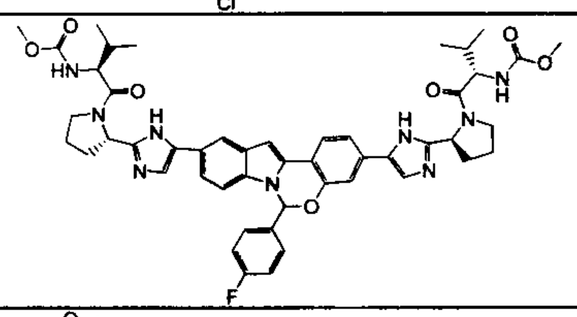
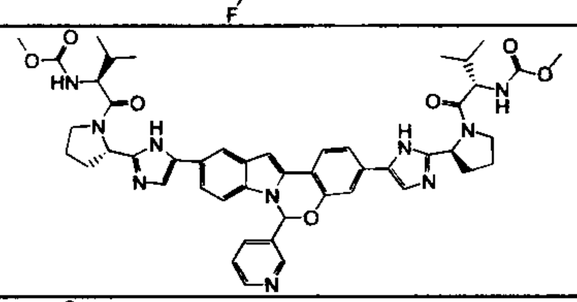
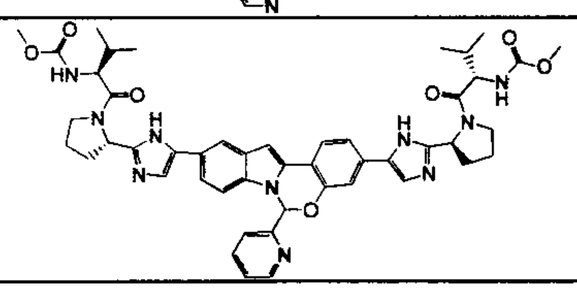
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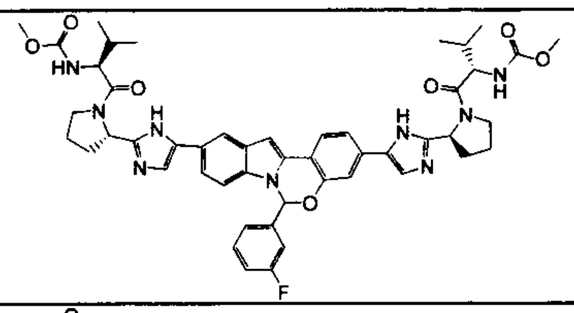
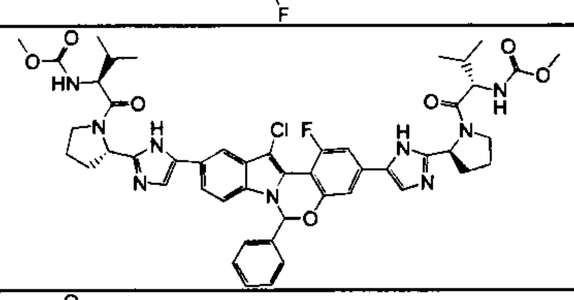
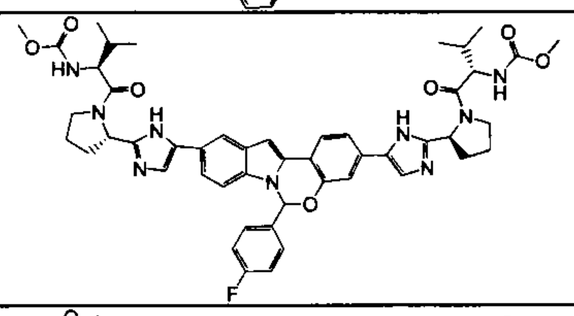
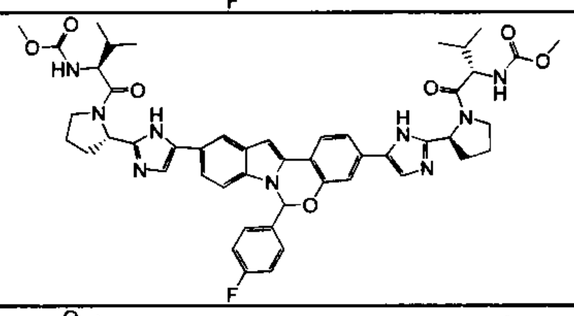
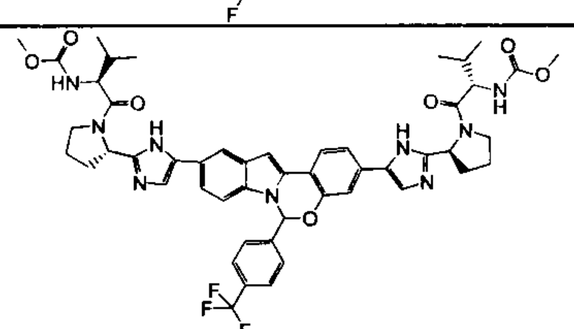
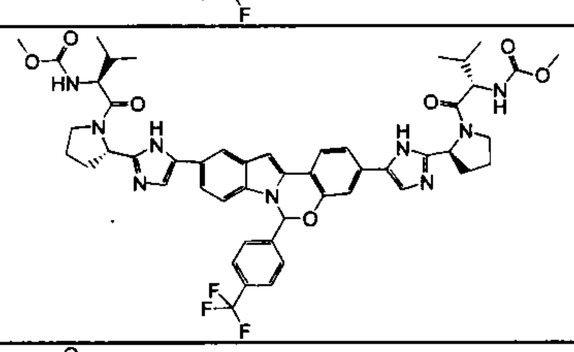
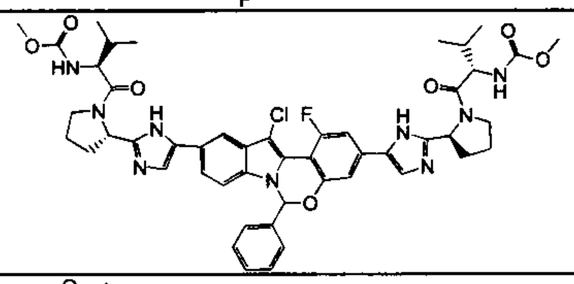
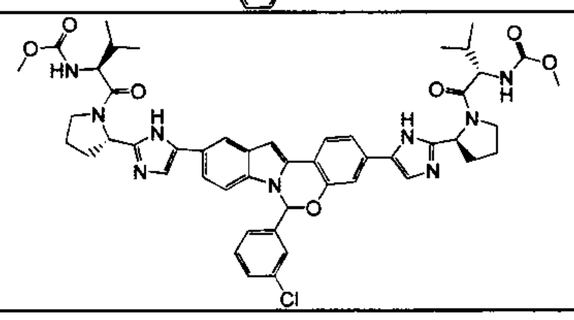
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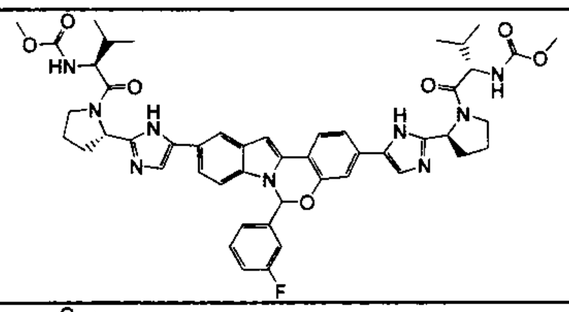
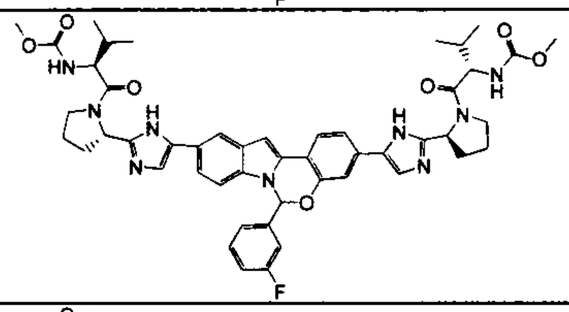
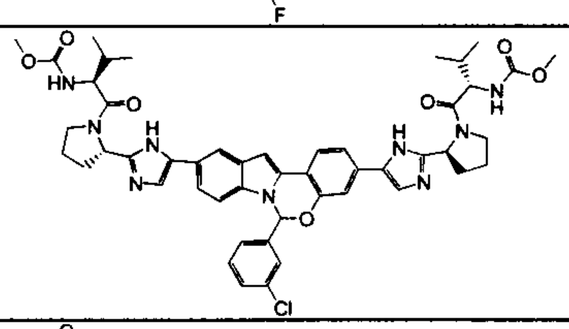
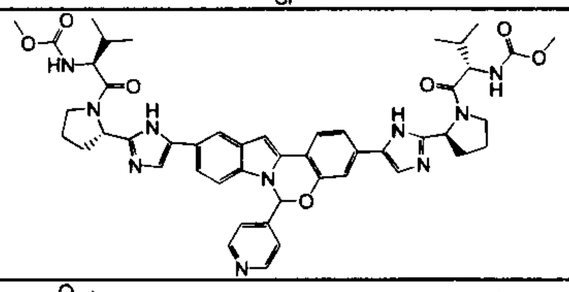
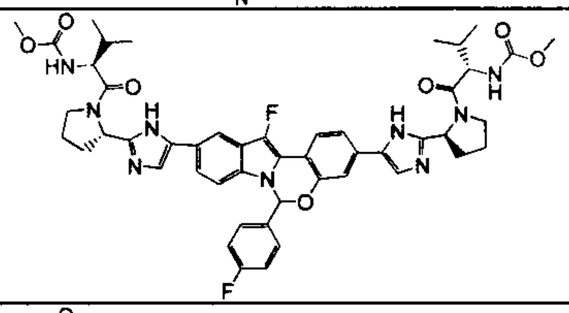
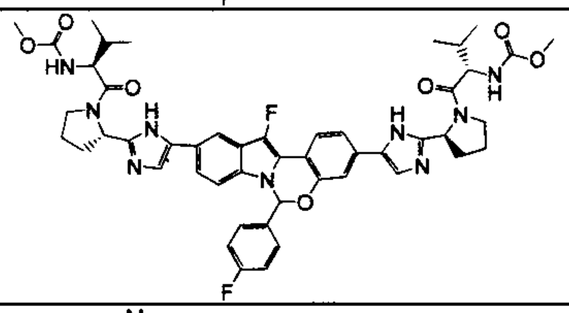
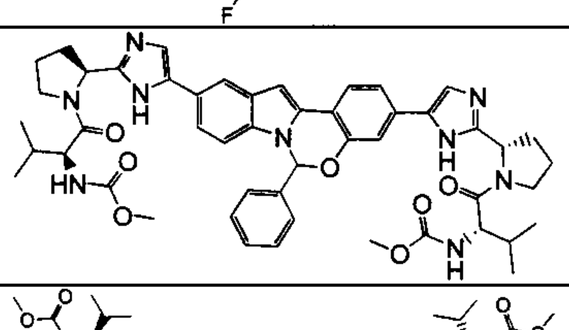
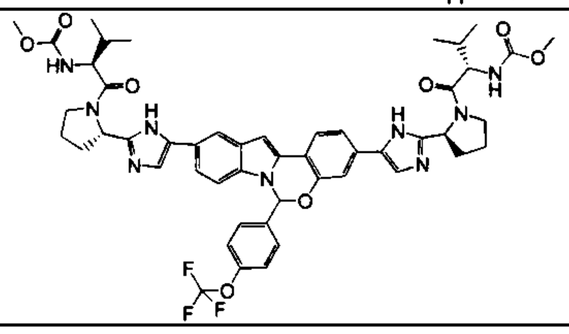
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79		865

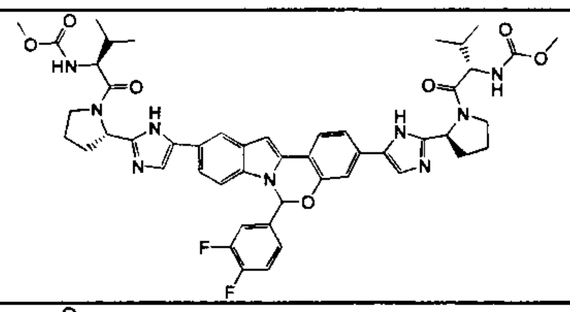
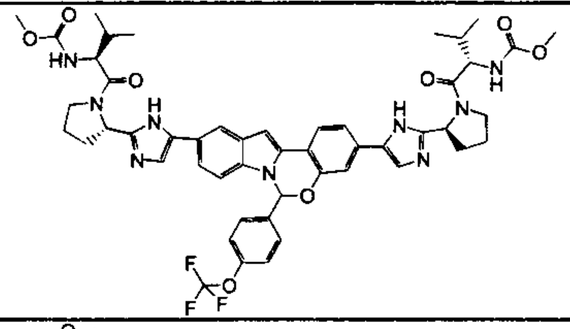
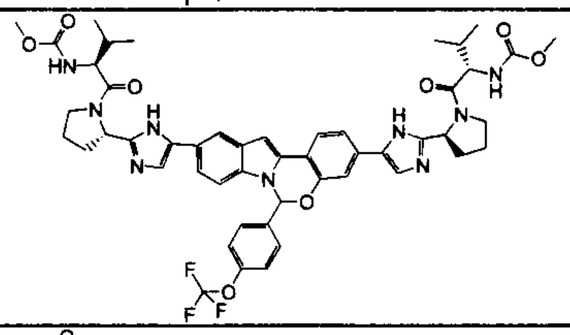
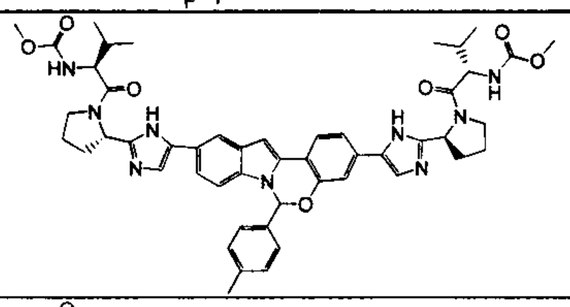
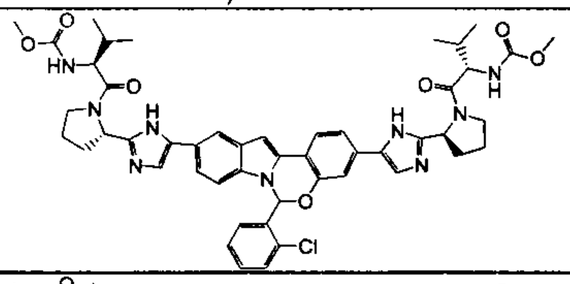
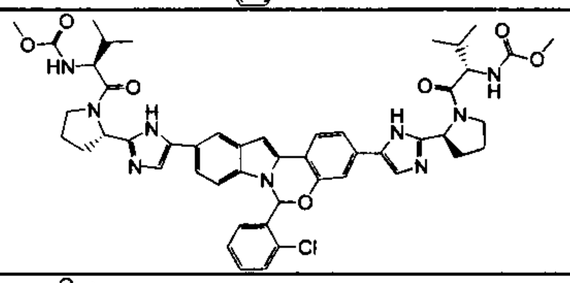
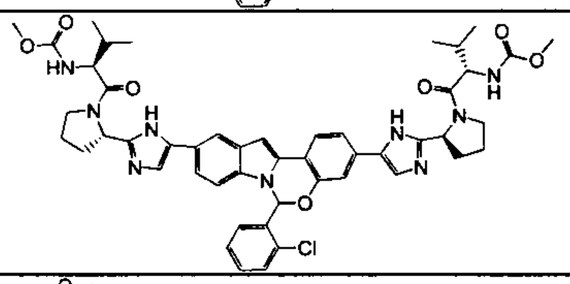
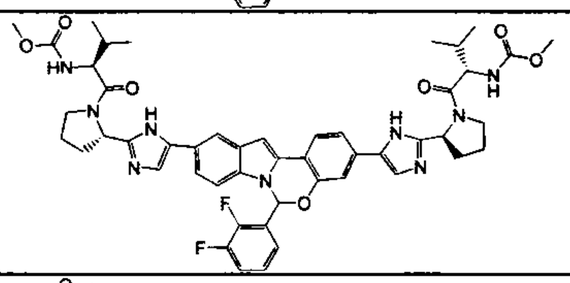
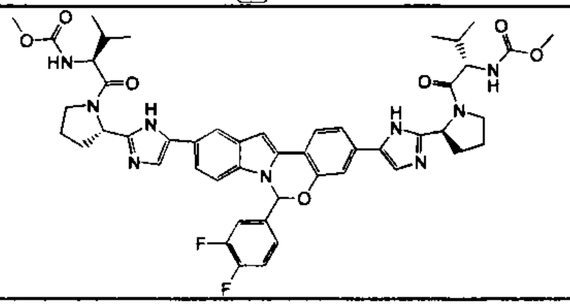
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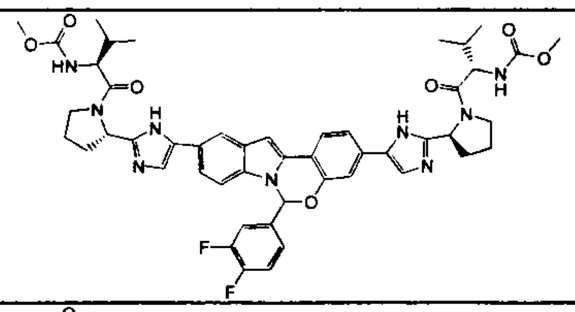
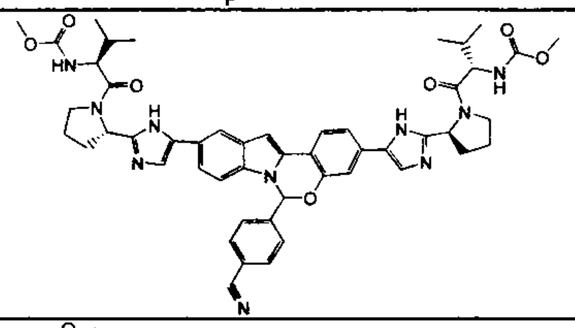
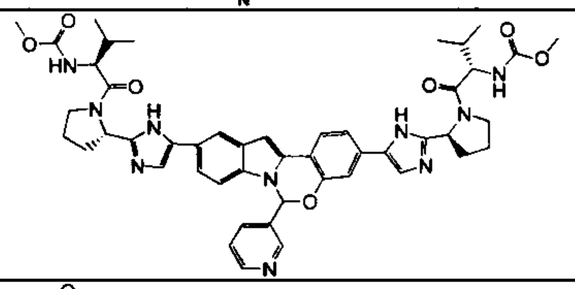
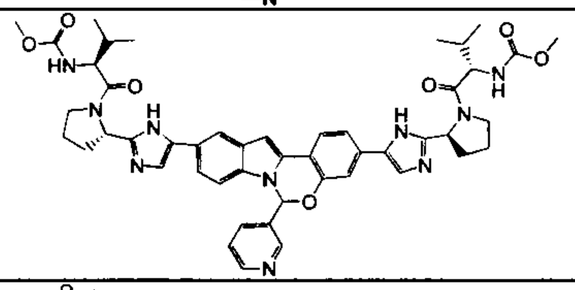
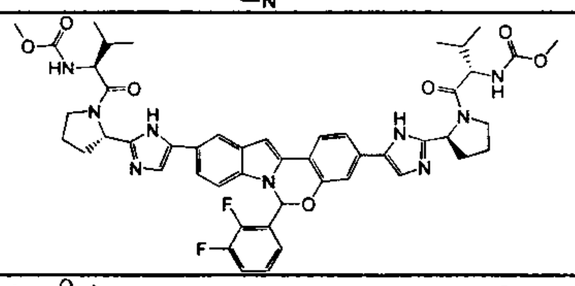
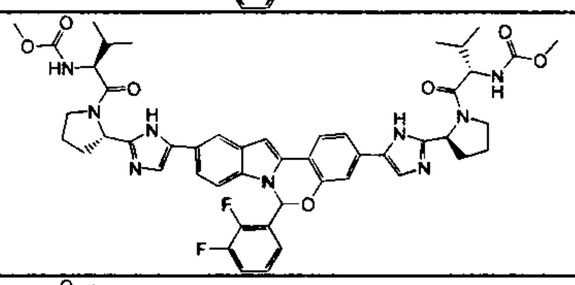
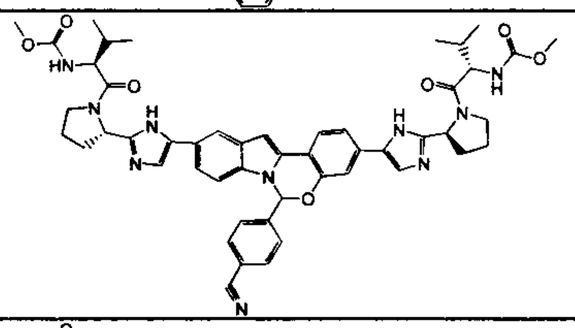
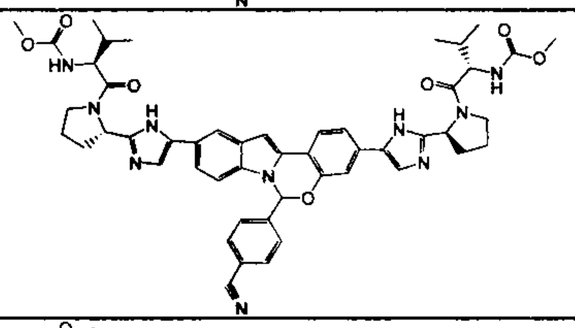
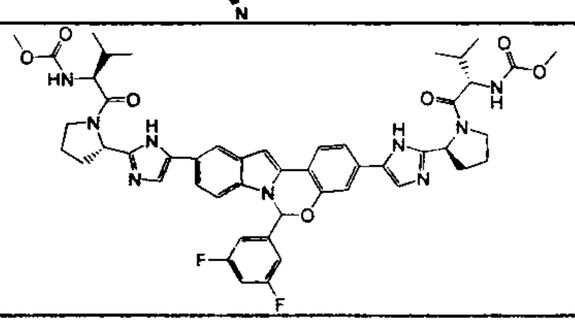
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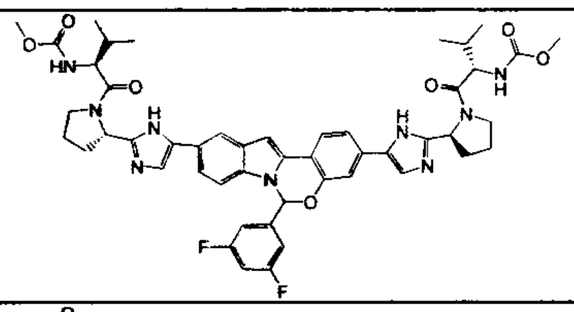
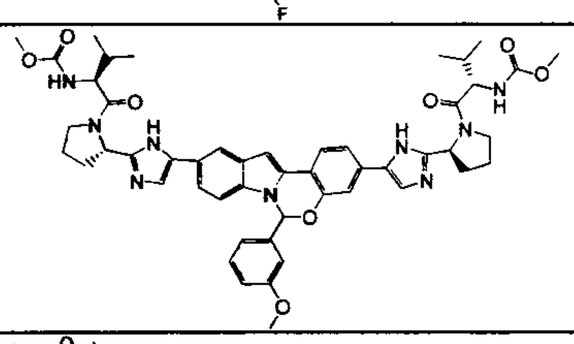
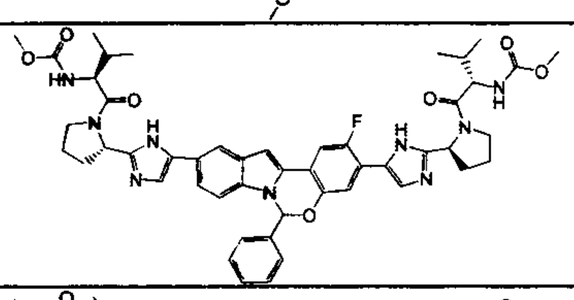
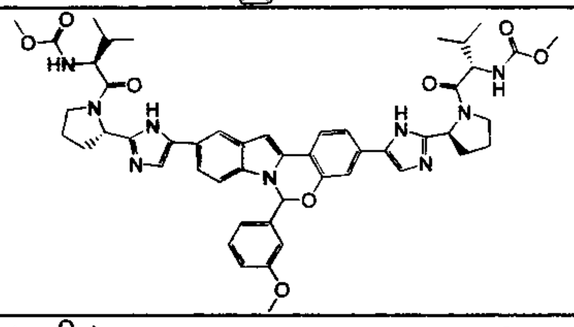
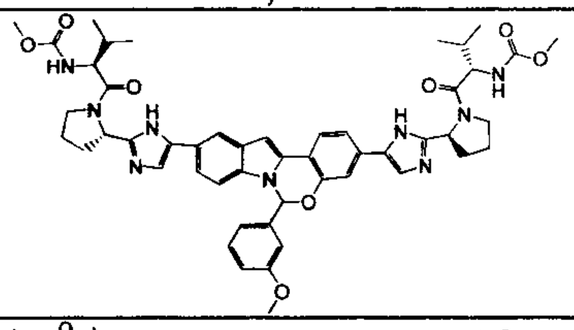
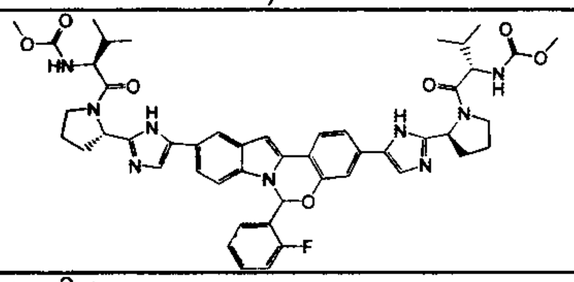
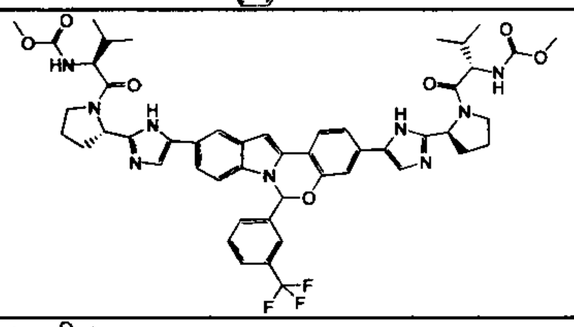
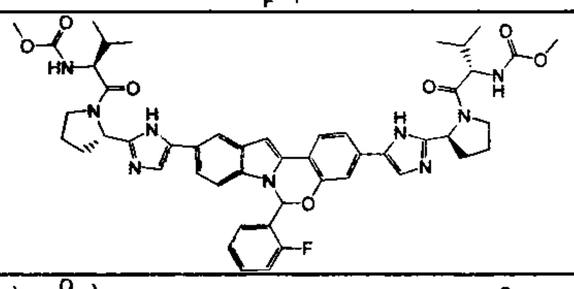
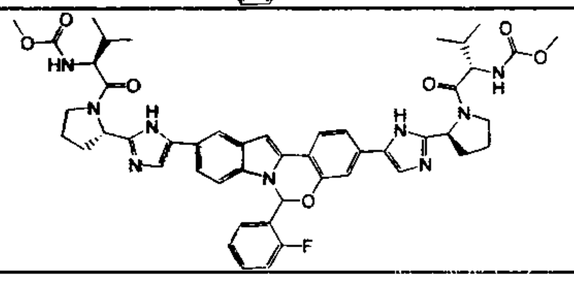
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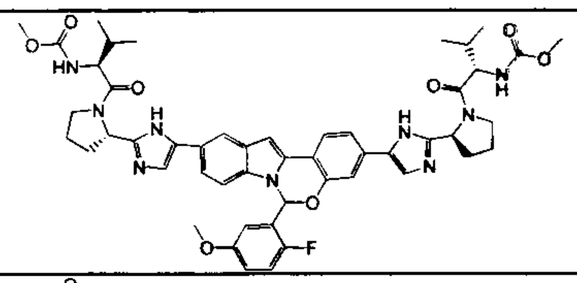
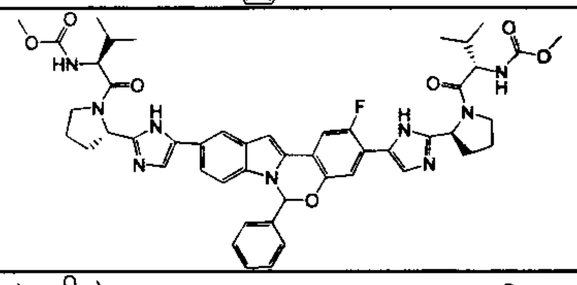
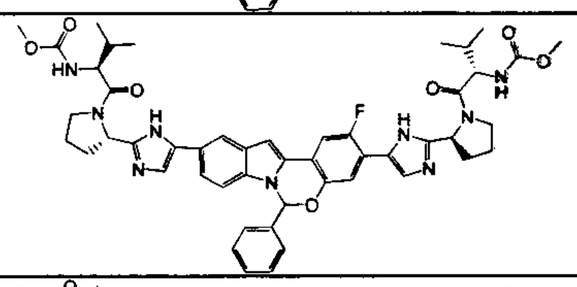
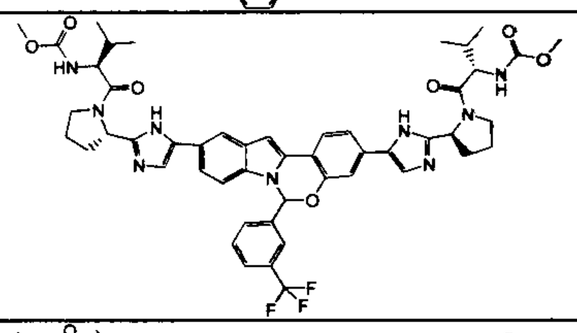
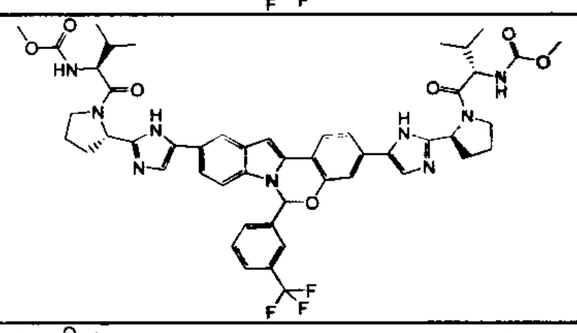
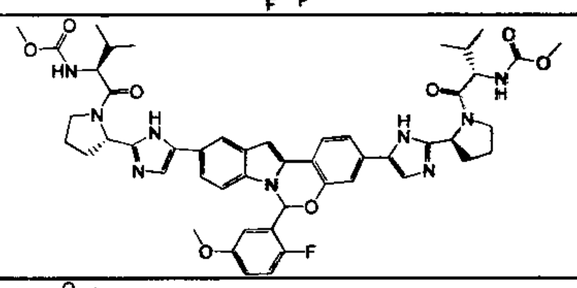
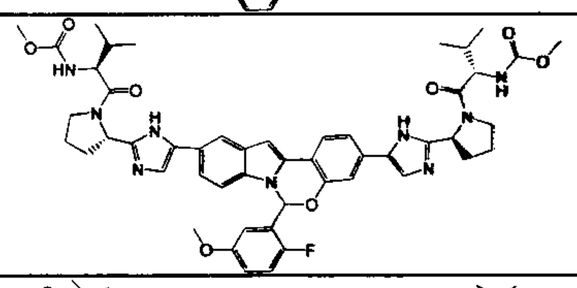
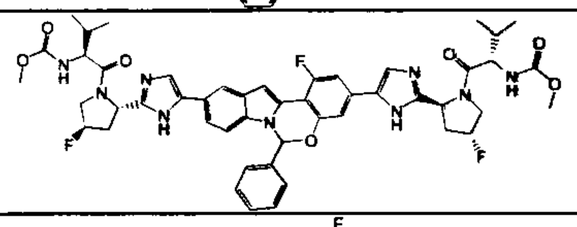
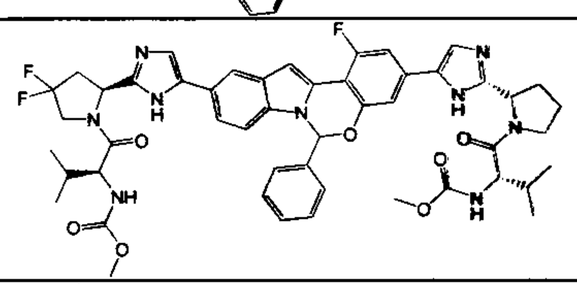
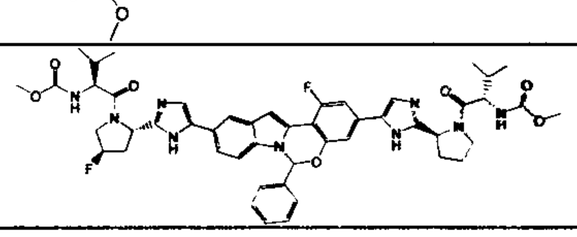
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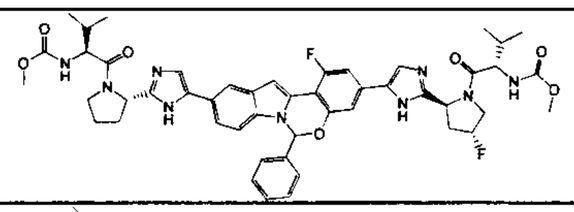
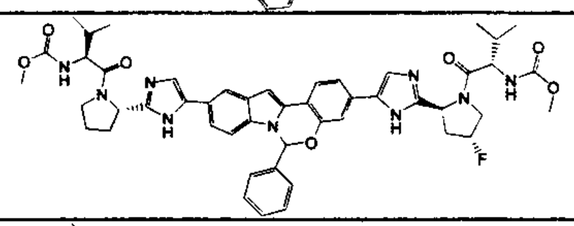
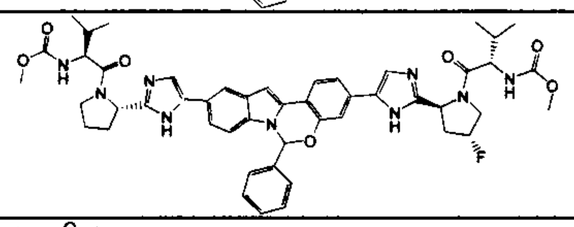
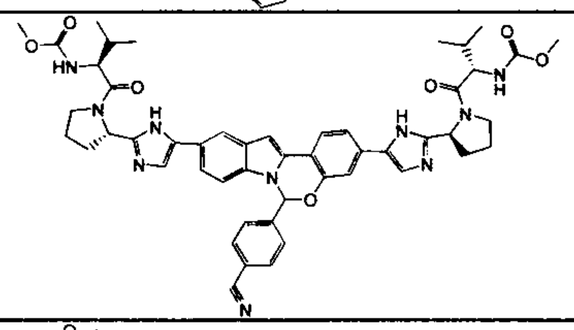
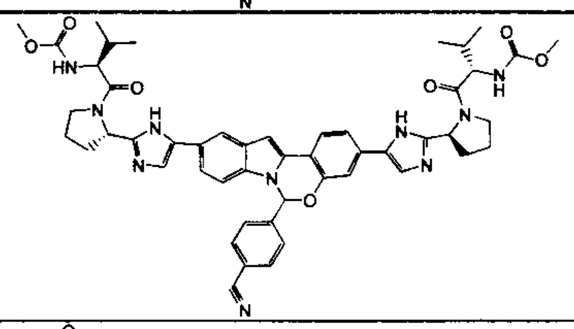
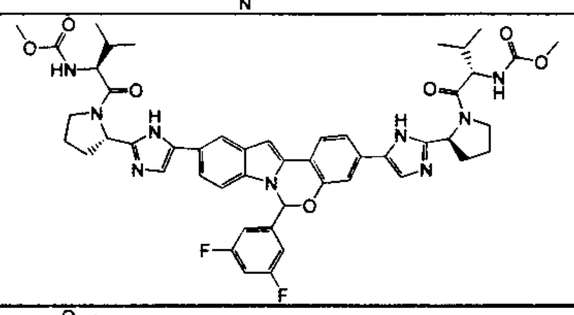
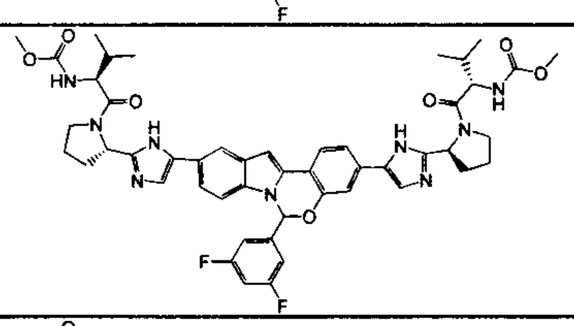
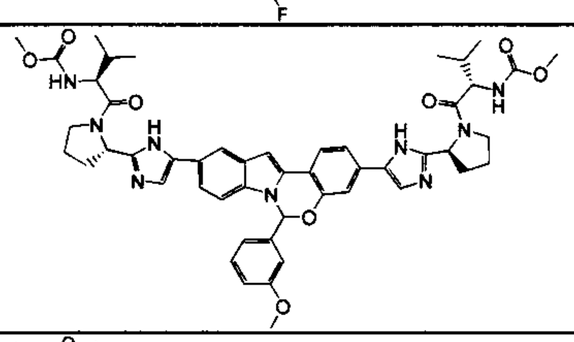
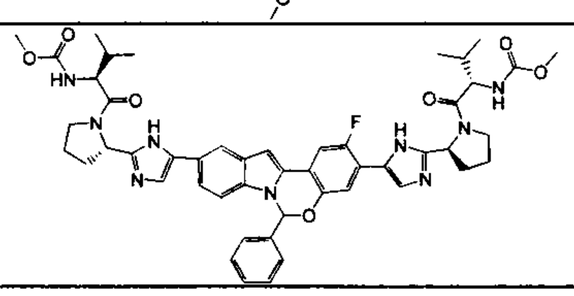
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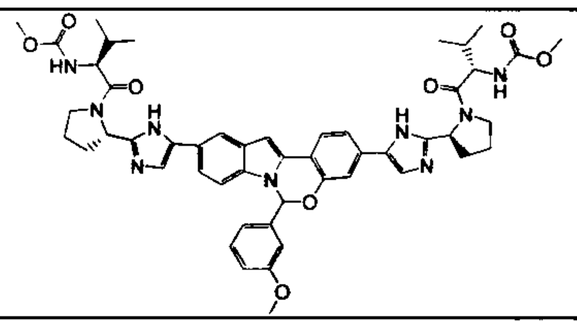
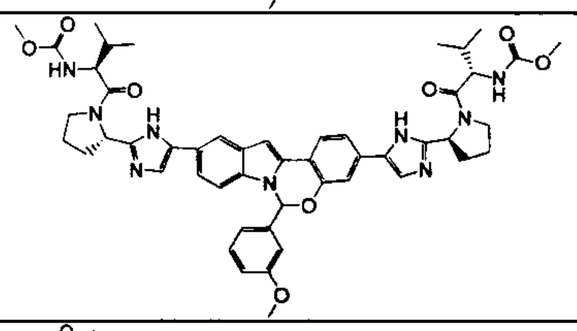
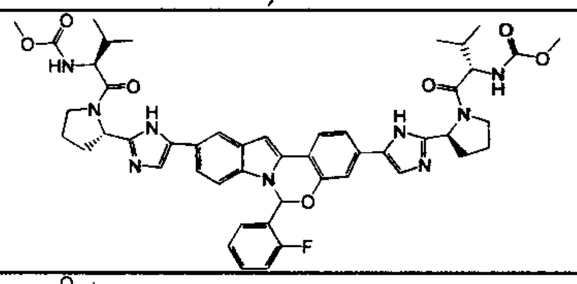
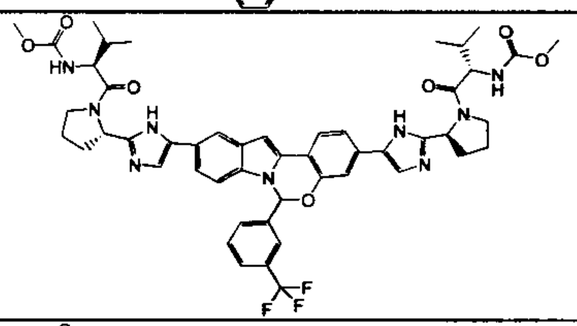
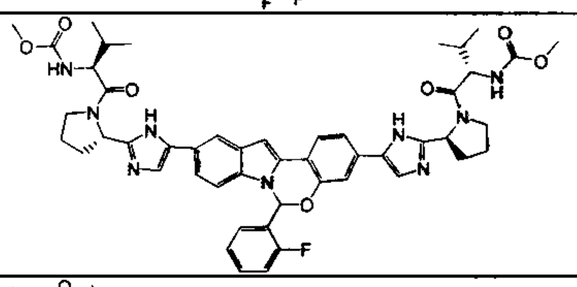
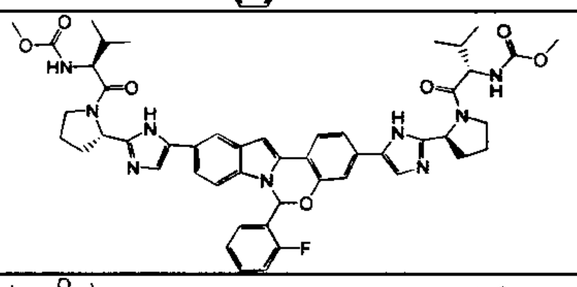
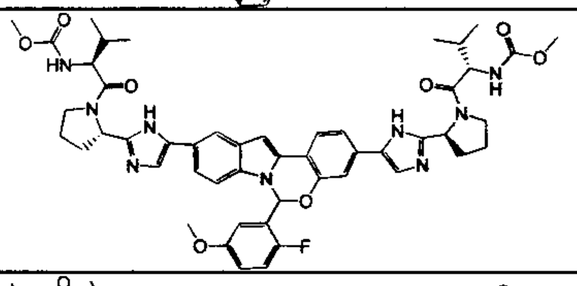
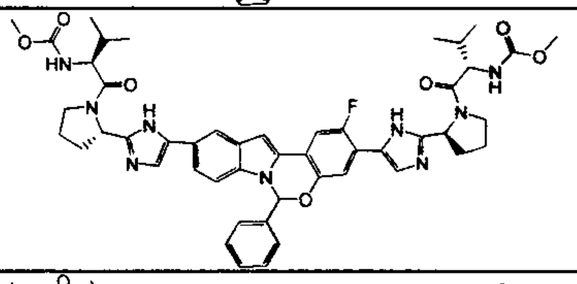
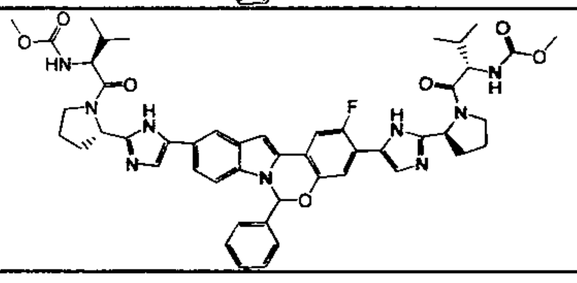
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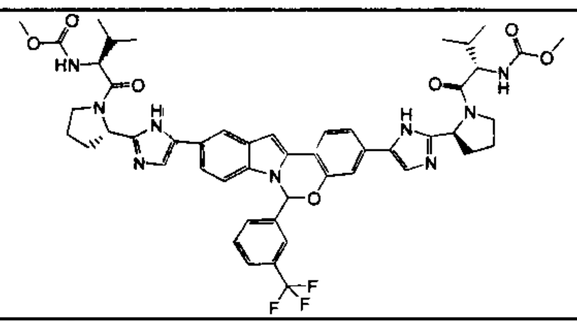
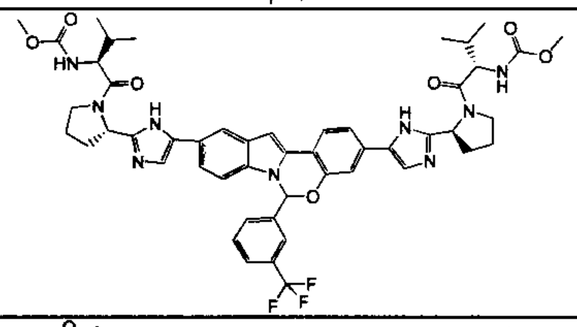
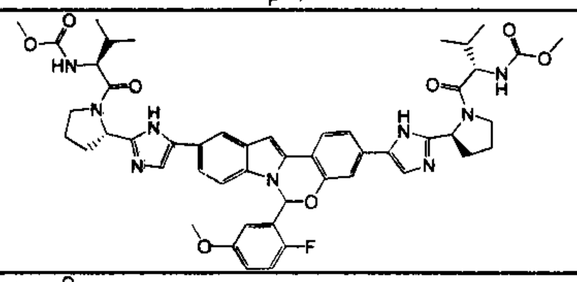
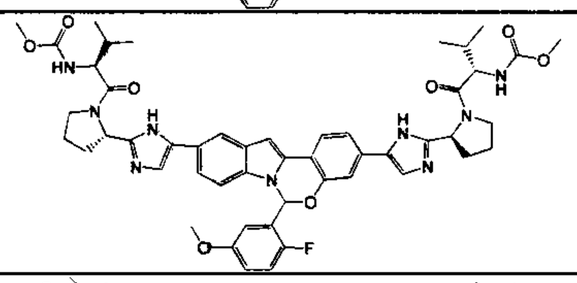
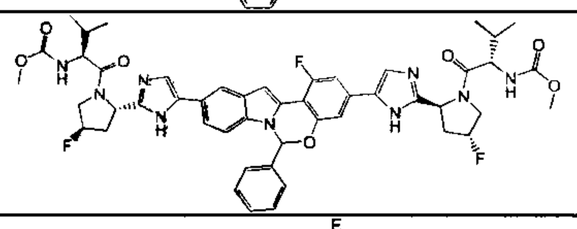
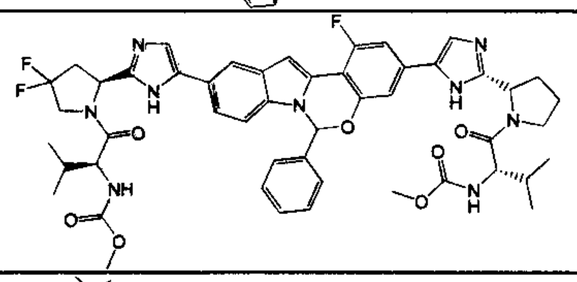
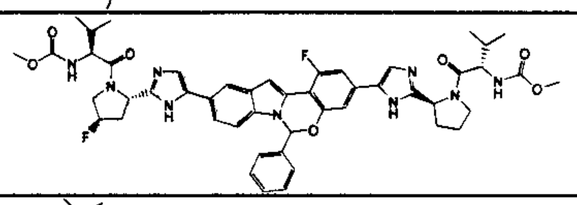
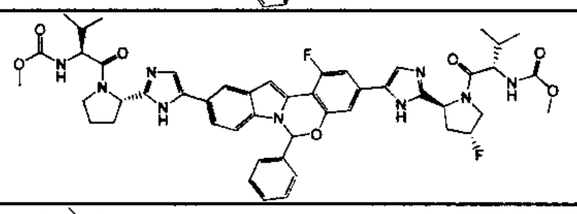
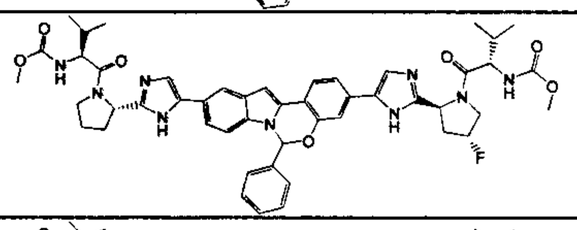
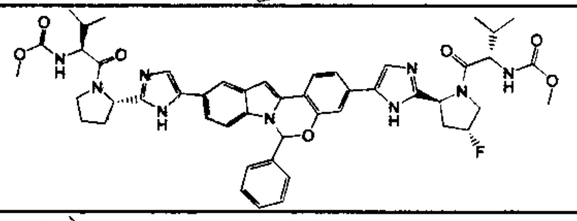
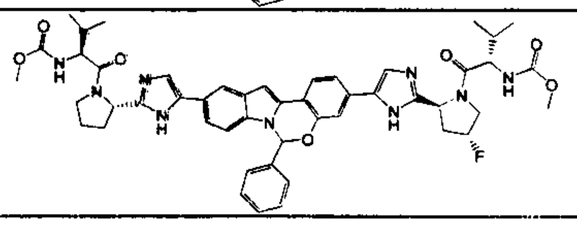
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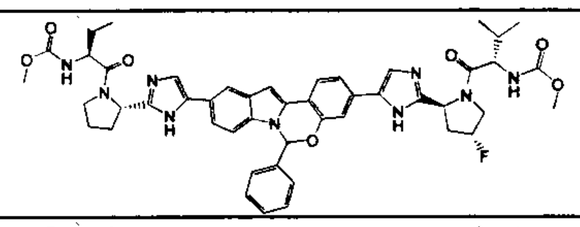
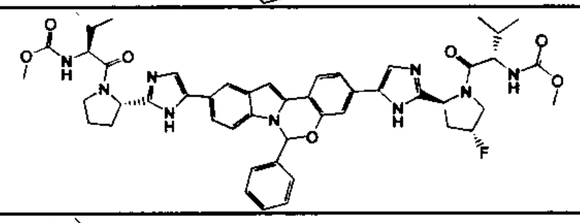
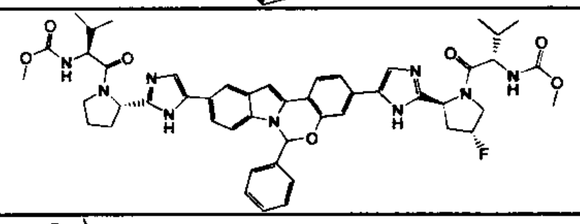
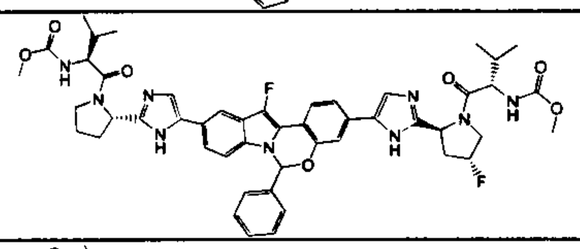
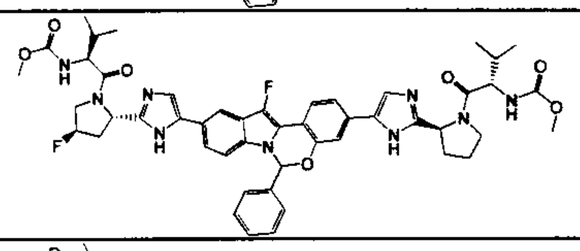
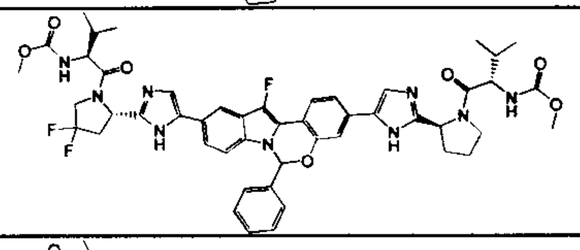
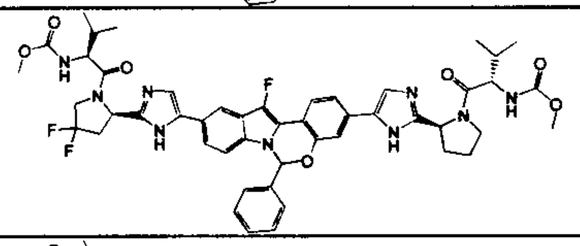
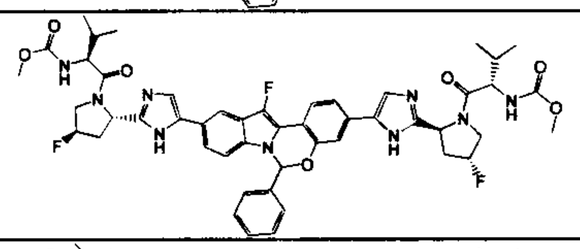
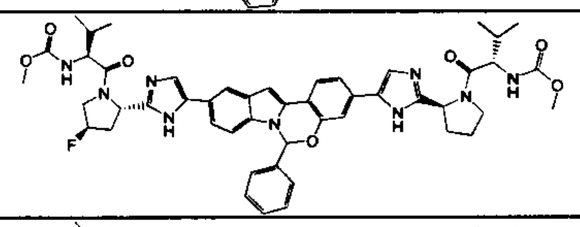
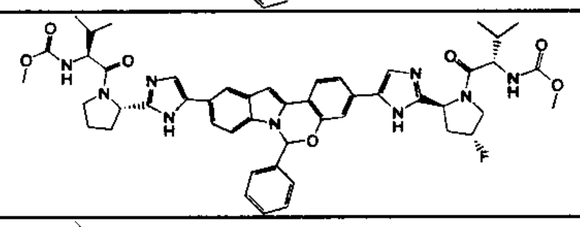
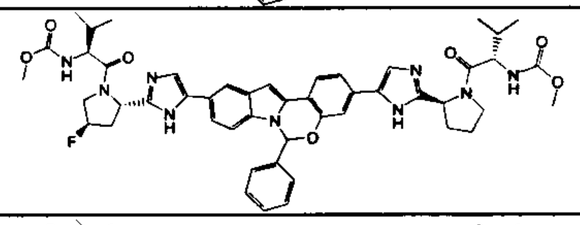
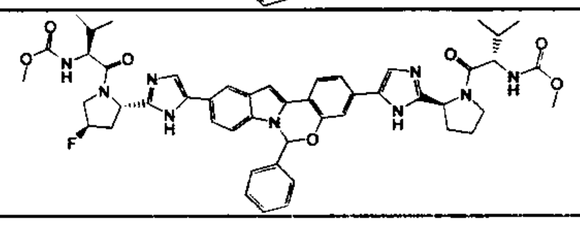
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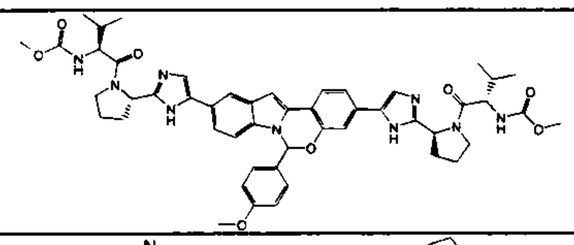
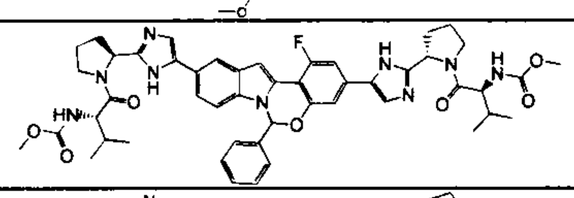
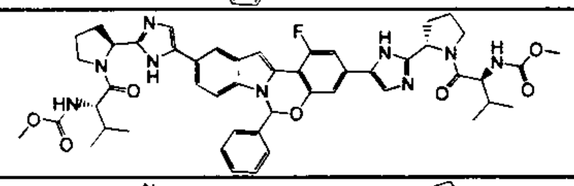
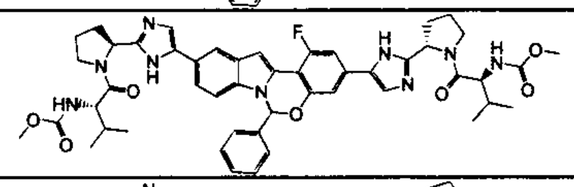
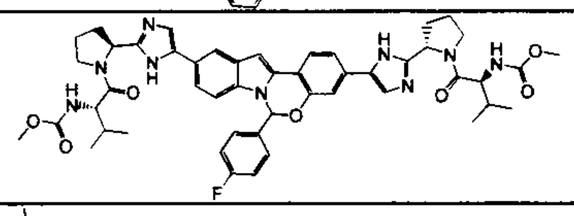
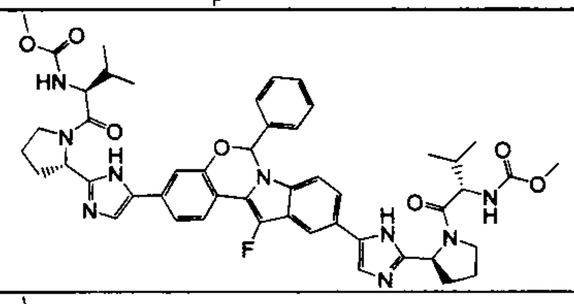
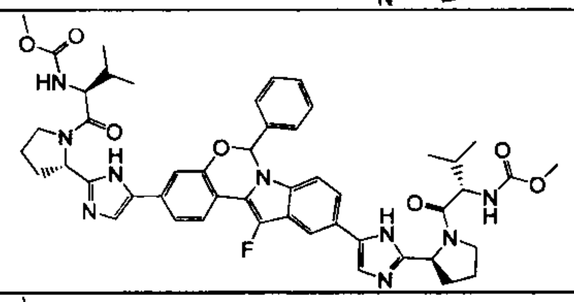
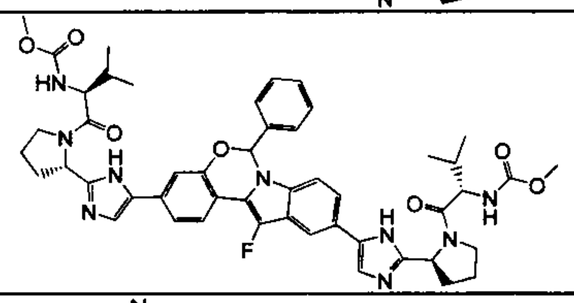
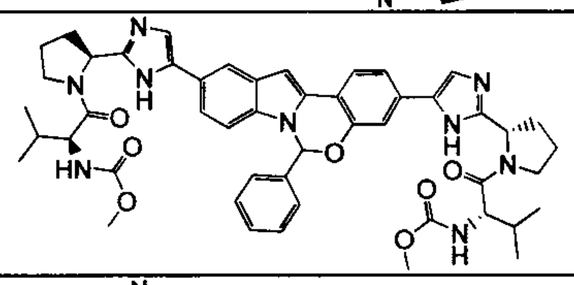
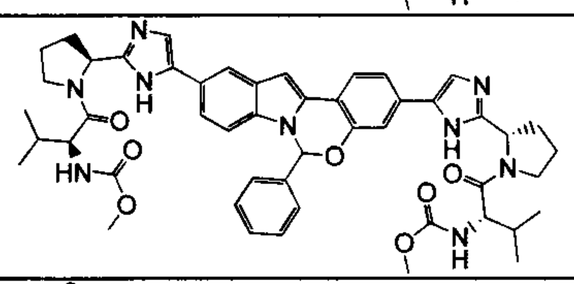
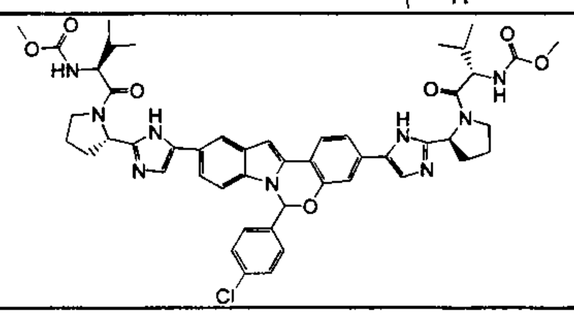
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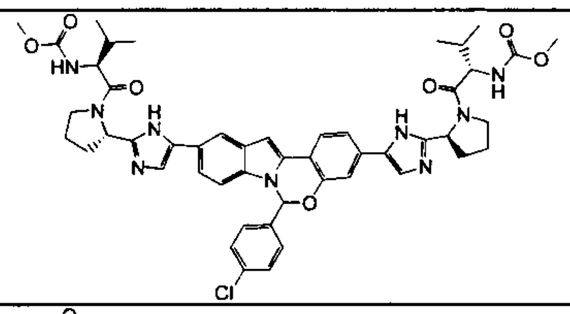
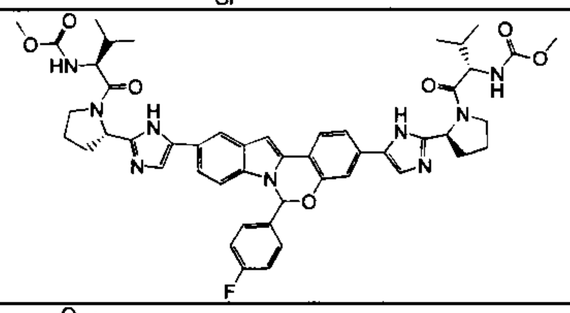
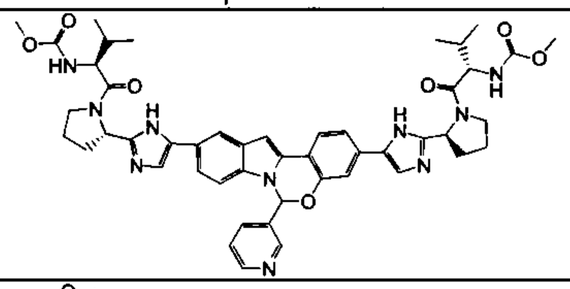
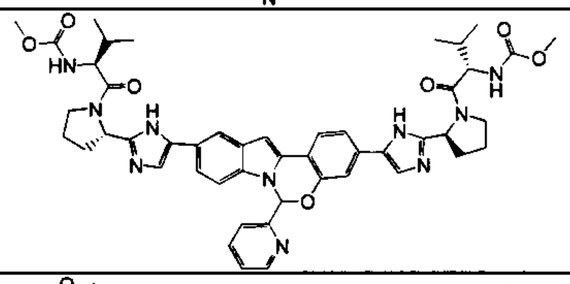
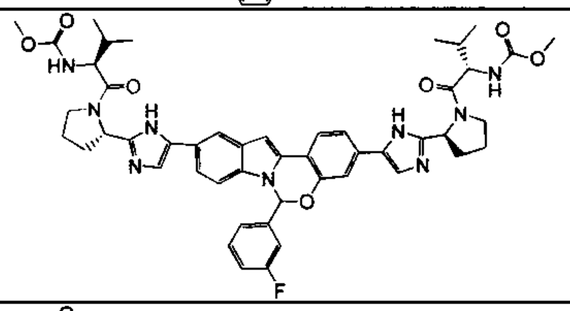
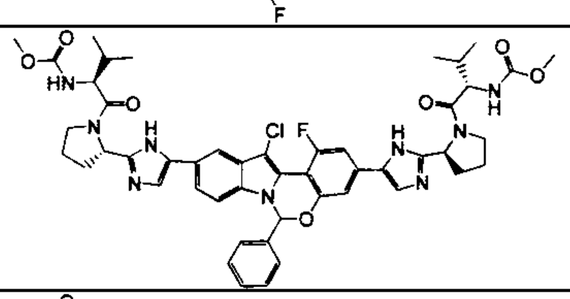
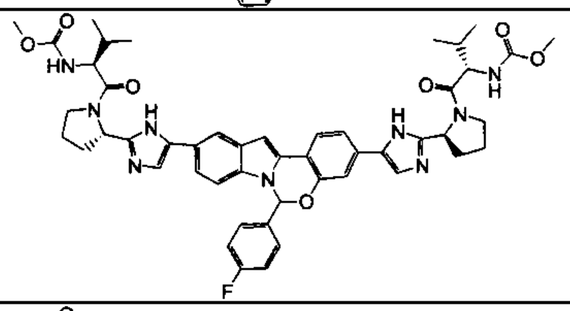
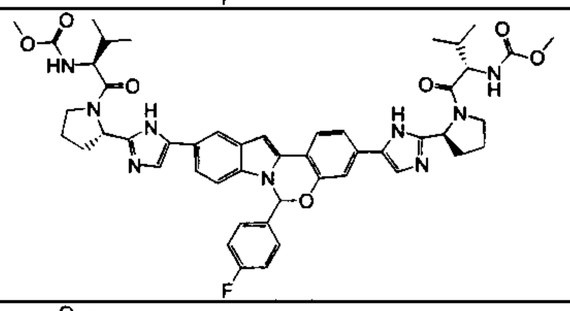
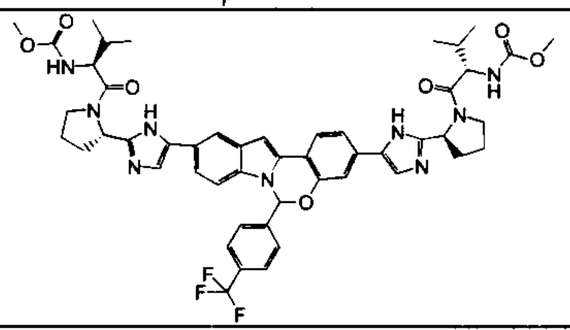
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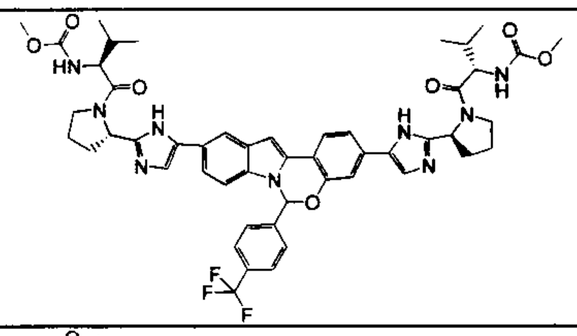
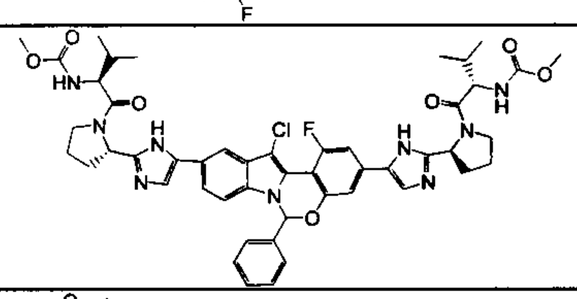
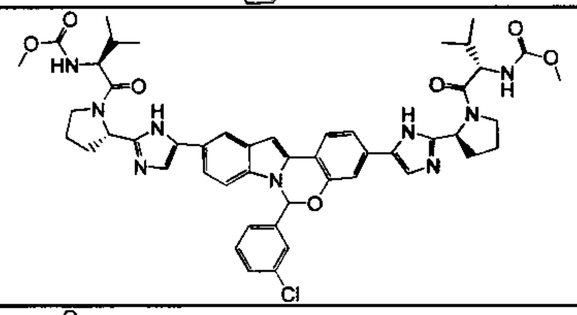
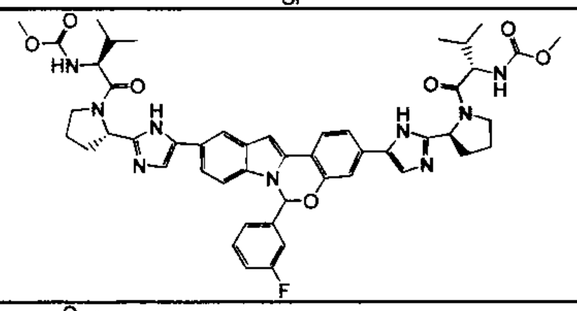
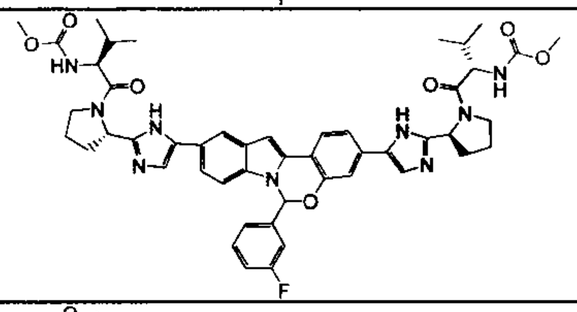
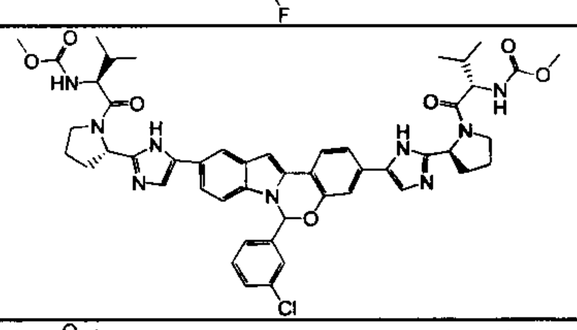
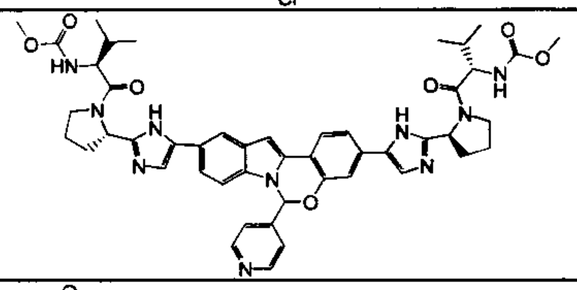
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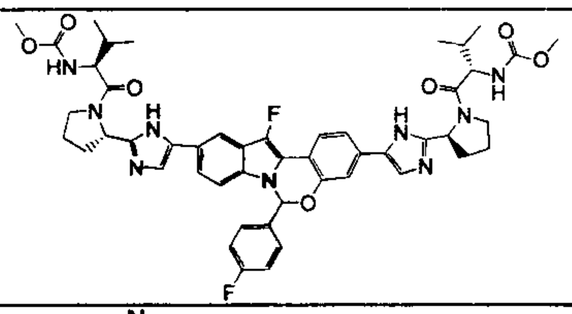
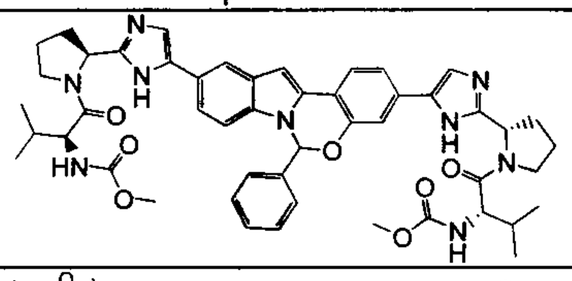
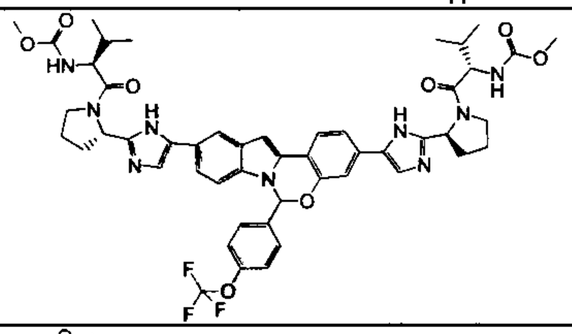
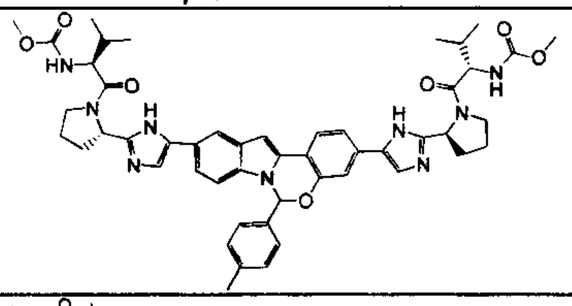
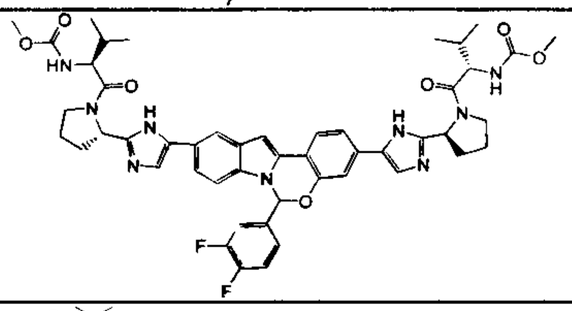
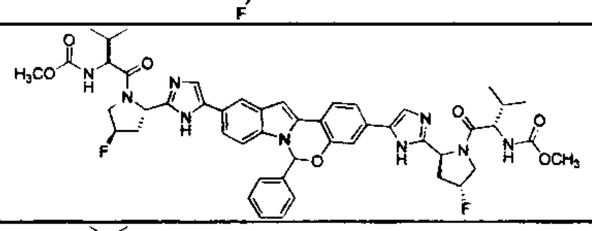
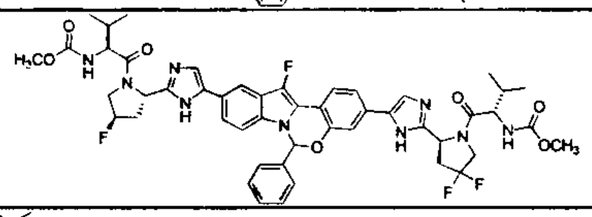
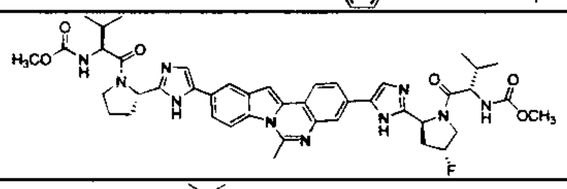
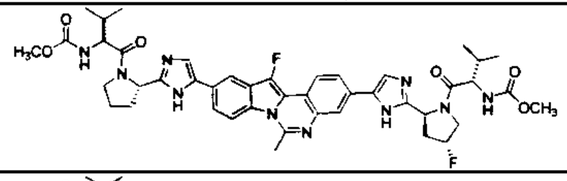
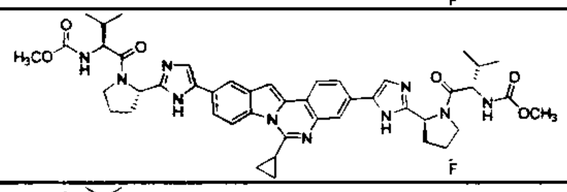
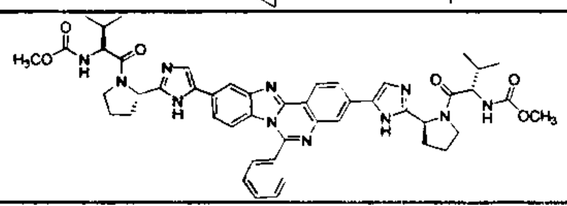
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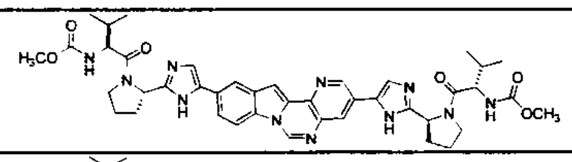
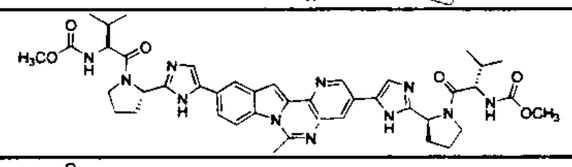
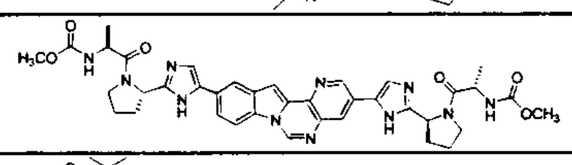
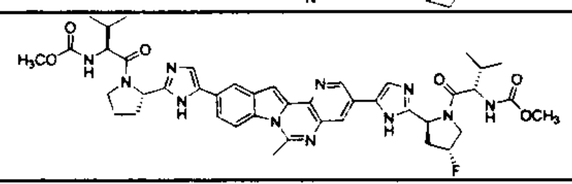
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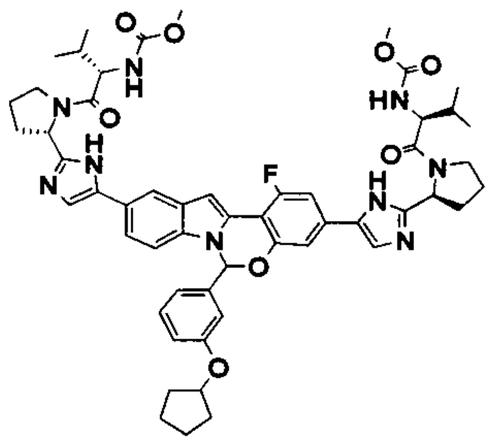
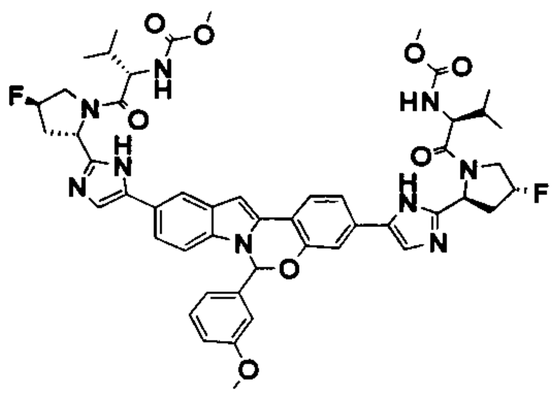
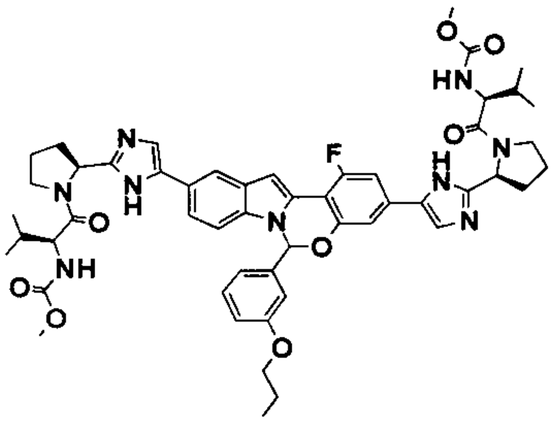
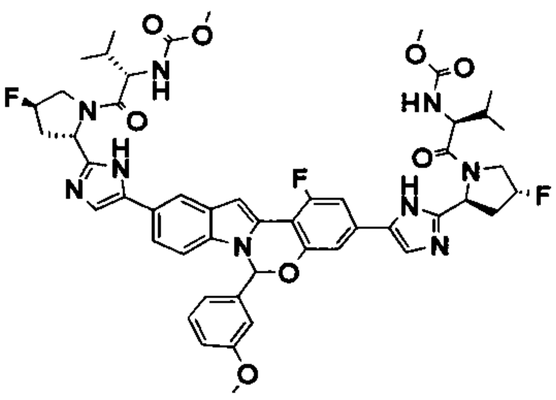
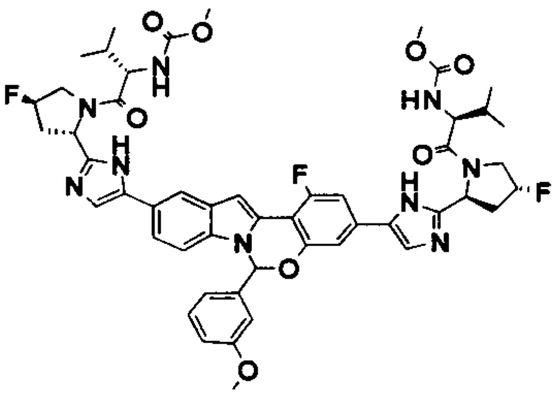
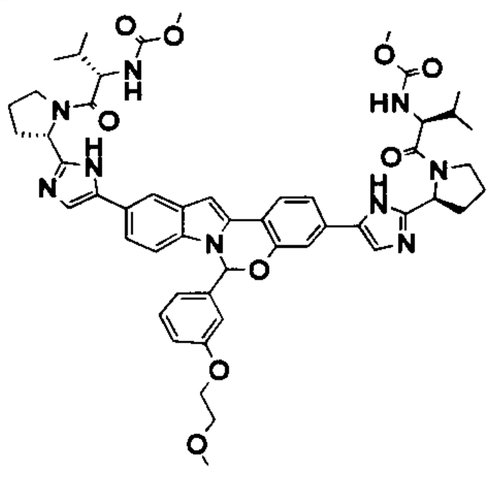
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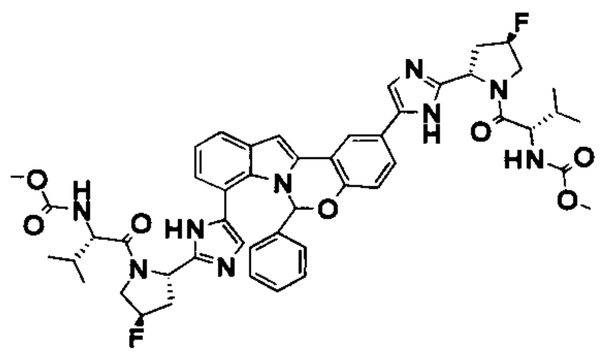
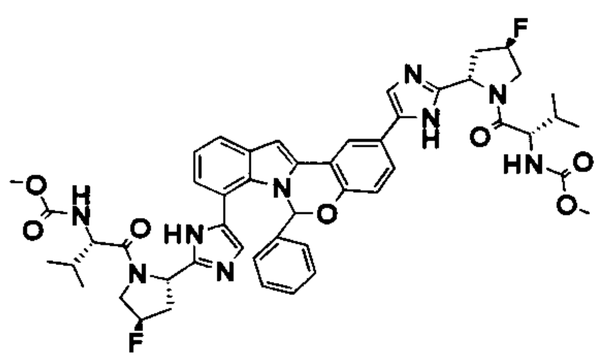
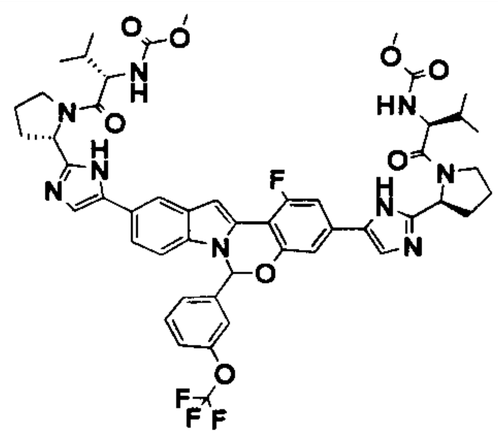
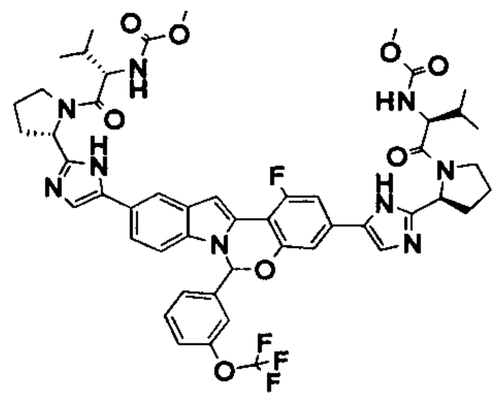
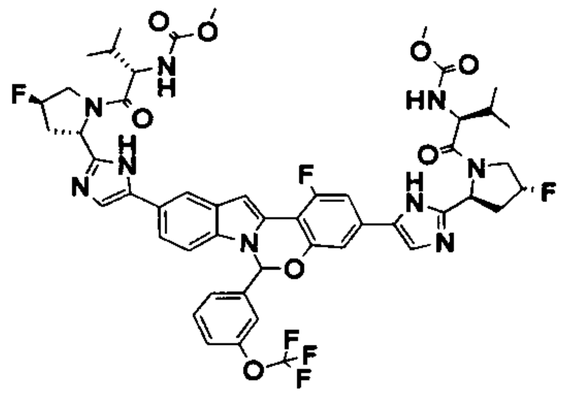
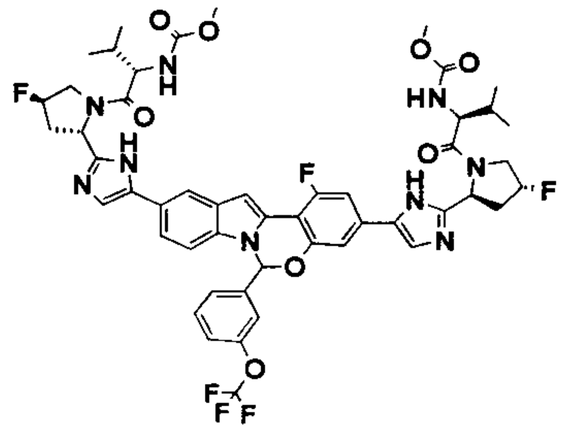
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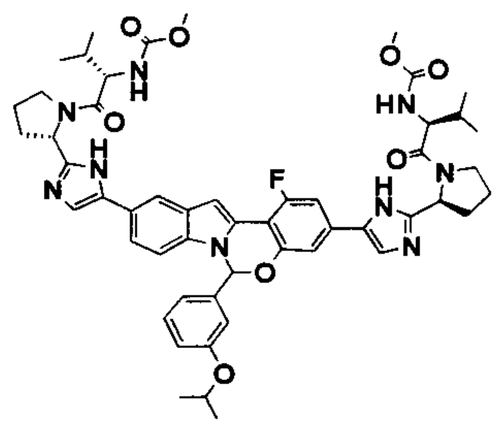
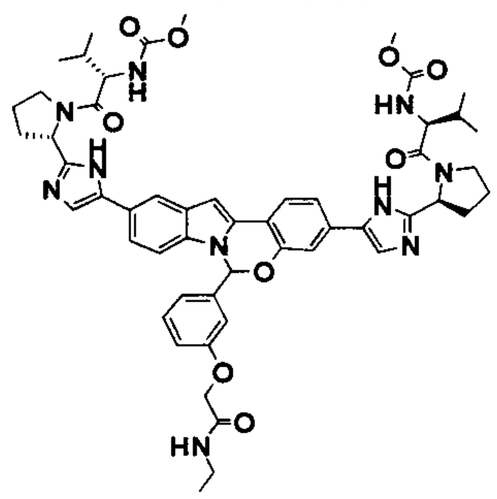
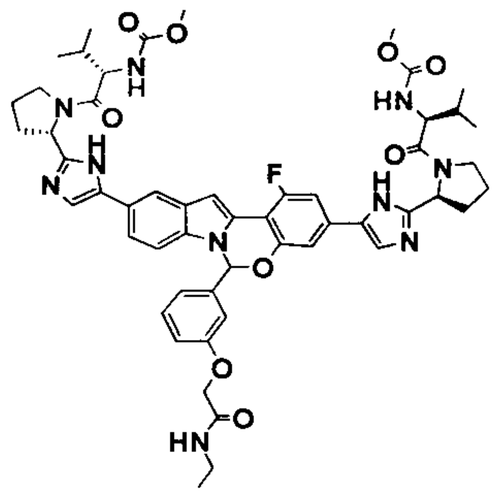
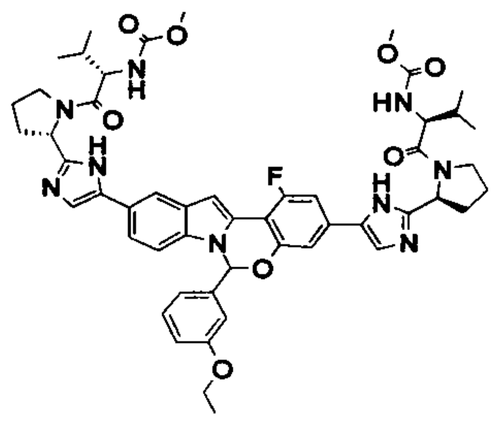
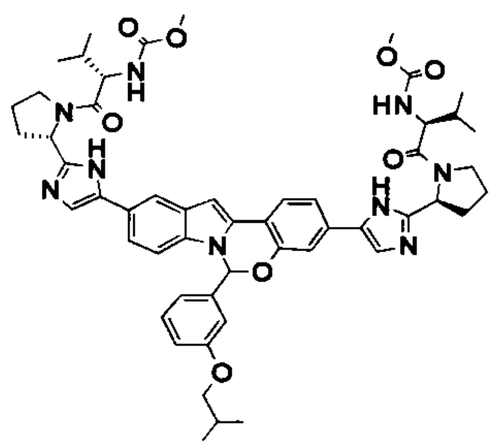
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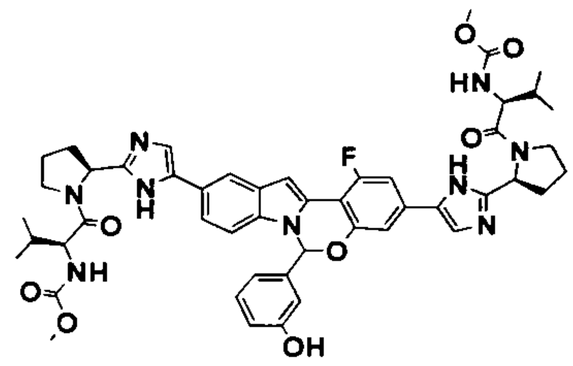
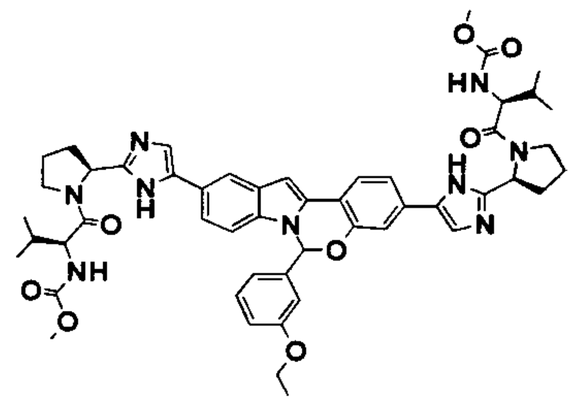
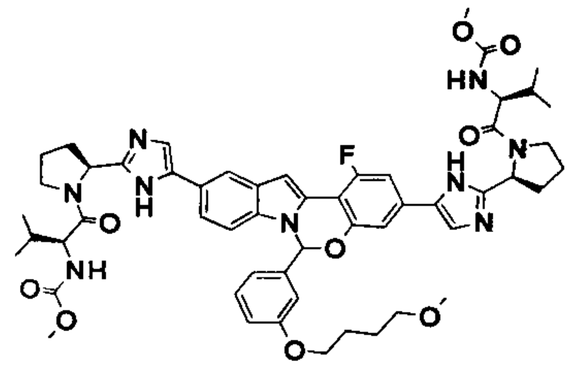
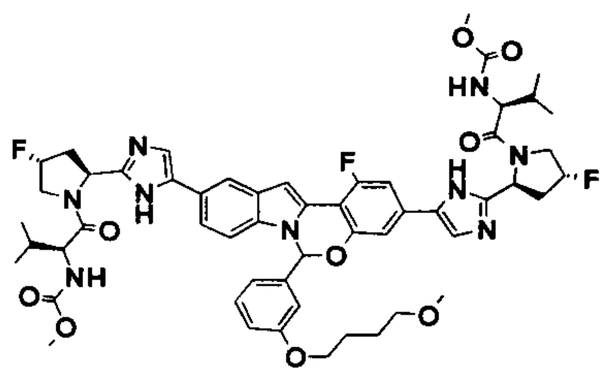
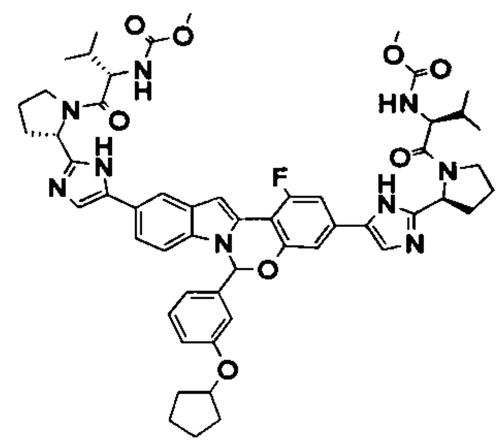
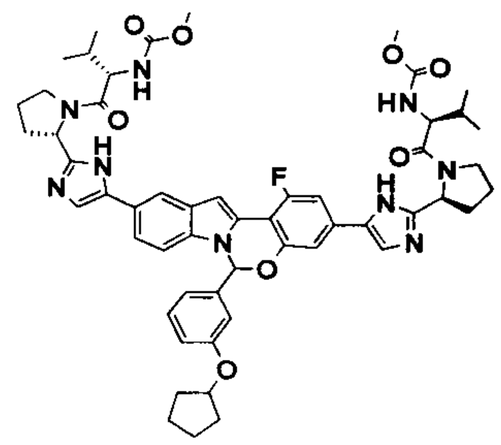
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244		818.4
245		748.4
246		837.5

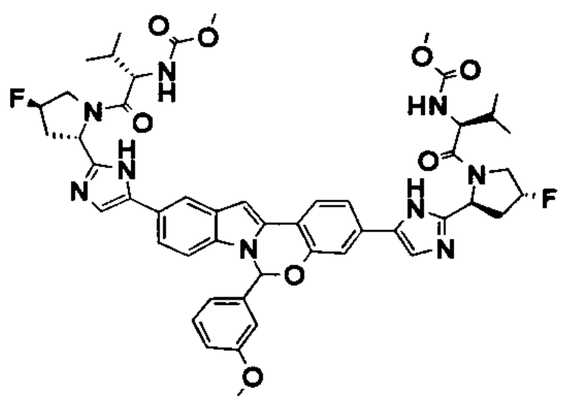
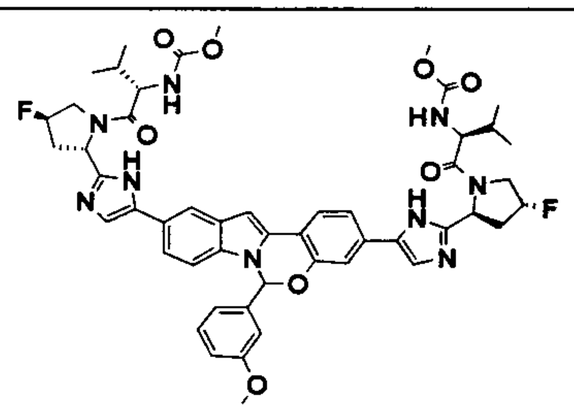
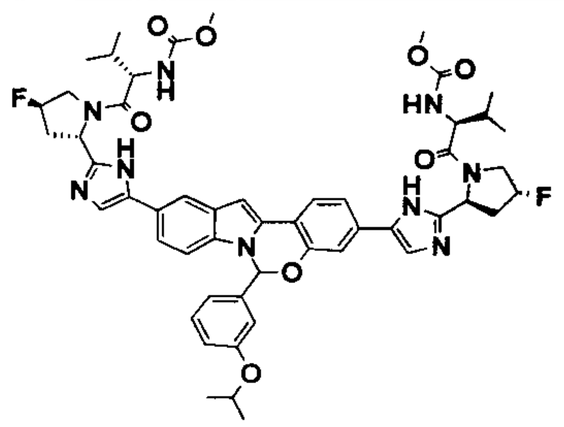
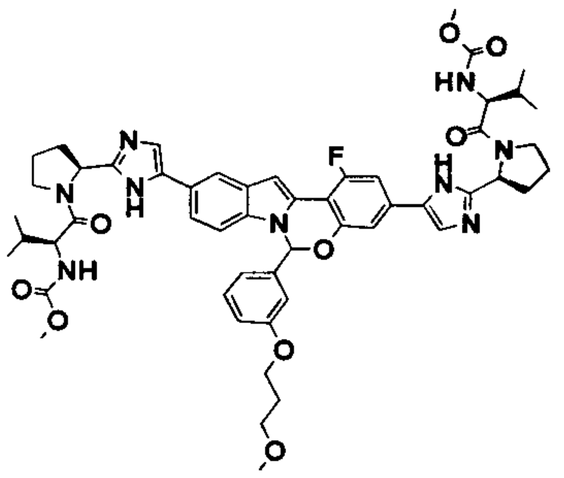
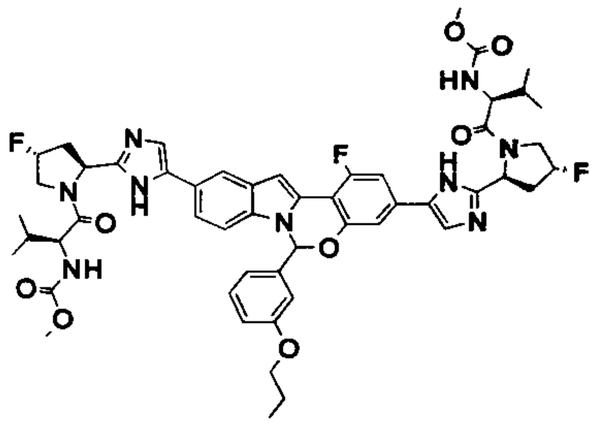
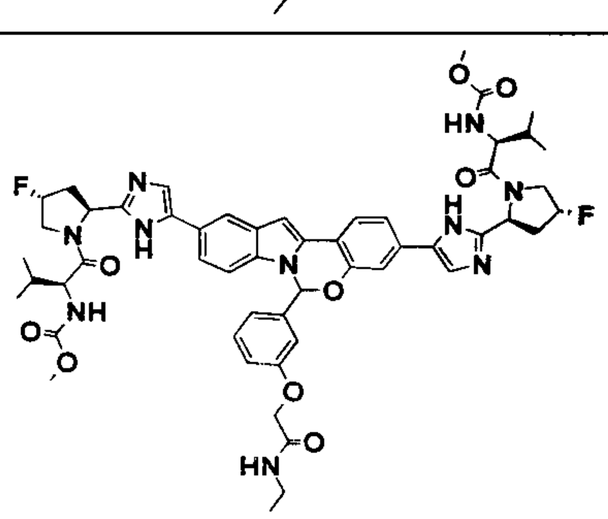
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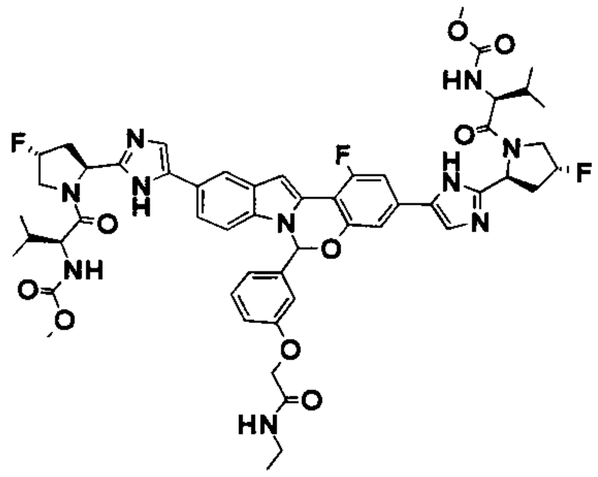
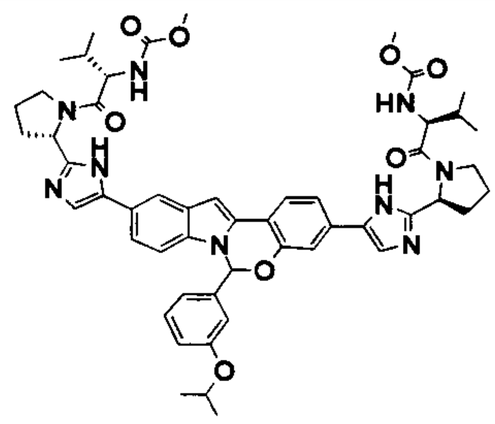
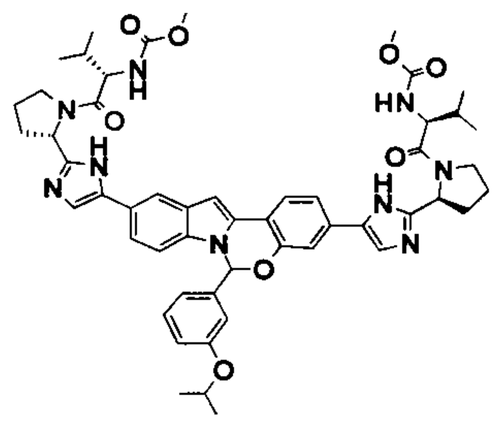
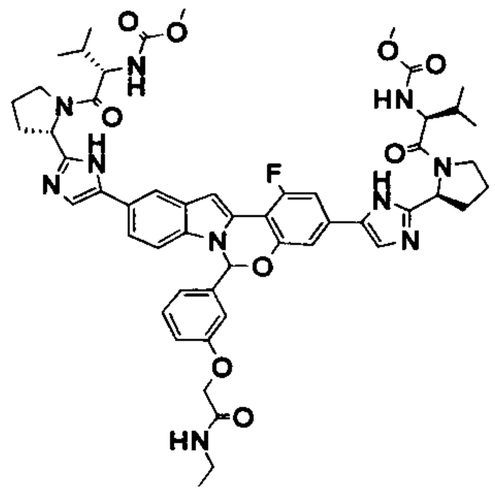
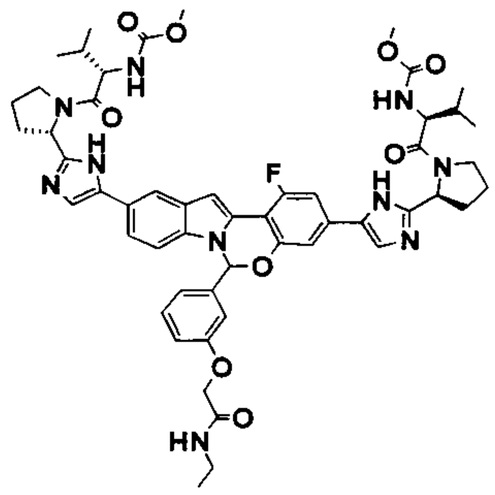
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
247		0.003	1.4	0.1	0.004	8	984.15	985.1	Mixture of isomers
248		0.013		2.54	0.005	17	948.05	948.5	Mixture of isomers
249		0.009	0.8		0.004	4	958.11	959	Mixture of isomers
250		0.013	0.3	4.05	0.003	36	966.04	966.7	Single isomer
251		0.003		1.12	0.004	25	966.04	966.7	Single isomer
252		0.024	9.9	1.15	0.011	15	956.12	957	Mixture of isomers

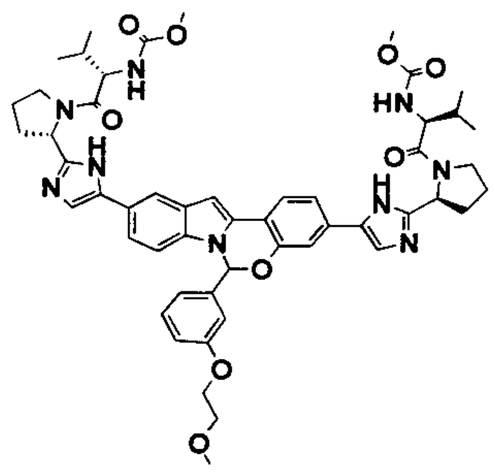
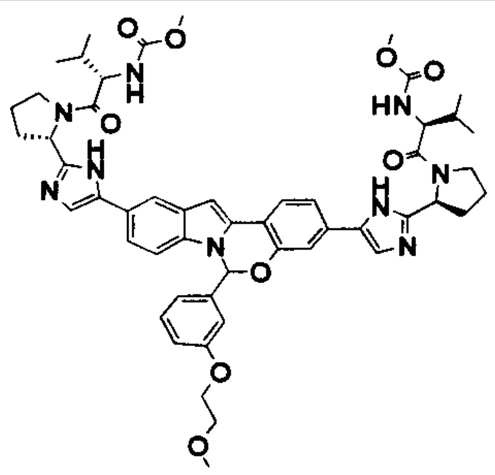
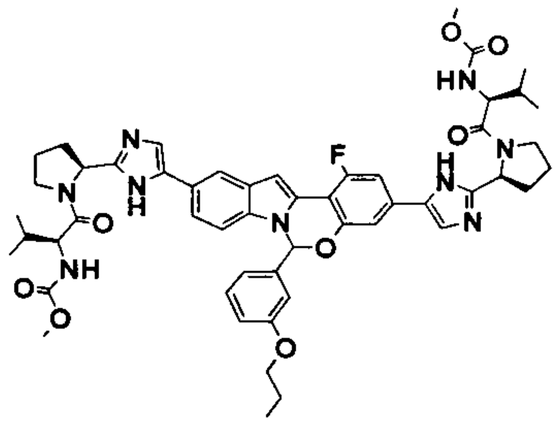
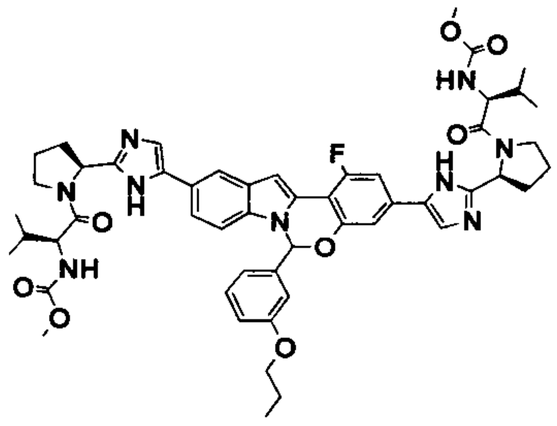
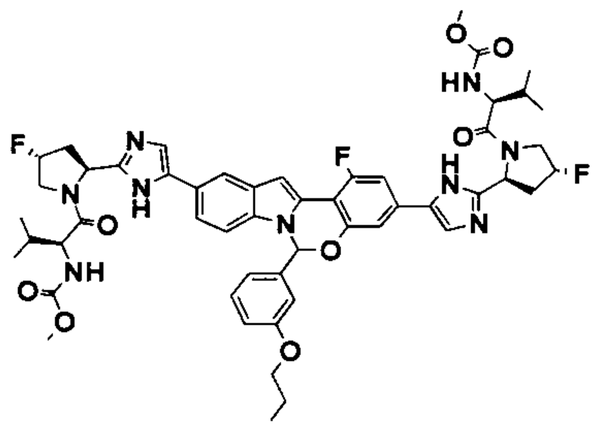
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
253		56.000	500				918.02	918.6	Single isomer
254		127.000	489				918.02	918.6	Single isomer
255		0.008	3.2	0.28	0.004	4	984.03	985	Single isomer
256		0.007	12.9			14	984.03	984.8	Single isomer
257		0.030	0.44	4.73	0.003	110	1020.01	1021	Single isomer
258		0.003		3.94	0.003	46	1020.01	1021	Single isomer

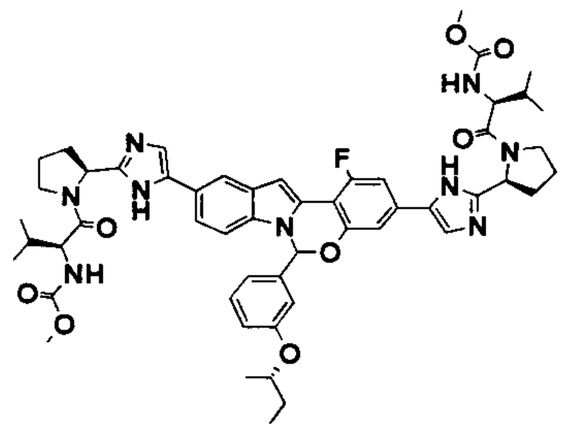
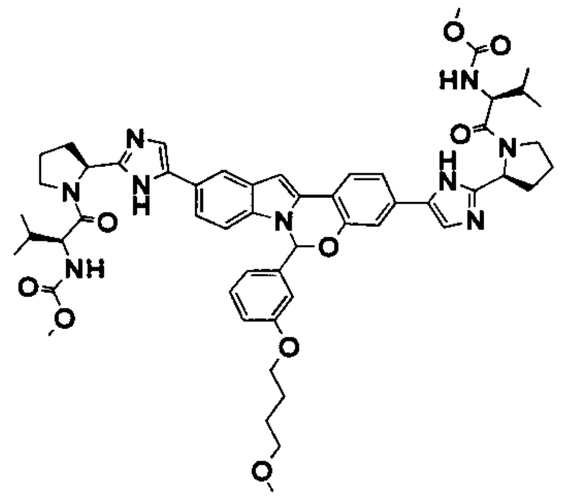
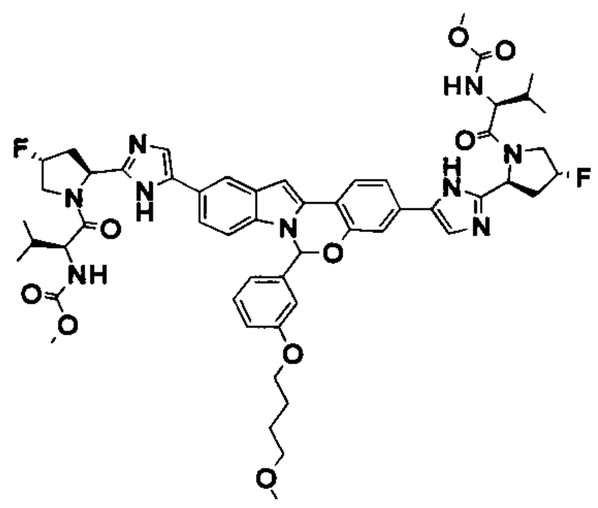
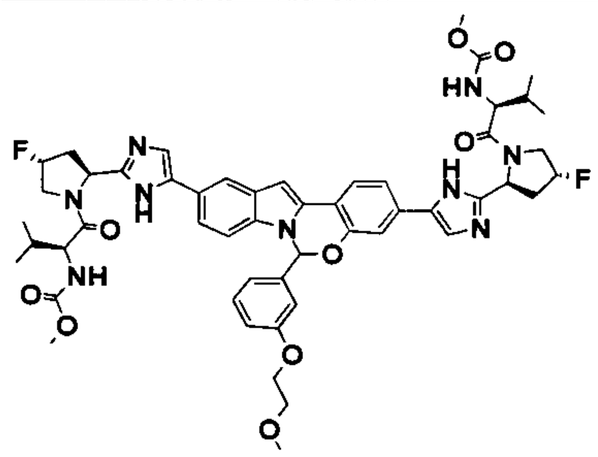
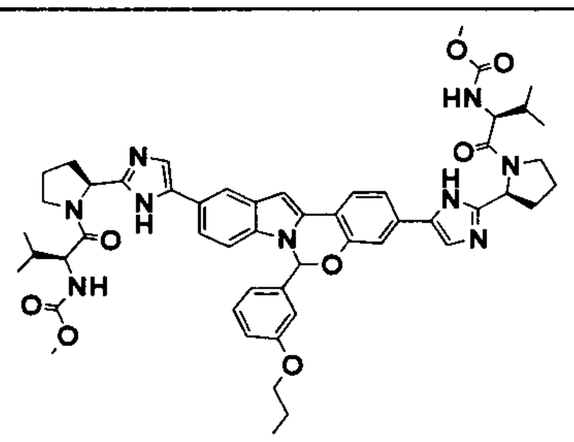
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
259							958.11	959	Mixture of isomers
260							983.15	983.9	Mixture of isomers
261		0.010	50.3	0.918	0.009	21.5	1001.14	1002	Mixture of isomers
262		0.011	1.2		0.005	3.6	944.09	944.9	Mixture of isomers
263			8.1	0.55		4	954.15	955.1	Mixture of isomers

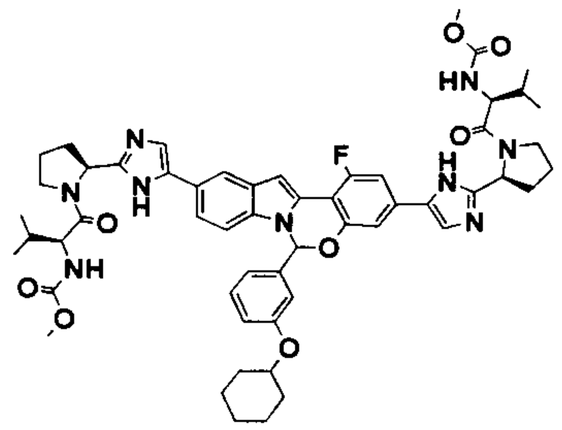
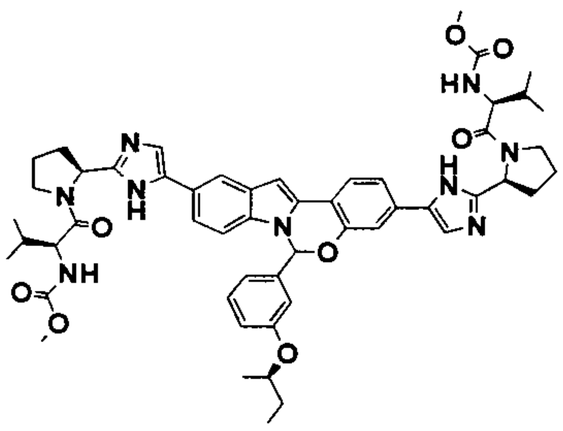
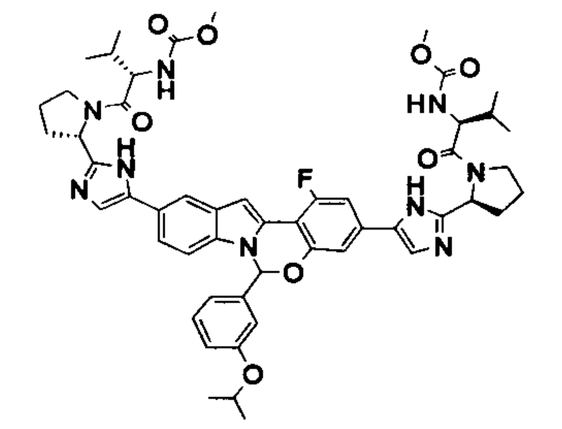
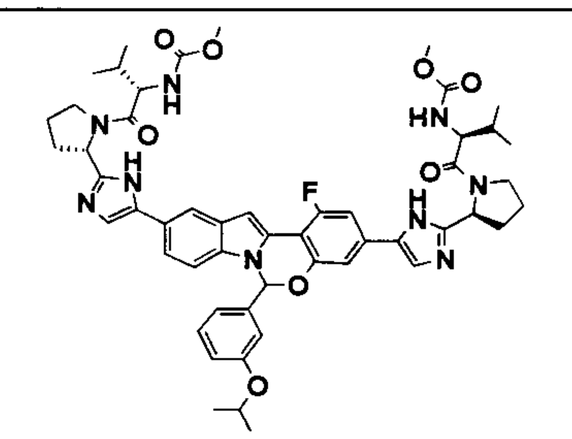
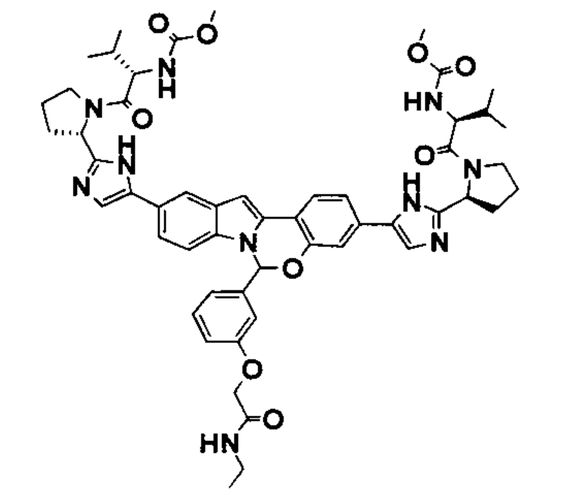
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
264		0.009	6.7	0.411	0.008	6.9	916.03	917	Mixture of isomers
265		0.012	6.39	0.2	0.005	3.3	926.09	926.7	Mixture of isomers
266		0.009	4.8	0.35	0.006	4	1002.17	1003	Mixture of isomers
267		0.006	0.5	0.459	0.005	40	1038.15	1003	Mixture of isomers
268		0.009	0.6	0.205	0.005	1	984.15	985.1	Single isomer
269		0.004	10.86	0.3	0.004	16.8	984.15	985.1	Single isomer

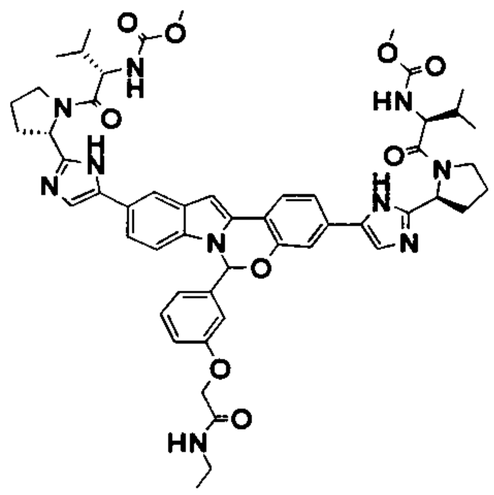
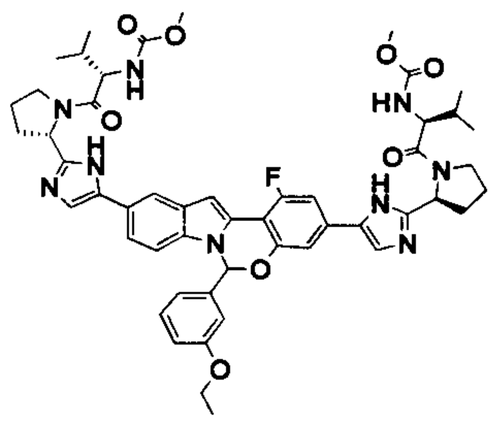
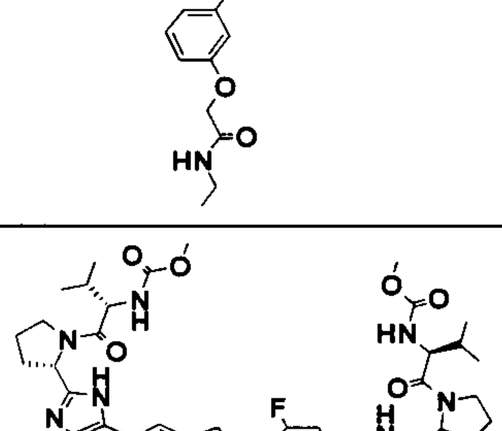
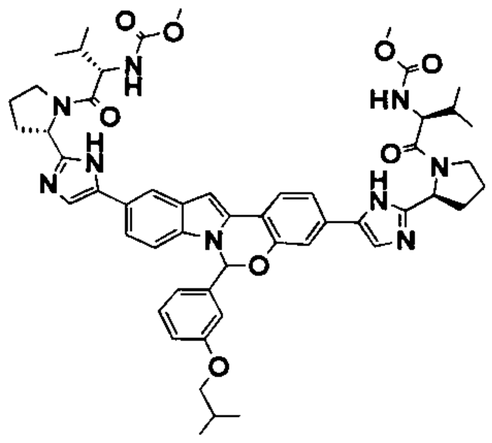
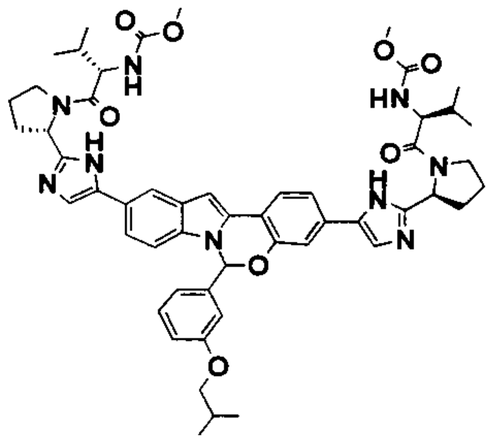
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
270		0.027	0.9	6.659	0.006	47	948.05	949	Single isomer
271		0.006	2.2	2.222	0.008	32	948.05	949	Single isomer
272							976.10	977	Mixture of isomers
273							988.14	988.9	Mixture of isomers
274							994.09	995	Single isomer
275							1019.13	1019.9	Mixture of isomers

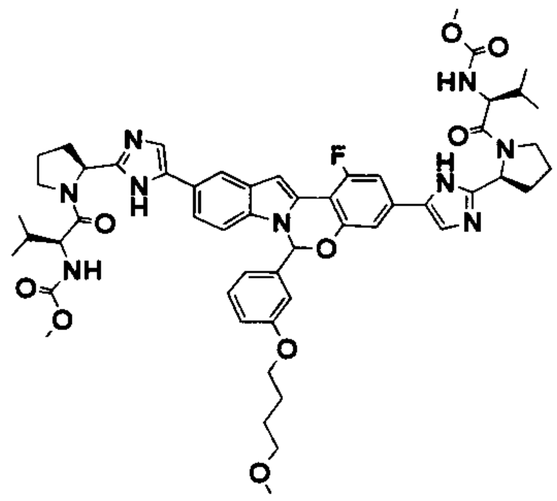
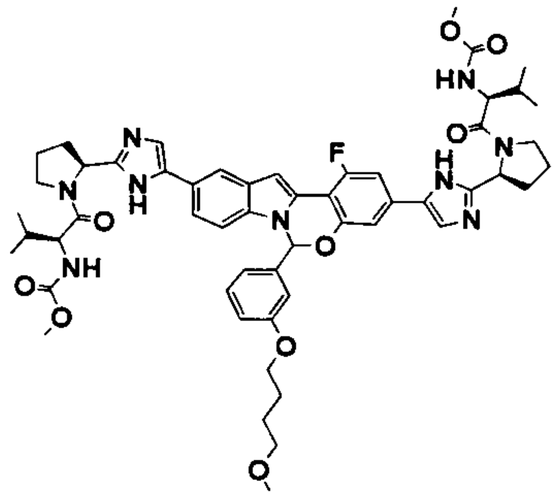
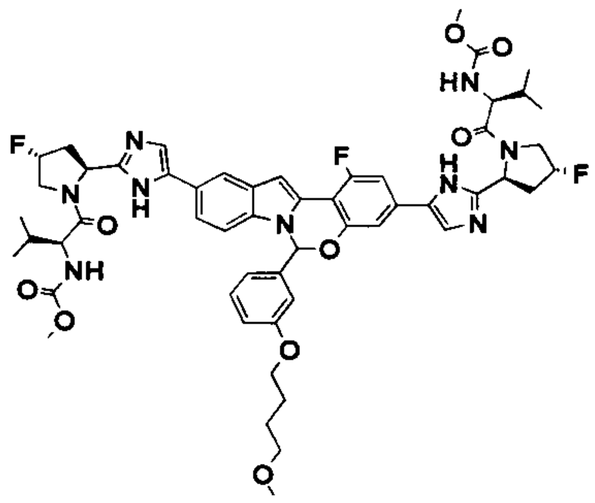
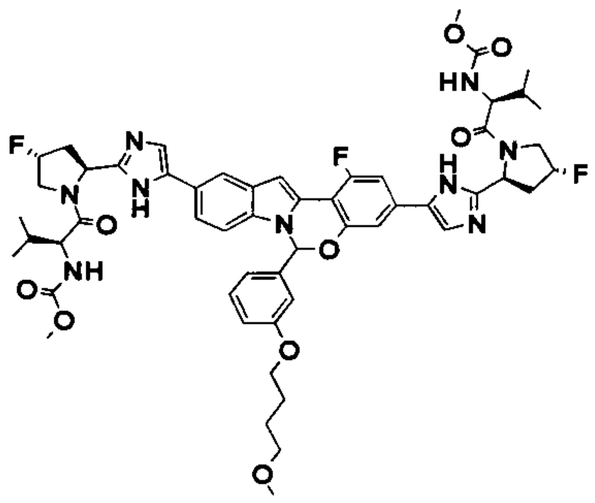
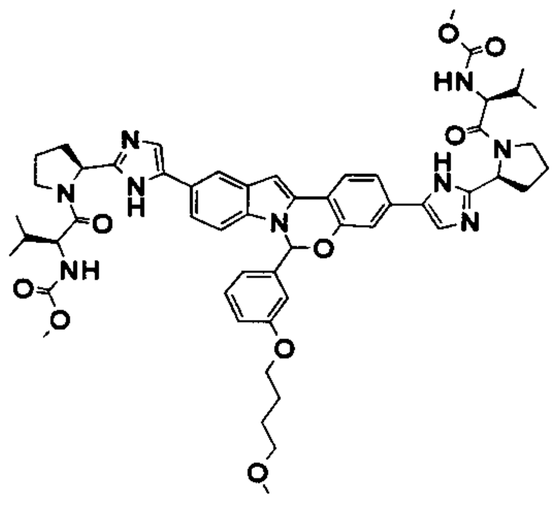
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
276		0.045	2.1	11.9	0.014	98.3	1037.12	1019.9	Mixture of isomers
277							940.12	941	Single isomer
278							940.12	941	Single isomer
279							1001.14	1002	Single isomer
280							1001.14	1002	Single isomer

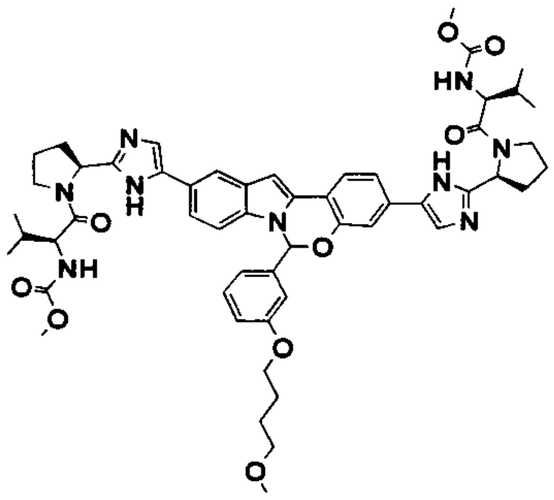
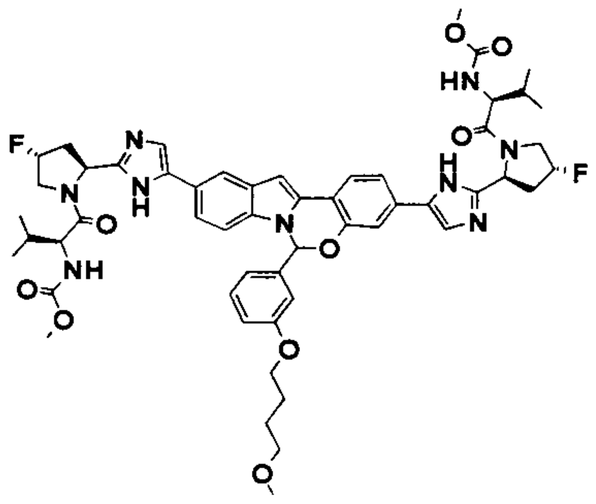
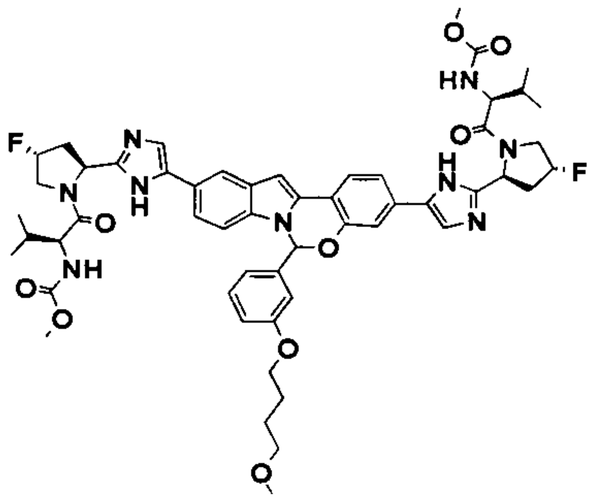
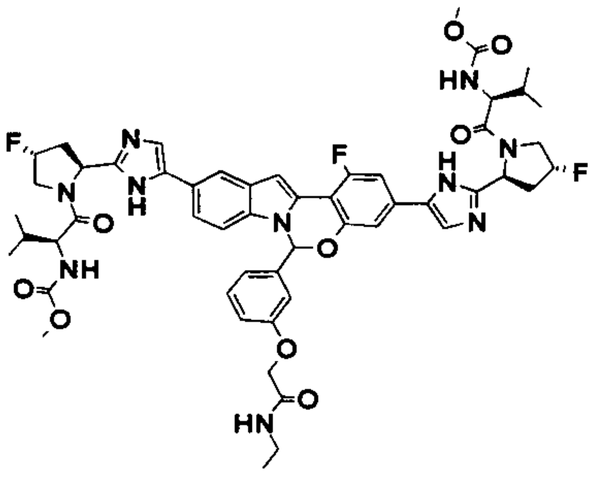
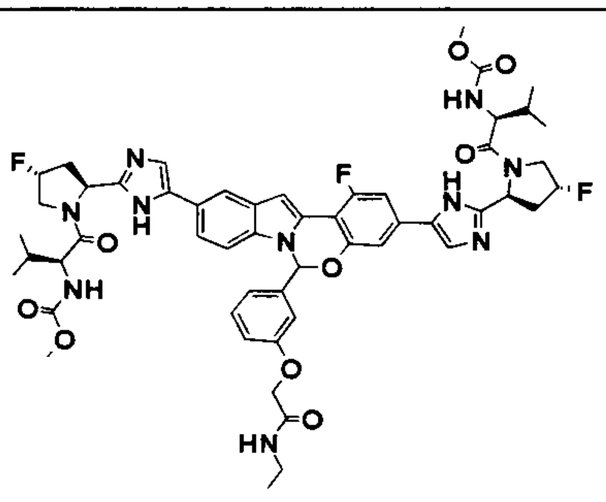
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
281		0.003	58.4	0.7	0.006	13.7	956.12	956.8	Single isomer
282							956.12	956.8	Single isomer
283							958.11	958.9	Single isomer
284		0.026	24.3		0.007	9.4	958.11	959	Single isomer
285		0.015		3.4	0.005	47.7	994.09	995	Single isomer

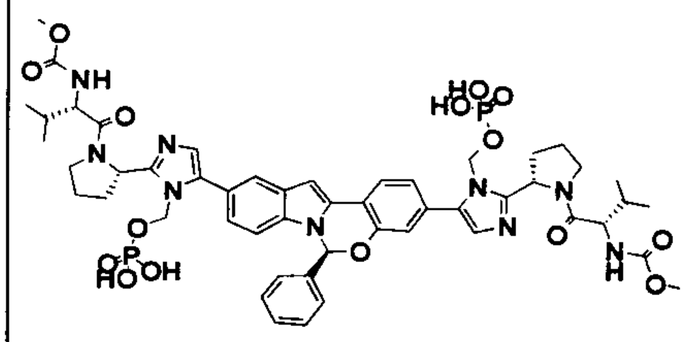
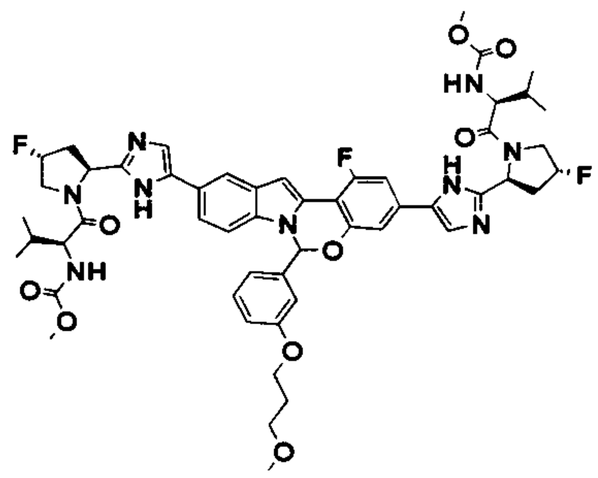
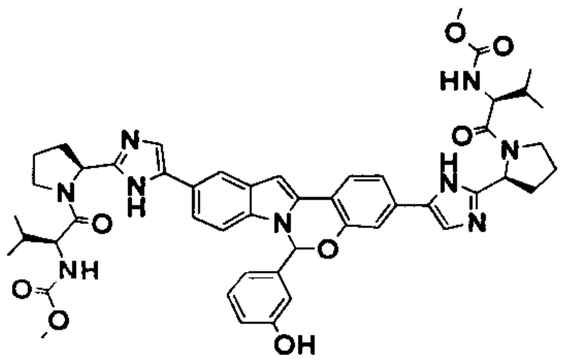
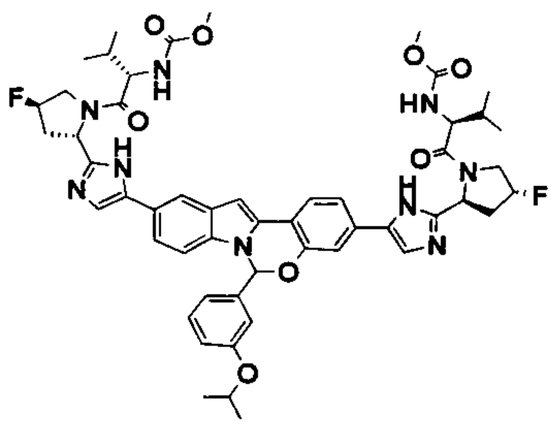
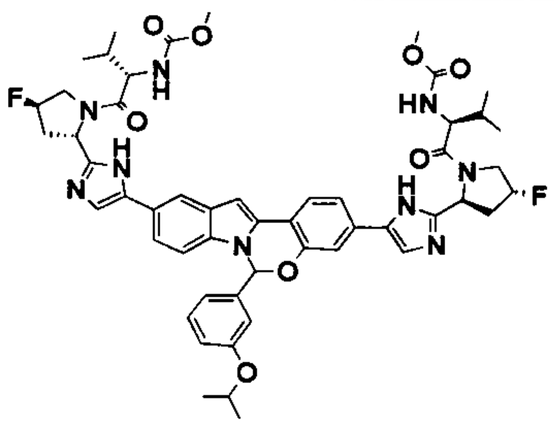
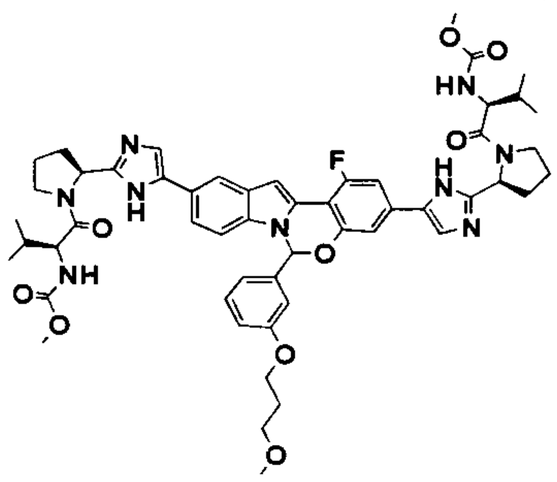
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
286		0.016	5.8	0.4	0.006	14.6	972.14	973.1	Mixture of isomers
287		0.028		0.7	0.009	9.8	984.18	984	Mixture of isomers
288		0.006	0.3	3.9	0.005	32.4	1020.16	1021	Mixture of isomers
289		0.058	0.4	9.7	0.010	> 100	992.10	993	Mixture of isomers
290		0.016	10	1.2	0.010	11.6	940.12	940.8	Mixture of isomers

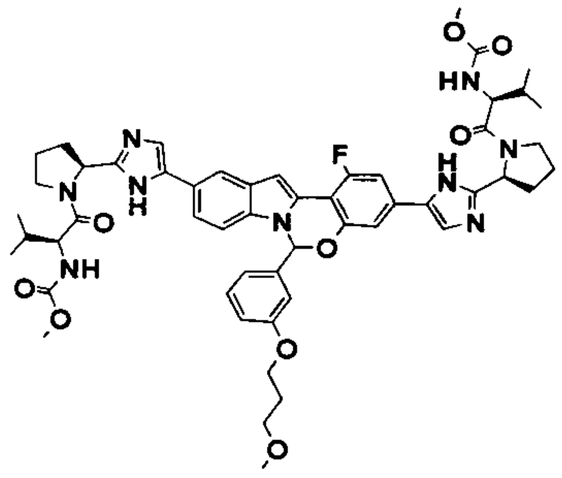
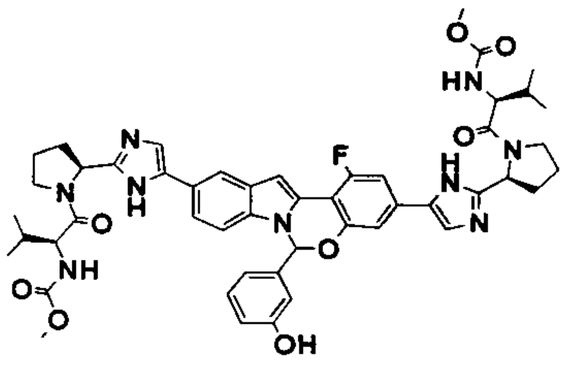
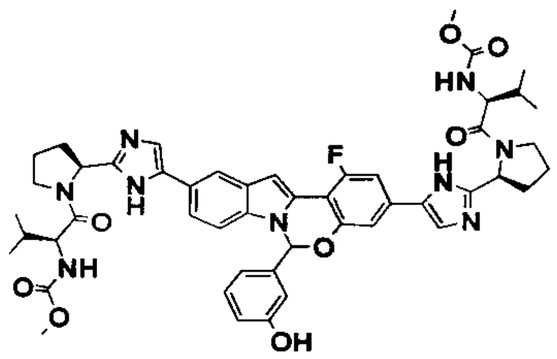
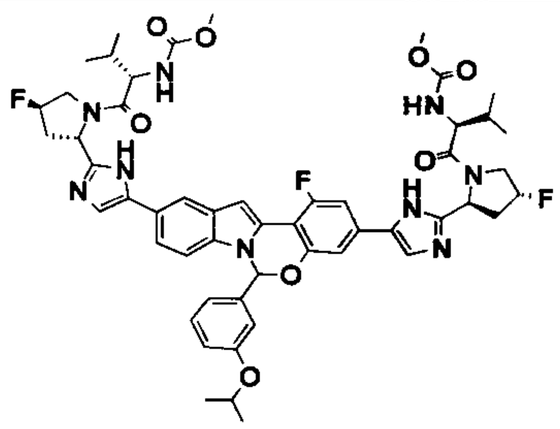
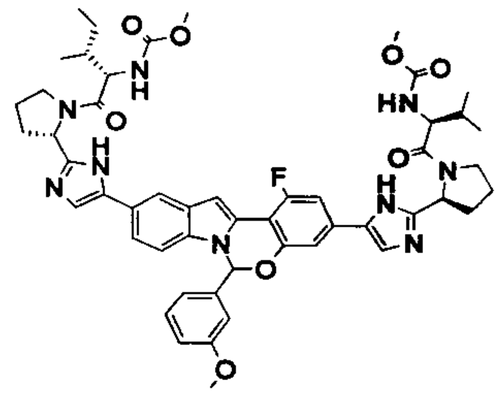
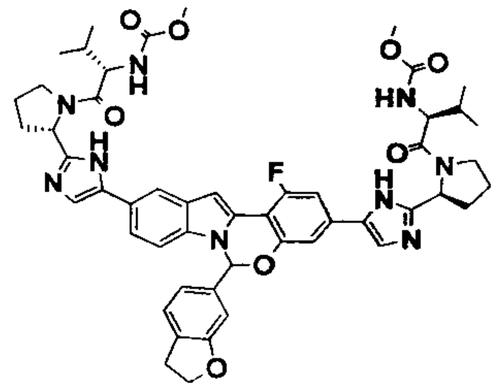
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
291							998.18	999	Mixture of isomers
292		0.015	13.5	0.3	0.007	13.7	954.15	955.1	Mixture of isomers
293		0.008	1.3		0.003	7.1	958.11	958.9	Single isomer
294		0.013	18.9	0.6	0.005	18.9	958.11	958.9	Single isomer
295							983.15	984	Single isomer

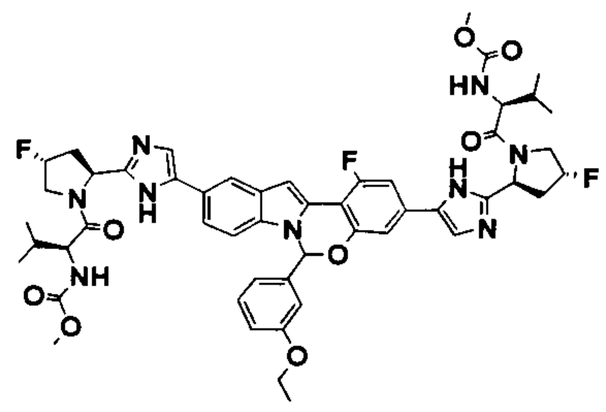
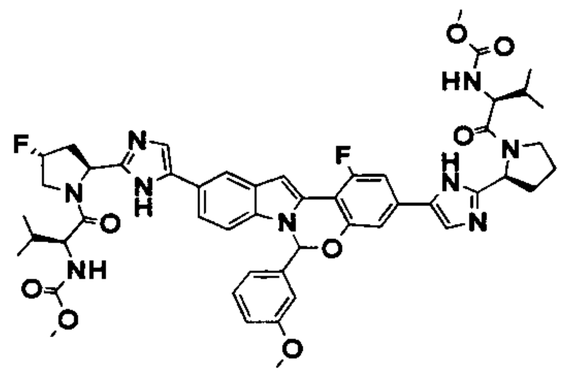
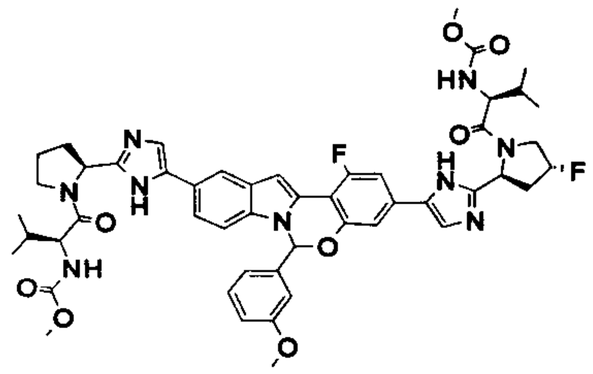
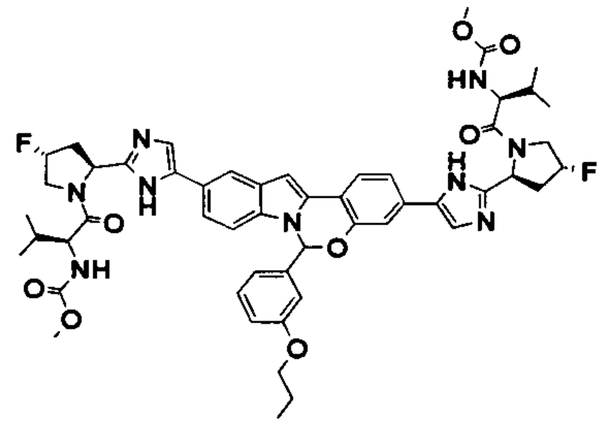
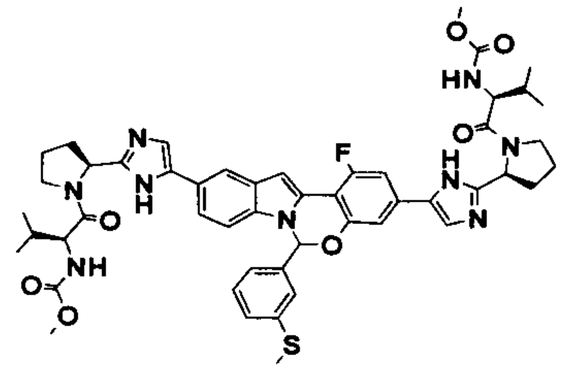
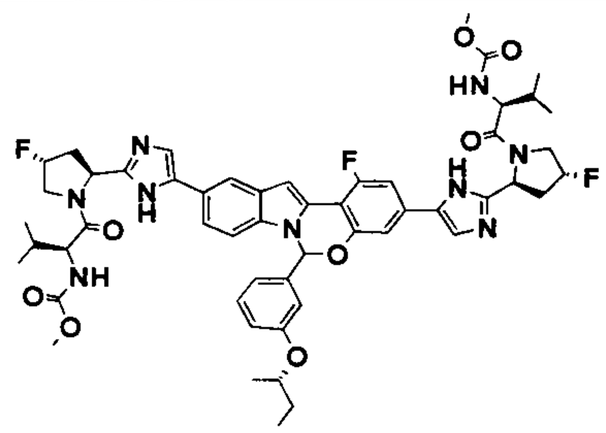
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
296							983.15	984	Single isomer
297							944.09	945	Single isomer
298							944.09	944.9	Single isomer
299		0.009	40.3		0.004	14.4	954.15	954.9	Single isomer
300		0.014	5.1	0.7	0.004	12.4	954.15	955	Single isomer

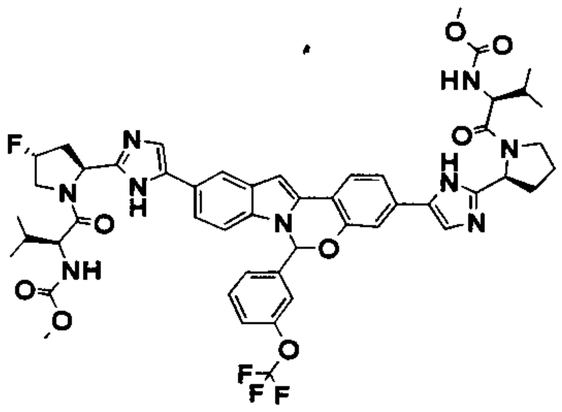
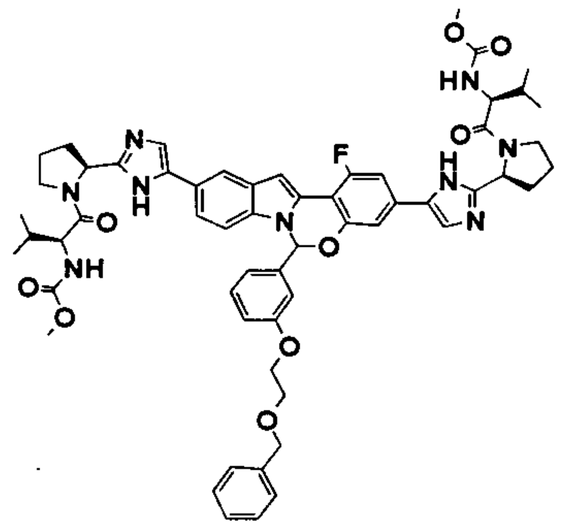
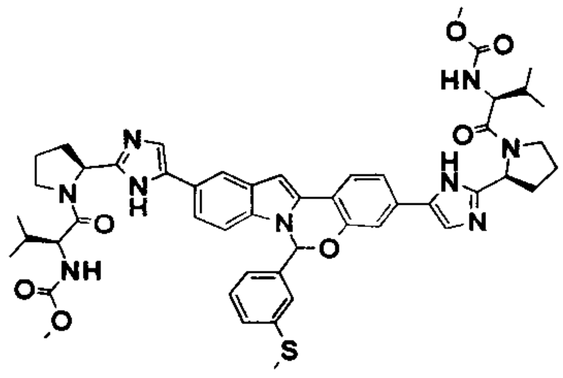
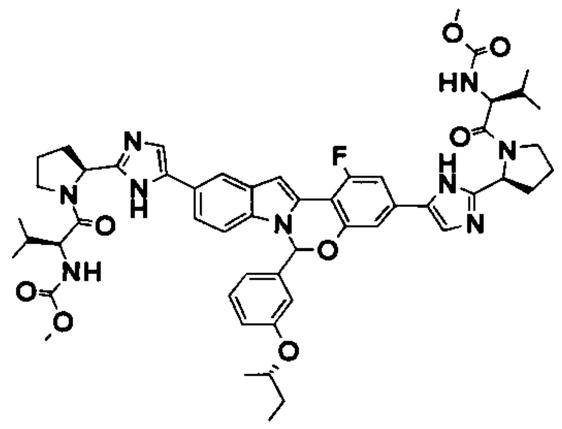
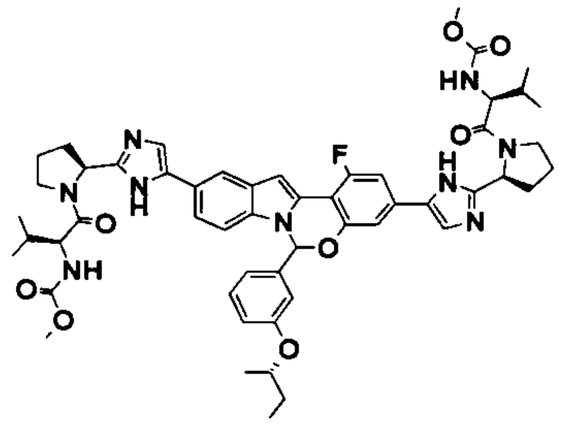
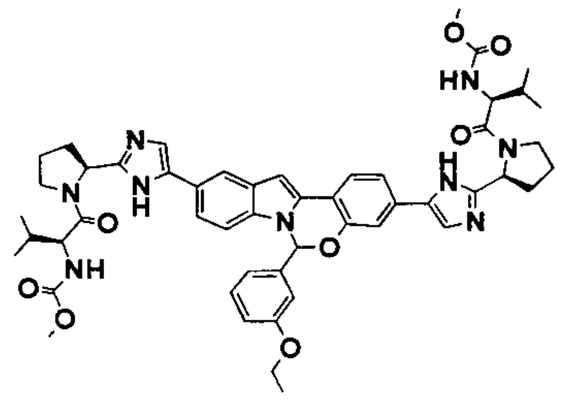
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
301		0.013	5.5		0.005	8.3	1002.17	1003	Single isomer
302							1002.17	1003	Single isomer
303		0.007	0.1		0.006	69.4	1038.15	1038.9	Single isomer
304		0.026	0.5	4.3	0.007	50.4	1038.15	1038.9	Single isomer
305							984.18	985	Single isomer

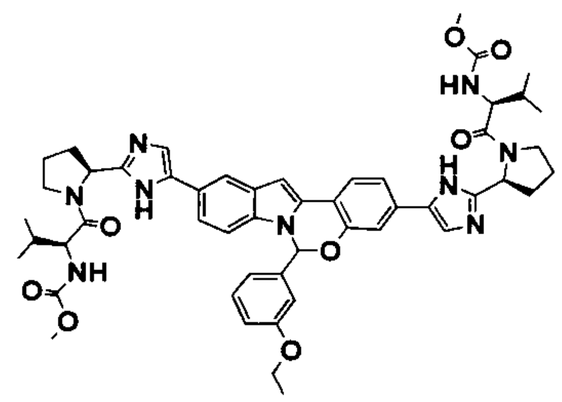
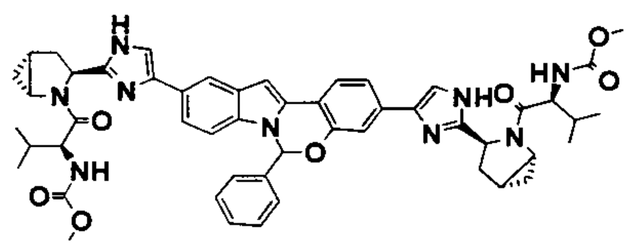
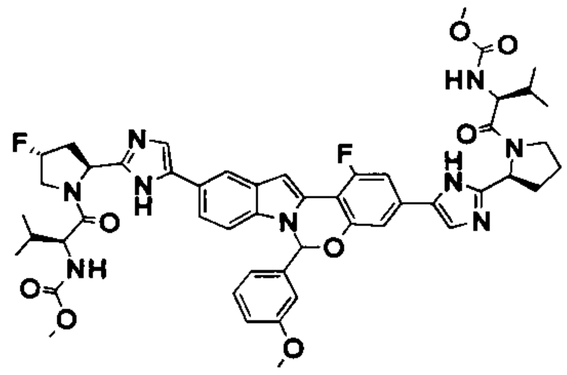
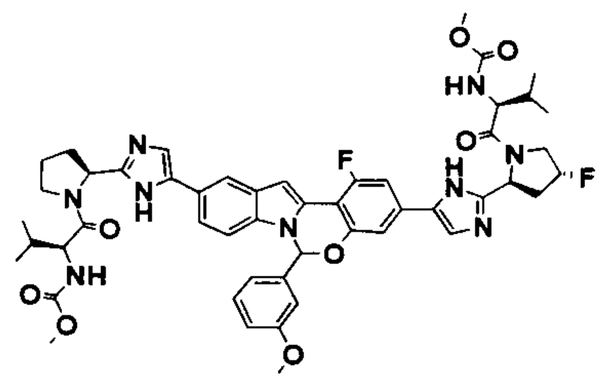
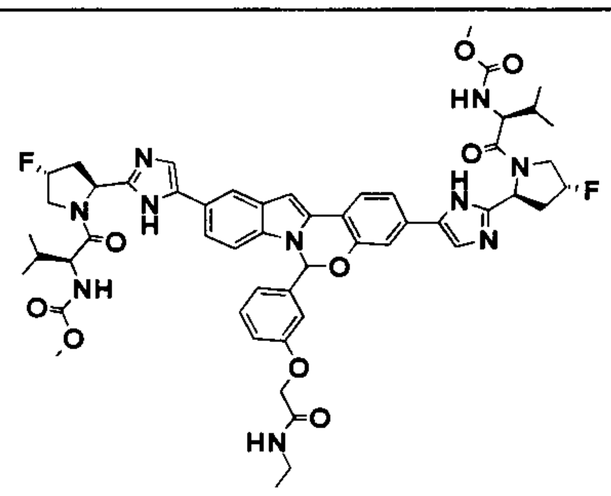
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
306		0.007	4.8	0.3	0.006	6.6	984.18	985	Single isomer
307							1020.16	1021	Single isomer
308							1020.16	1021	Single isomer
309		0.029		22.9	0.015	> 100	1037.12	1038	Single isomer
310		0.143	13.3	19.1	0.018	> 100	1037.12	1038	Single isomer

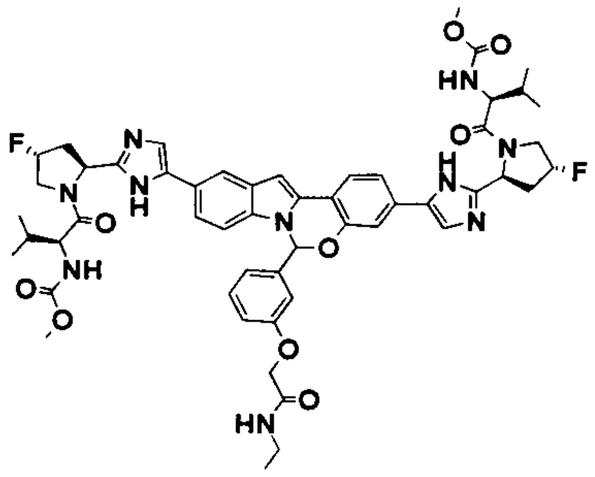
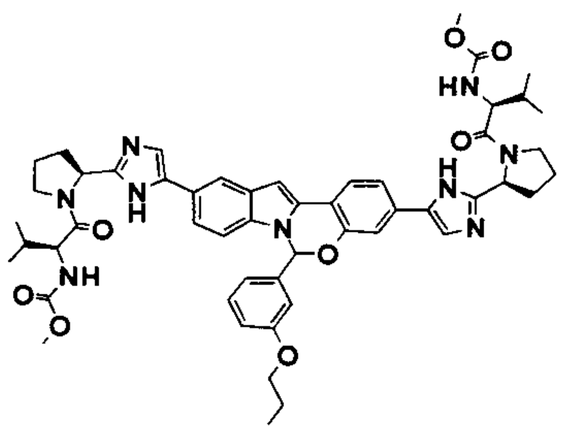
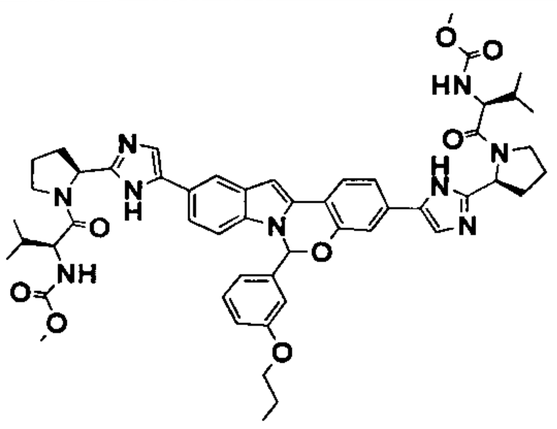
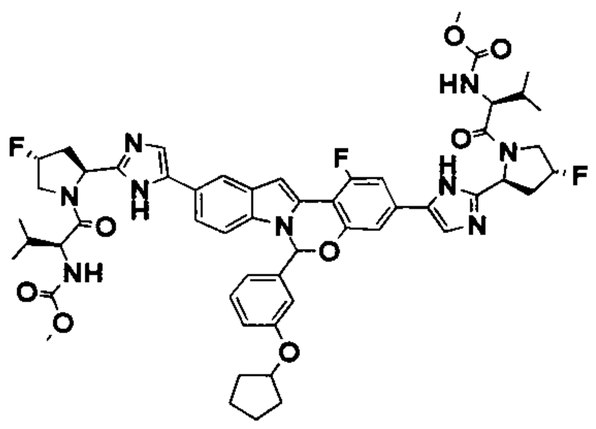
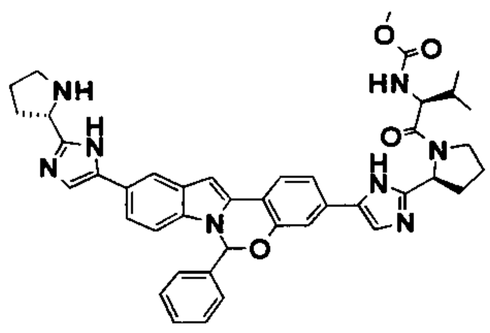
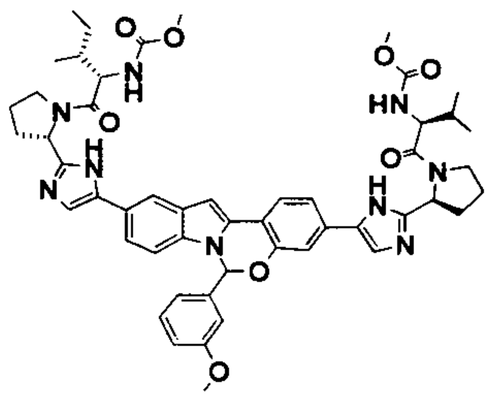
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
311							1102.05		Single isomer
312		0.01361	0.04242	2.006		104.5	1024.12	1024.9	Mixture of isomers
313		0.01139	22.11	0.4472		5.979	898.04	899..1	Mixture of isomers
314		0.05816	1.466	2.87		87.12	976.10	976.7	Single isomer
315				2.532		90.01	976.10	976.7	Single isomer
316		0.005	18.02	0.36		23.24	988.14	988.9	Single isomer

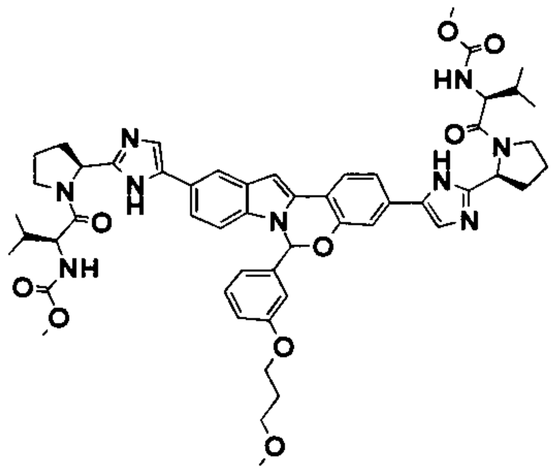
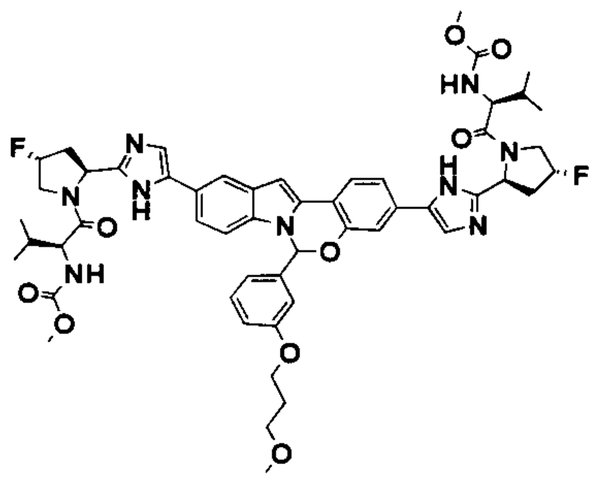
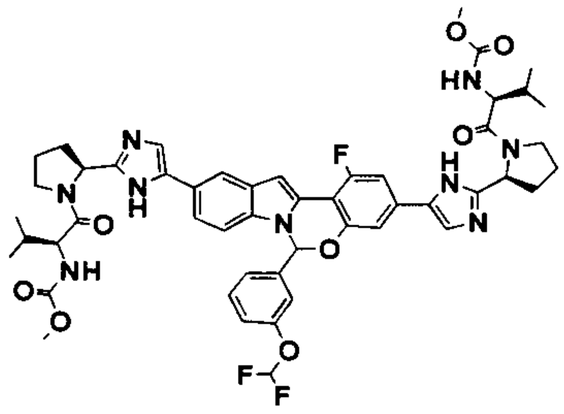
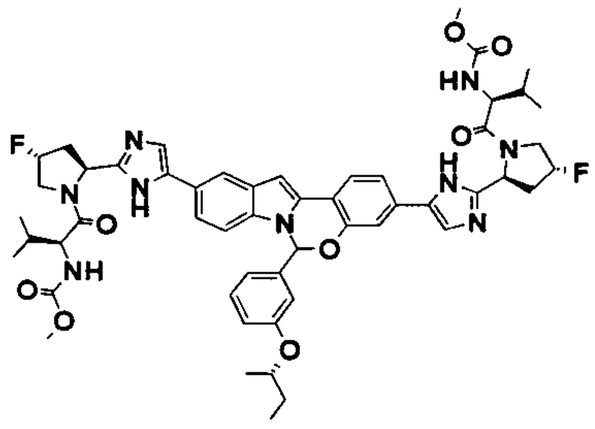
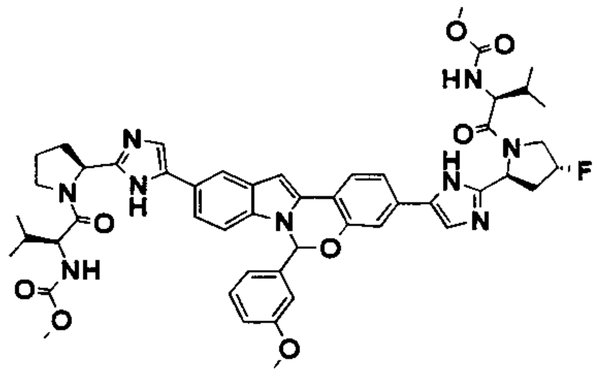
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
317		0.00817	1.184	0.195		6.912	988.14	988.9	Single isomer
318		0.015	0.5	0.3209		13.88	916.03	916.8	Single isomer
319		0.004	41.02	0.3329		9	916.03	916.8	Single isomer
320		0.01128	0.1398	1.207		87.61	994.09	995	Mixture of isomers
321		0.00982	2.132	0.195		2.146	944.09	945.1	Mixture of isomers
322		0.0162	0.4183	0.1426		1.192	942.07	943.1	Mixture of isomers

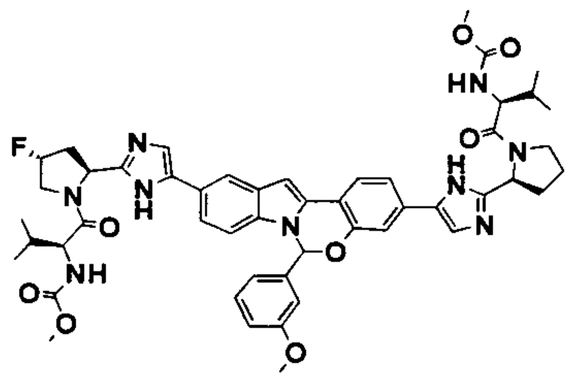
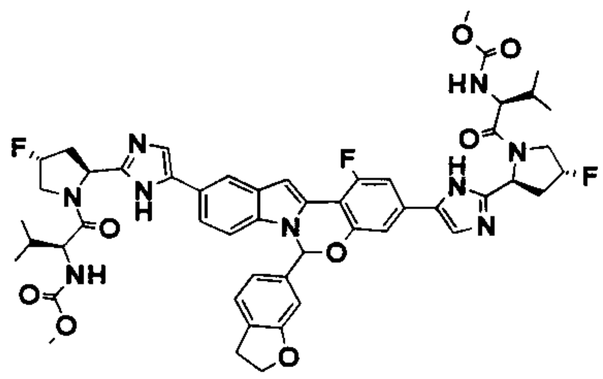
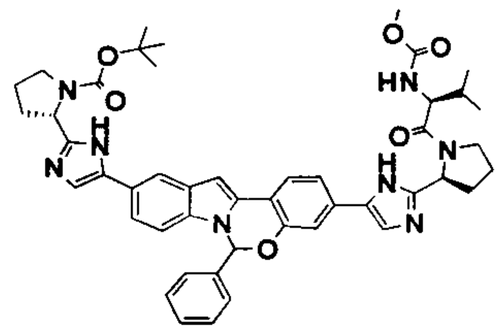
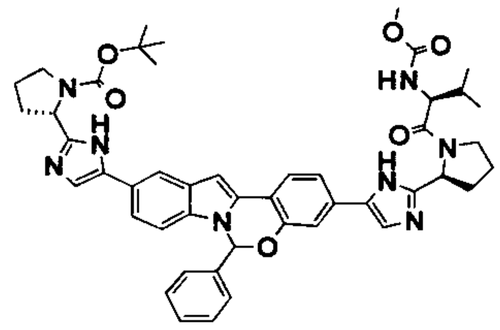
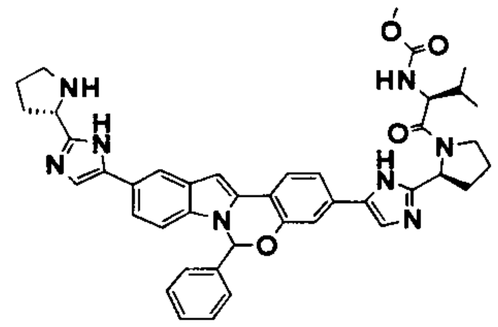
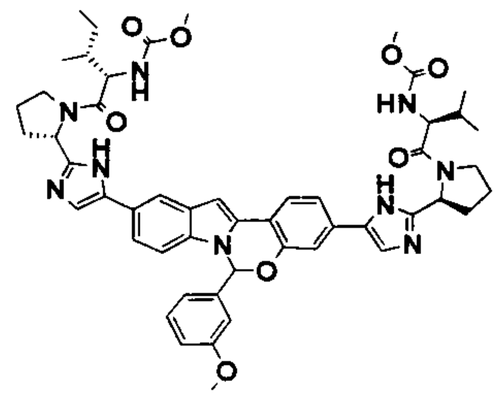
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
323		0.01563	0.02	2.674		68.32	980.07	981	Mixture of isomers
324		0.02436	6.242	1.81		25.43	948.05	948.9	Single isomer
325		1	100	100		100	948.05	948.9	Single isomer
326		0.02664		2.77		49.99	976.10	977	Mixture of isomers
327		0.01	2.3	0.1873		1.328	946.12	947	Mixture of isomers
328		0.01029	0.04	2.205		73	1008.12	1009.1	Mixture of isomers

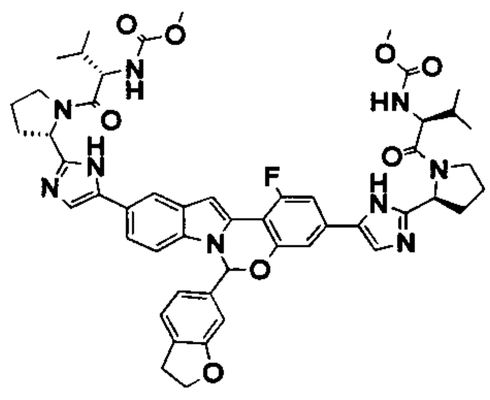
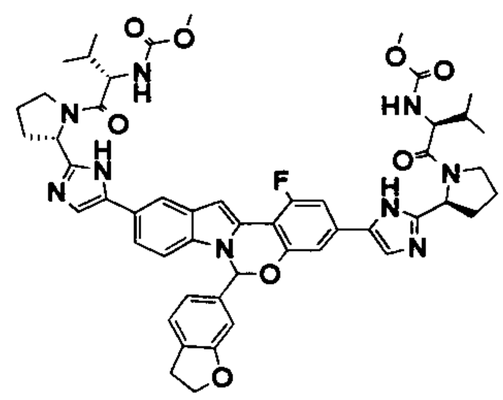
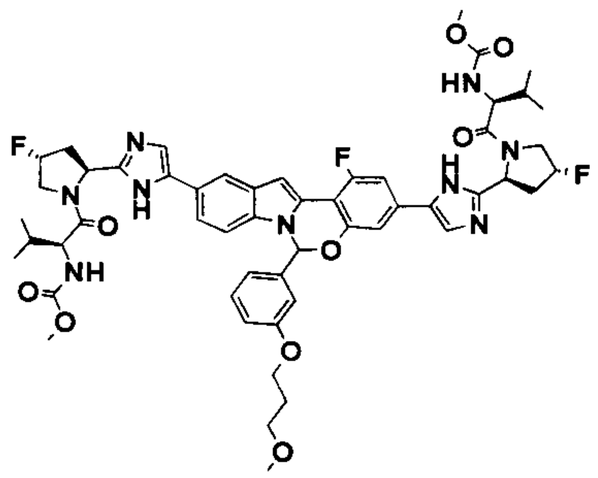
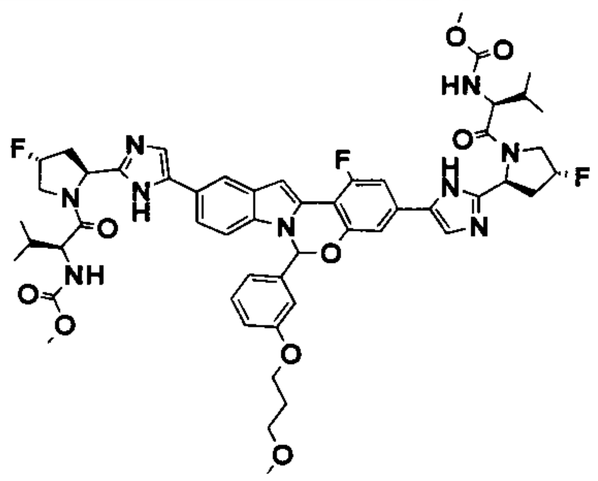
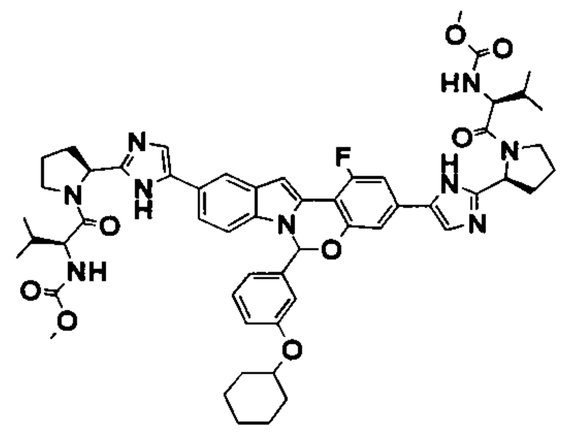
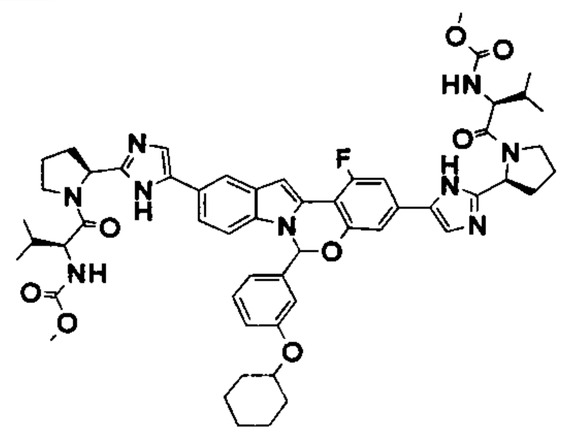
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
329		0.0056	1.517	1.656		18.49	984.03	985	Mixture of isomers
330		0.003	1.486	0.2152		7.645	1050.21	1051.1	Mixture of isomers
331		0.004	7.523	0.2071		4.54	928.13	928.8	Mixture of isomers
332		0.01225	43.76	0.4942		17.35	972.14	973	Single isomer
333		0.01234	1.19	0.195		5.178	972.14	973	Single isomer
334		0.005	52.66	0.2183		12.86	926.09	926.8	Single isomer

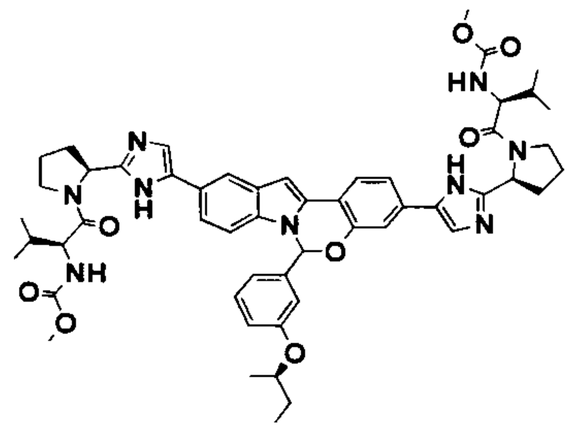
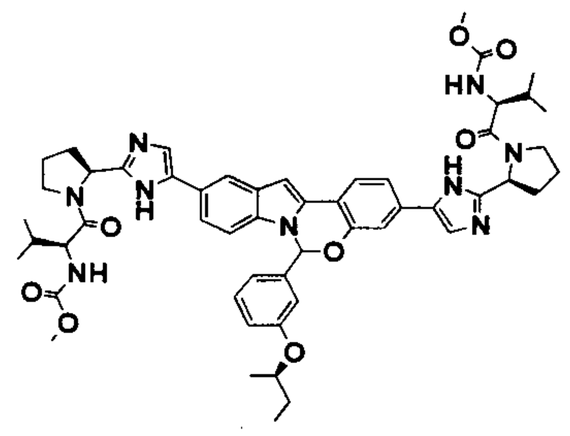
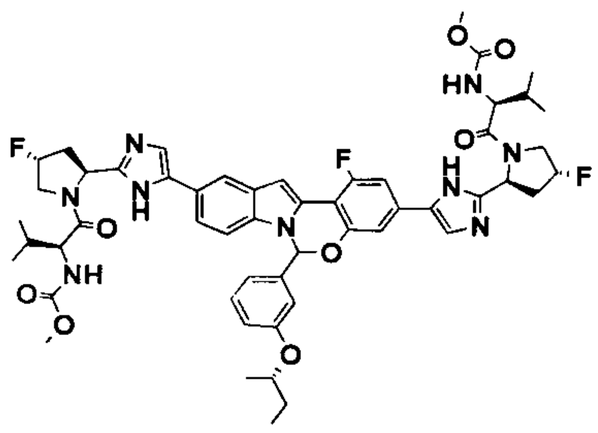
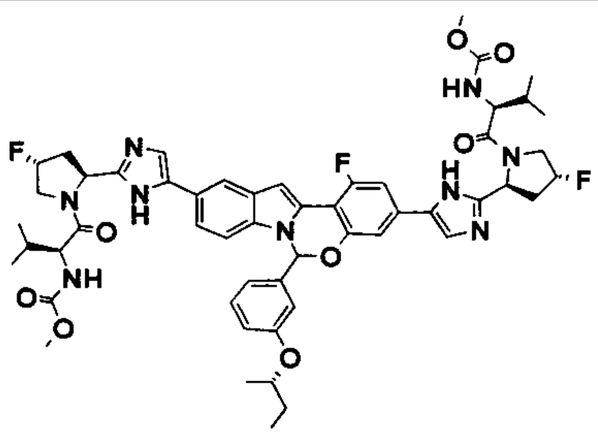
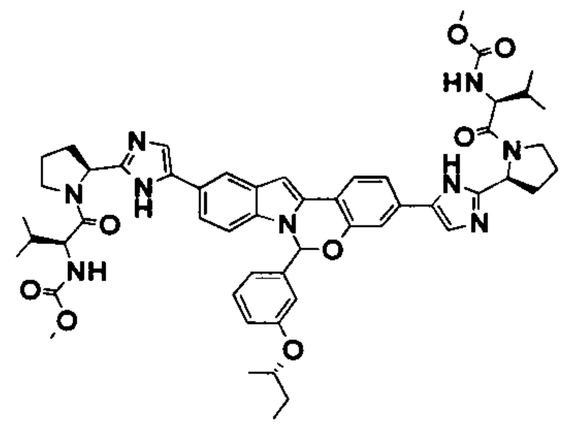
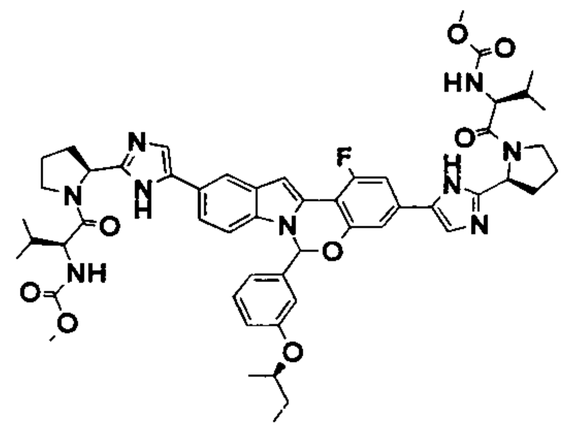
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
335		0.01505	1.8	0.2346		0.37	926.09	927.1	Single isomer
336		0.01157	13.82	0.1904		5.211	906.06	907.1	Mixture of isomers
337		0.0035	0.1841	0.195		7.701	948.05	949	Single isomer
338		0.01346	0.3647	0.195		7.558	948.05	949.1	Single isomer
339		0.953	100	100		100	1019.13	1020	Single isomer

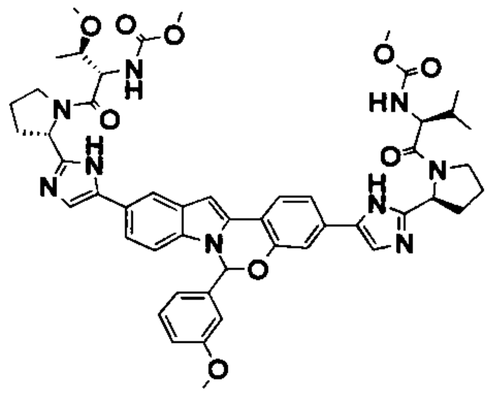
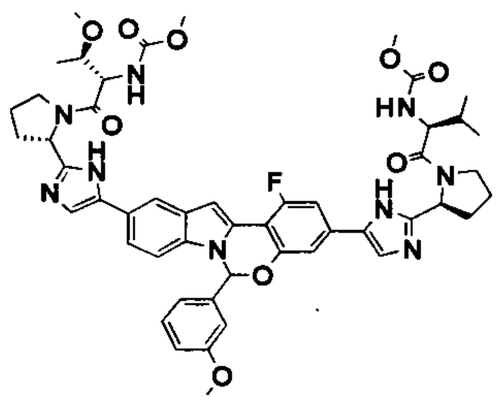
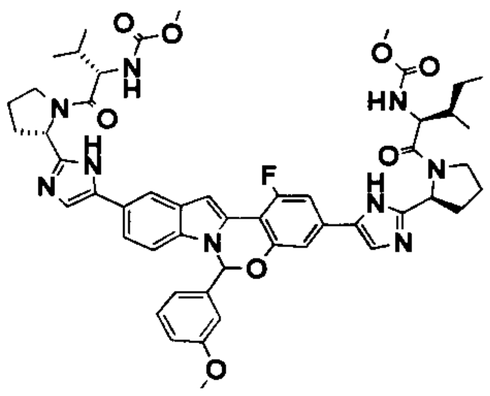
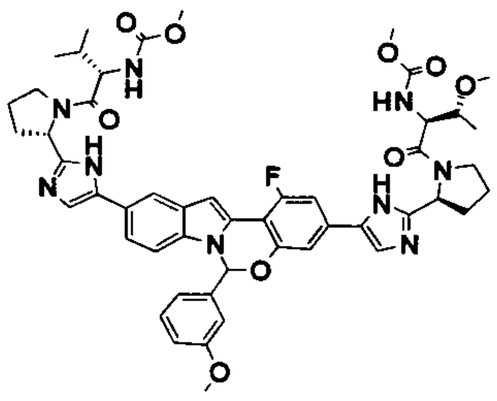
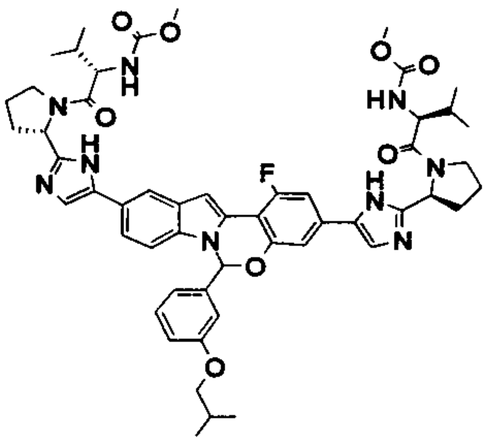
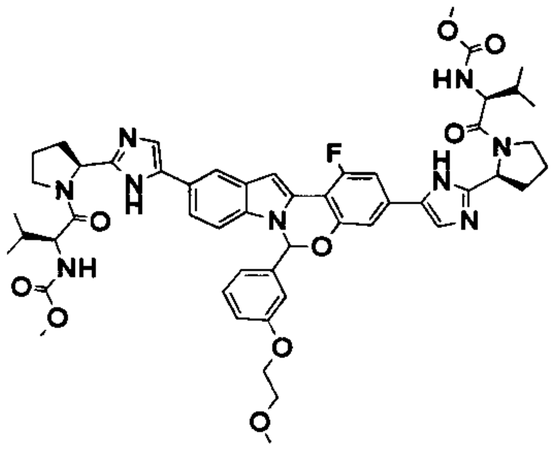
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
340		1	100	100		100	1019.13	1020.2	Single isomer
341		0.01328	54.63	0.2997		11.13	940.12	941.2	Single isomer
342		0.01308	2.627	0.2881		2.418	940.12	941.2	Single isomer
343		0.02634	0.07918	3.088		61.91	1020.13	1021	Mixture of isomers
344		15.9	469.9				724.87	725.5	Single isomer
345		0.01349	8.592	1.789		31.37	926.09	926.6	Single isomer

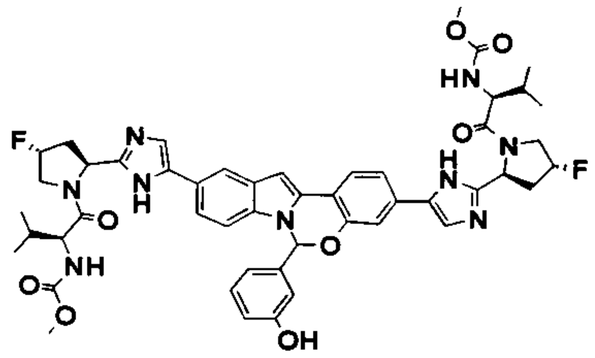
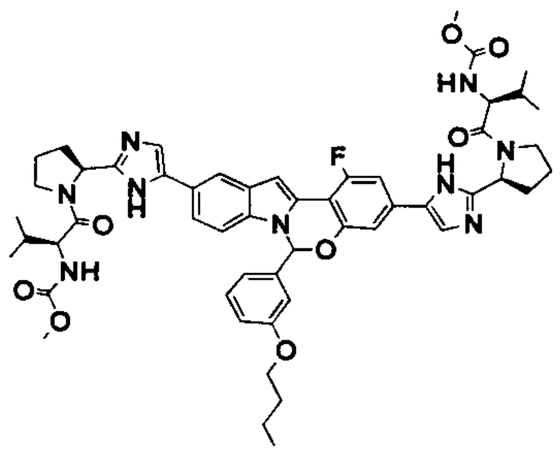
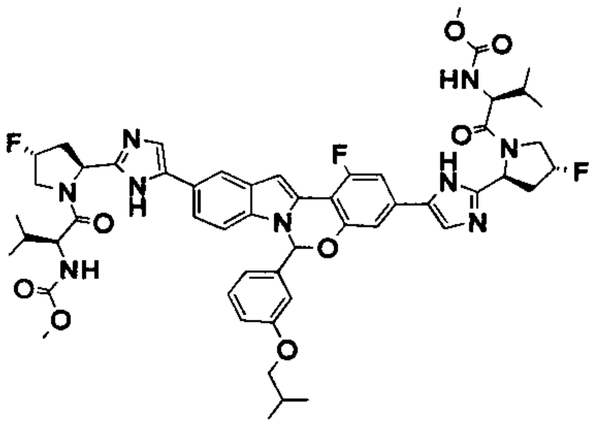
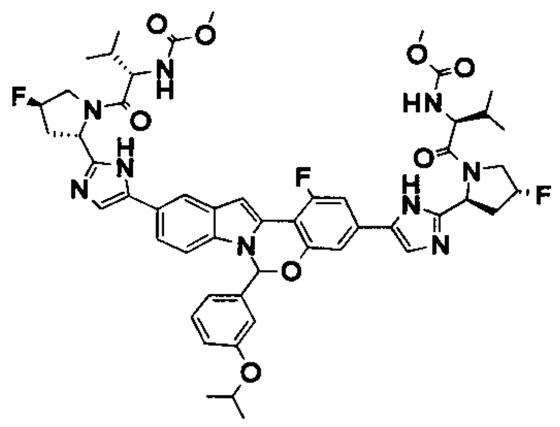
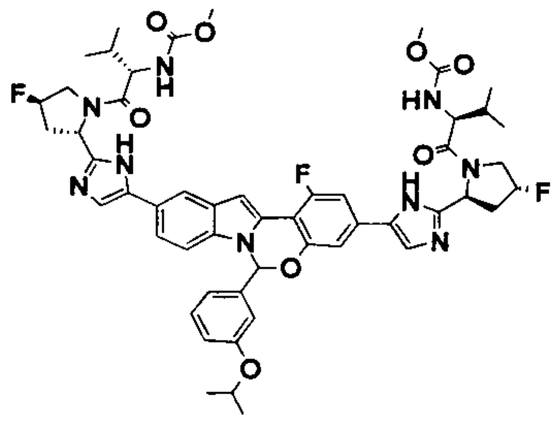
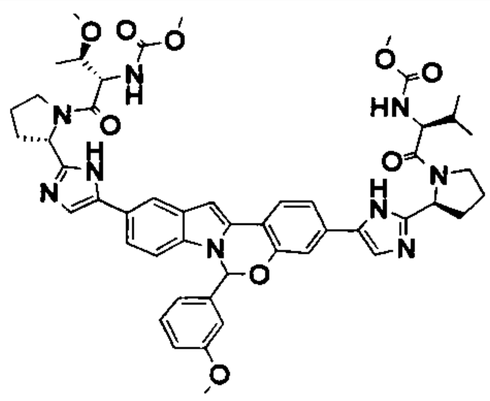
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
346		0.01386	6.028	0.4267		2.64	970.15	971	Single isomer
347		0.028	0.1566	6.892		188.4	1006.13	1007	Mixture of isomers
348		0.01713	7.981	0.4534		2.465	966.04	967.1	Mixture of isomers
349		0.01237	0.2279	2.721		84.03	990.13	991.1	Mixture of isomers
350		0.01097	0.8042	0.7204		8.253	930.06	931	Mixture of isomers

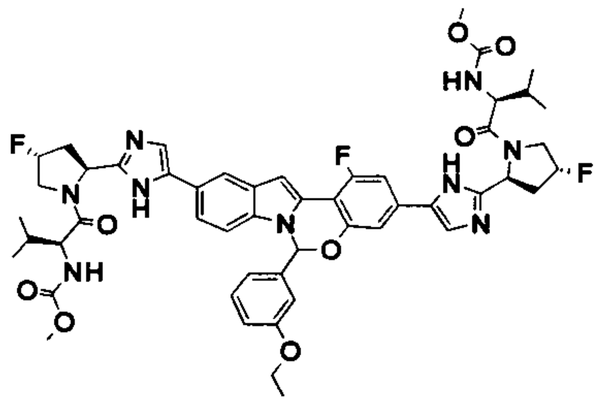
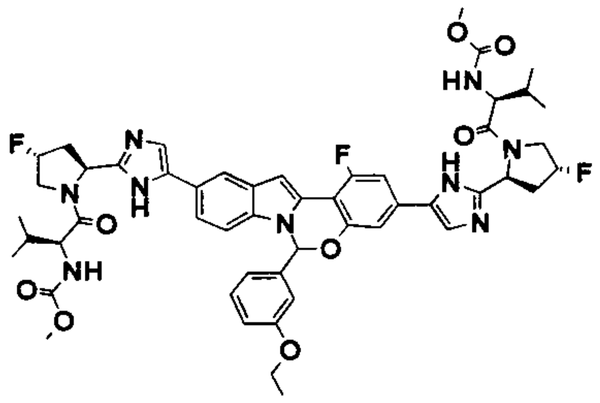
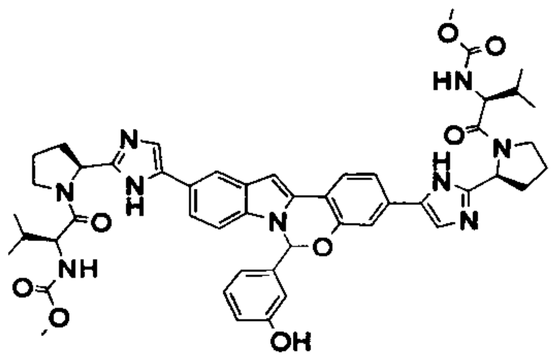
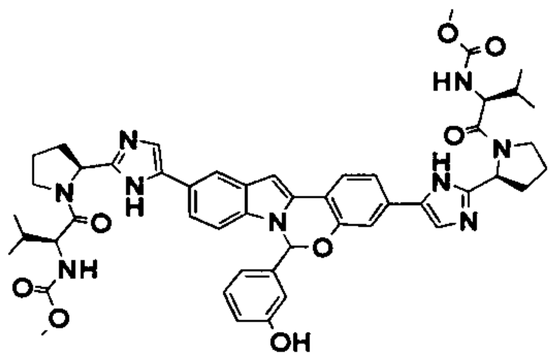
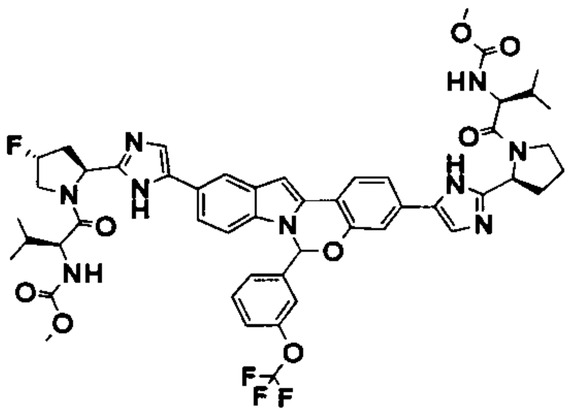
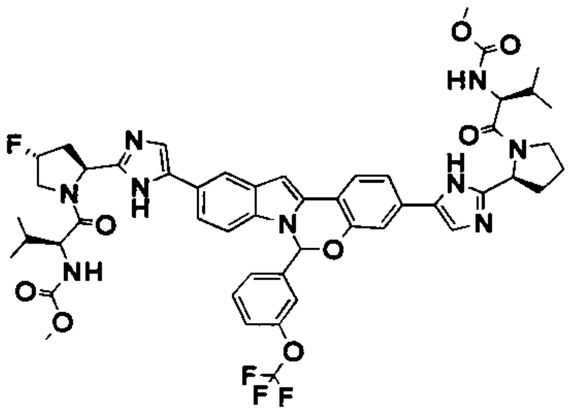
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
351		0.02156	0.4577	0.1775		9.245	930.06	931.1	Mixture of isomers
352		0.00976	0.04956	0.5672		9.561	978.05	979.2	Mixture of isomers
353		8.626	366				824.99	825.9	Single isomer
354		1.179	678.1				824.99	825.9	Single isomer
355		12.16	110.2				724.87	725.8	Single isomer
356		0.01505	3.088	0.2035		2.379	926.09	927	Single isomer

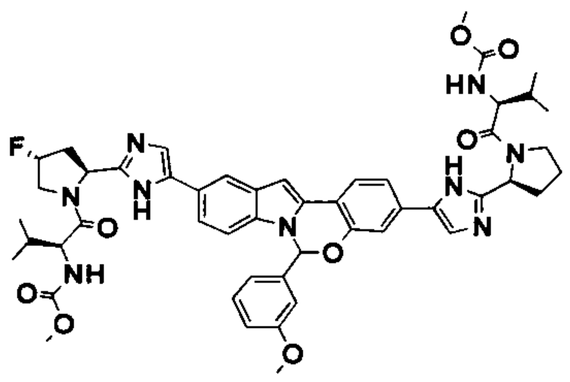
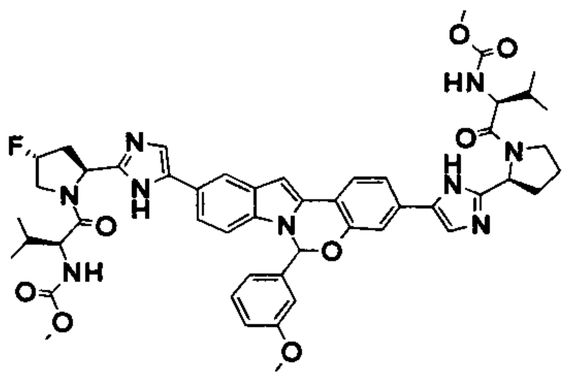
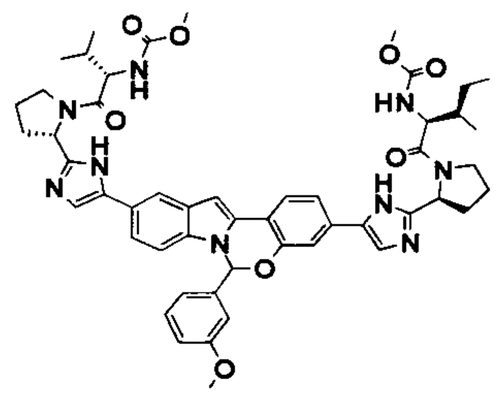
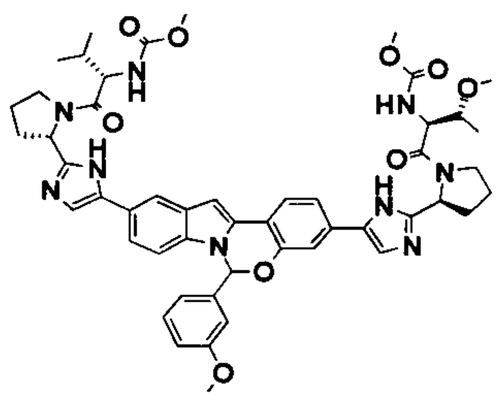
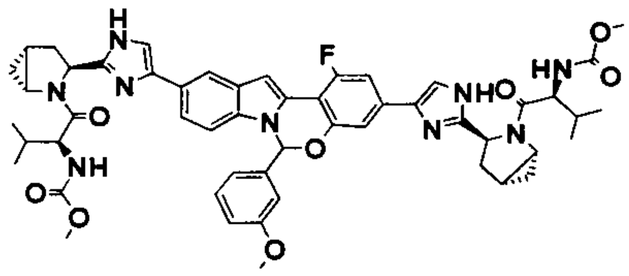
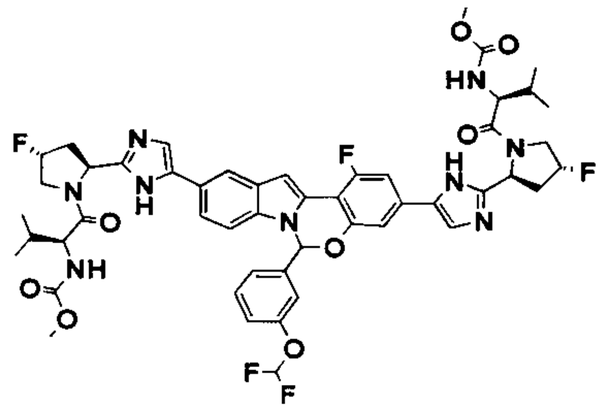
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
357		0.0162	20.67	0.3557		2.697	942.07	943	Single isomer
358		0.02086	1.514	0.03596		0.5689	942.07	943	Single isomer
359		0.02836	0.5365	4.157		76.52	1024.12	1025.2	Single isomer
360		0.01321	0.06267	2.885		111.6	1024.12	1025.2	Single isomer
361		0.01345	20.71	0.572		33.65	998.18	999.1	Single isomer
362		0.02602	2.432	0.07		4.6	998.18	999.1	Single isomer

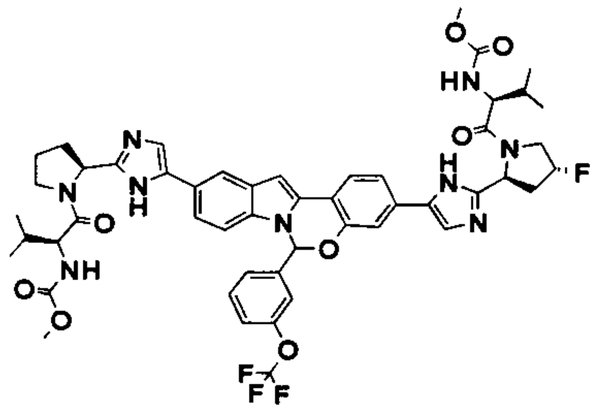
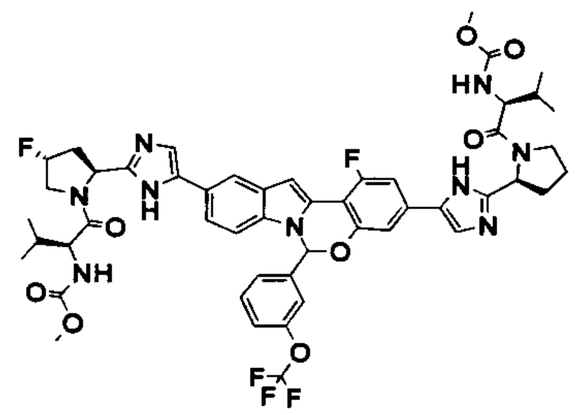
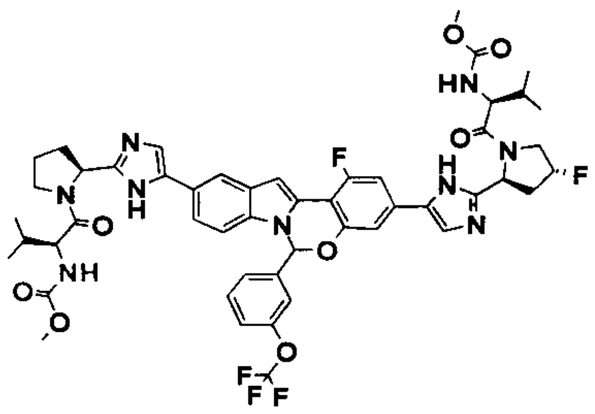
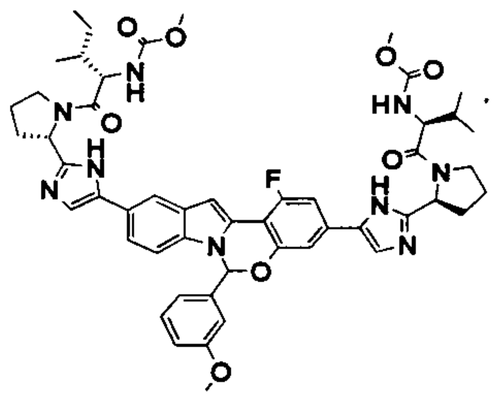
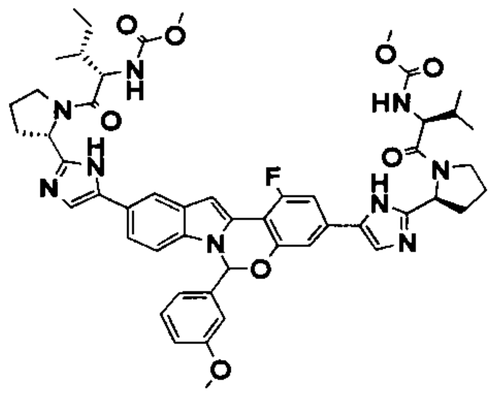
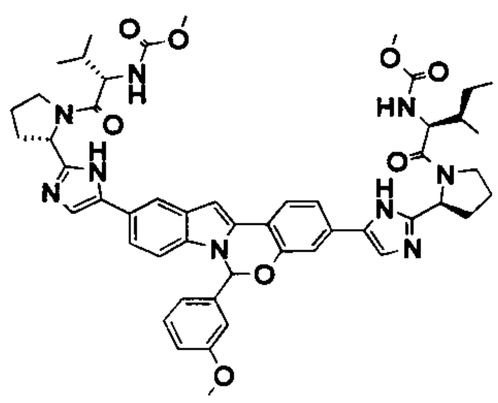
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
363		0.018	43.3	0.4796		10.63	954.15	955	Single isomer
364		0.028	48.67	0.6579		10.78	954.15	955	Single isomer
365		0.00804	0.04587	2.188		68.84	1008.12	1009.1	Single isomer
366		0.0389	0.2949	2.96		79.37	1008.12	1009.1	Single isomer
367		0.01121	5.385	0.2396		7.747	954.15	955.2	Mixture of isomers
368		0.02062	7.579	0.363		32.25	972.14	973	Mixture of isomers

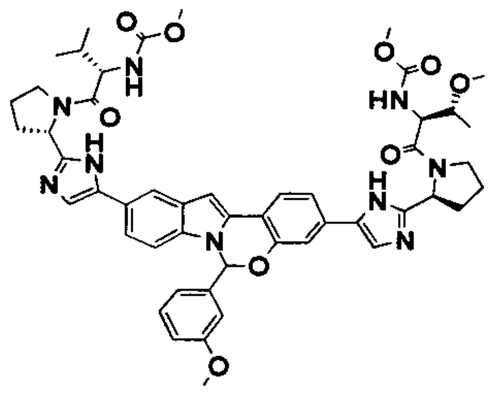
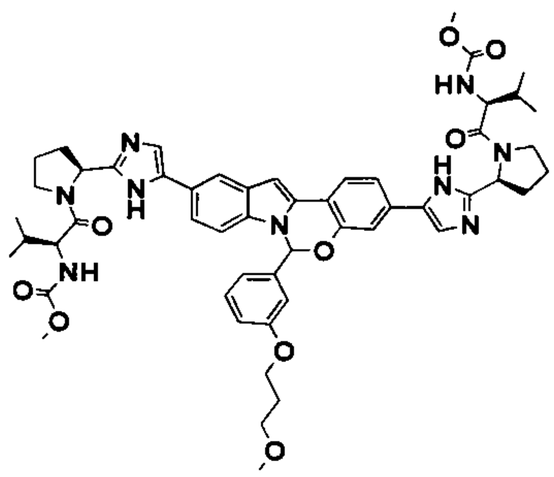
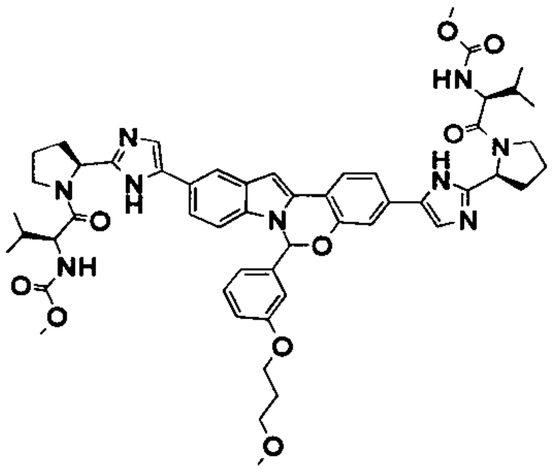
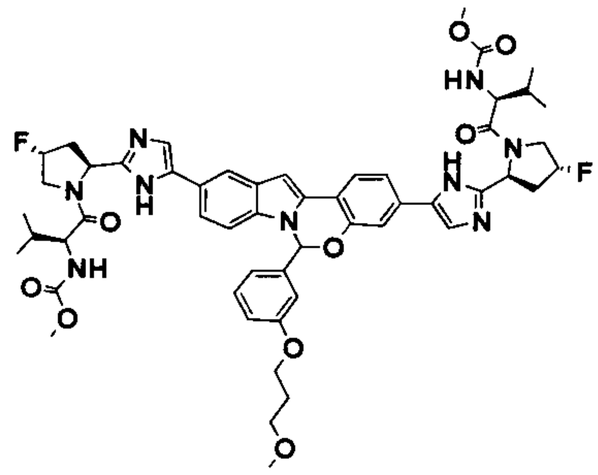
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
369		0.02	15.21	0.112		3.65	928.07	929.2	Single isomer
370		0.01857	7.238	0.028		0.55	946.06	946.7	Mixture of isomers
371		0.01427	2.28	0.2345		11.7	944.09	944.6	Mixture of isomers
372		0.02522	1.79	0.055			946.06	947.8	Mixture of isomers
373		0.01613	5.214	0.2444		5.925	972.14	973	Mixture of isomers
374		0.0105	8.422	0.3063		8.9	974.11	975	Mixture of isomers

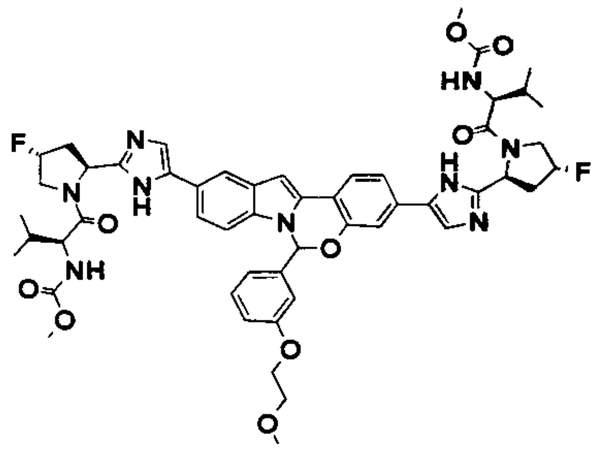
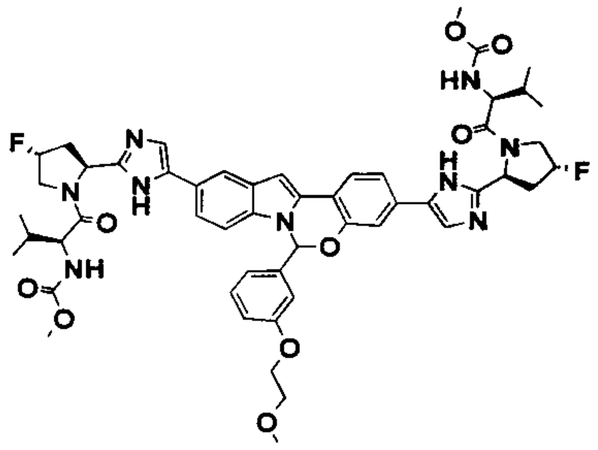
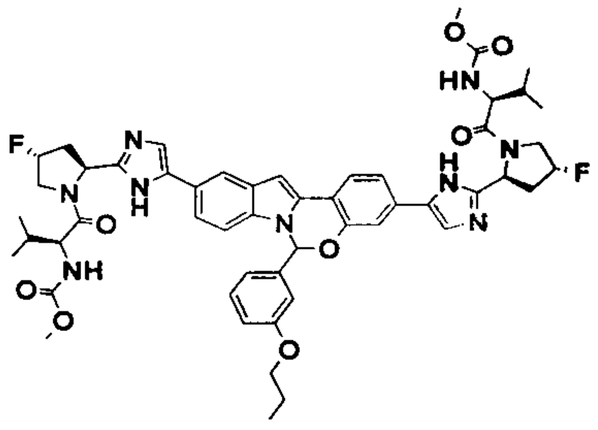
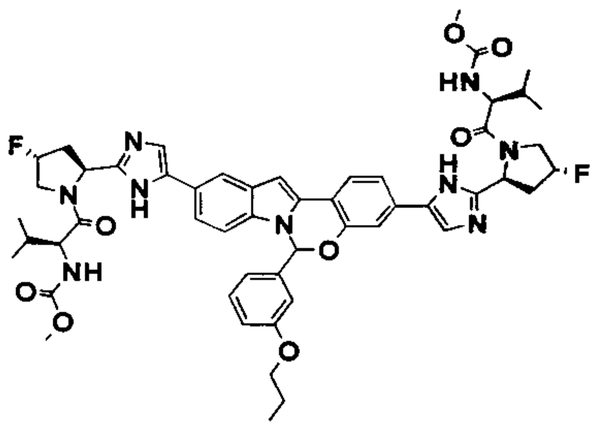
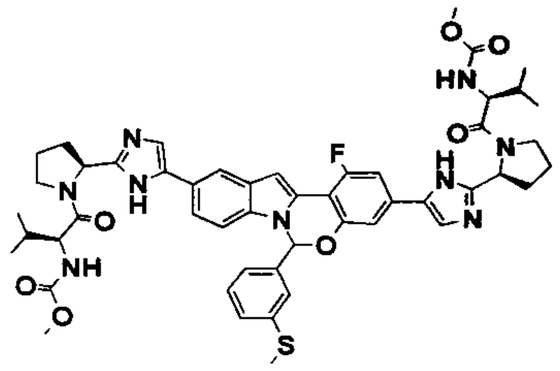
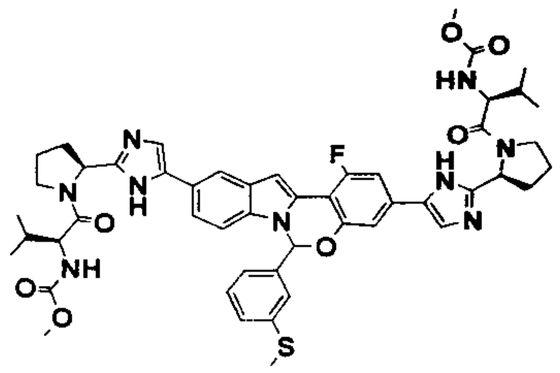
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
375		0.09597	1.528	6.8		198	934.02	935	Mixture of isomers
376		0.00973	2.25	0.035		11.21	972.14	973	Mixture of isomers
377		0.00736	0.025	1.792		59.8	1008.12	1009	Mixture of isomers
378		0.023	0.43	2.018		73.85	994.09	995	Single isomer
379		0.005	0.0098	2.687		71.51	994.09	995	Single isomer
380		0.01344	3.12	0.1024		0.4612	928.07	929	Single isomer

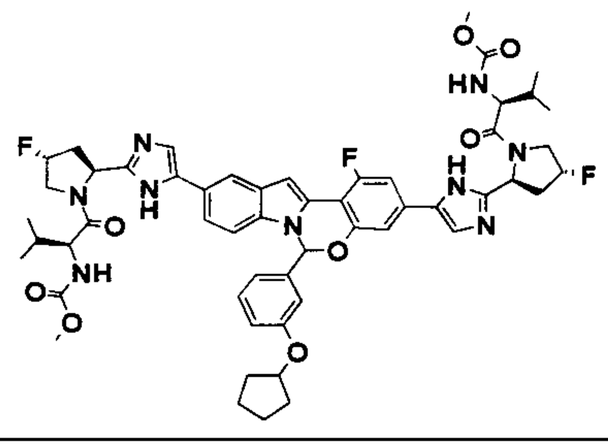
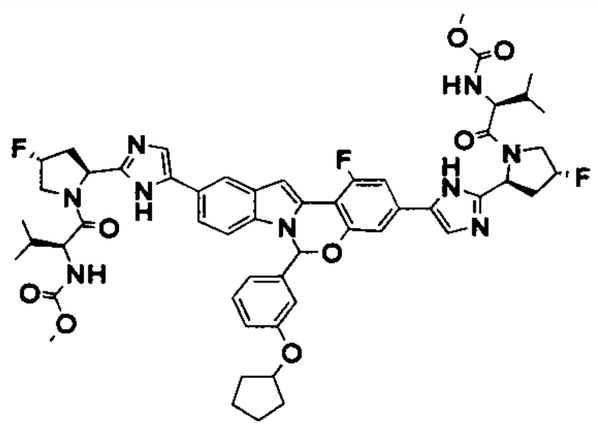
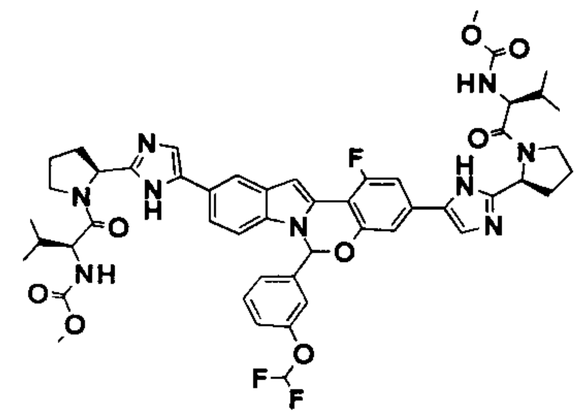
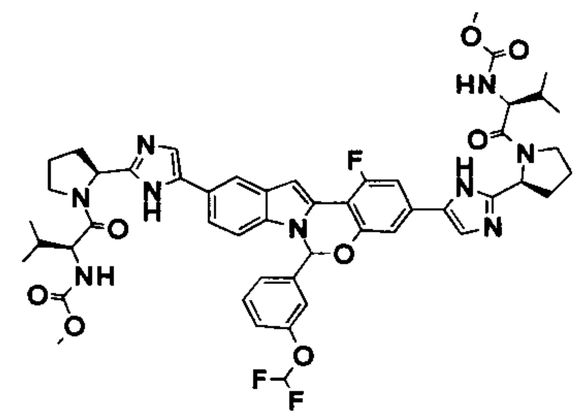
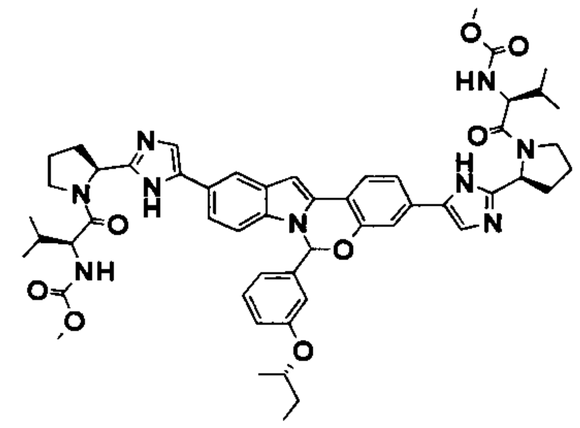
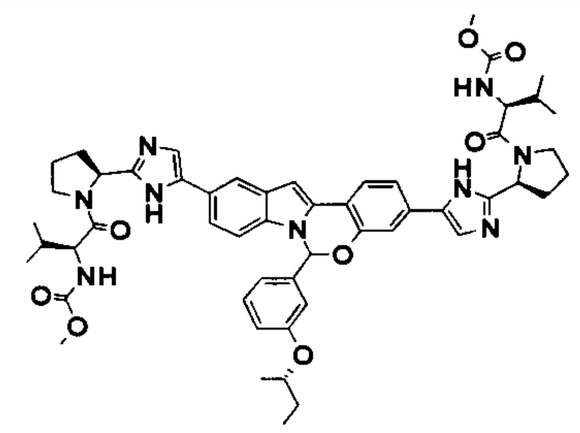
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
381		0.04486	0.3468	3.283		71.4	980.07	981	Single isomer
382		0.0036	0.0181	1.202		57.74	980.07	981	Single isomer
383							898.04	899.1	Single isomer
384							898.04	899.1	Single isomer
385							984.03	984.8	Single isomer
386							984.03	985	Single isomer

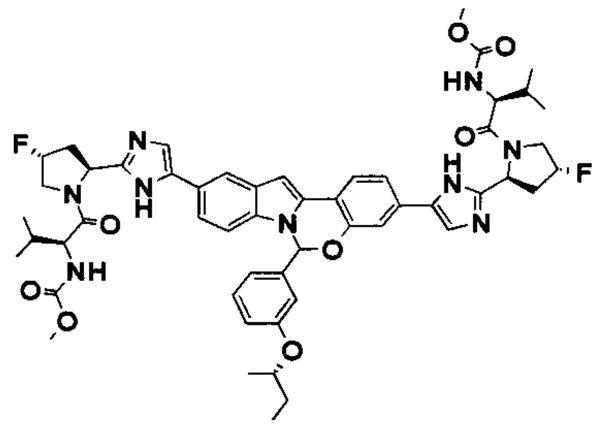
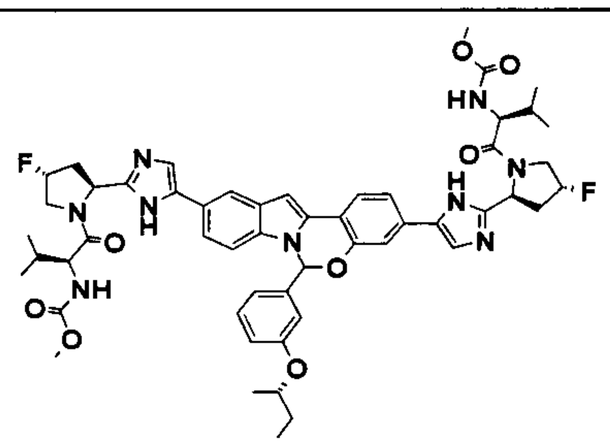
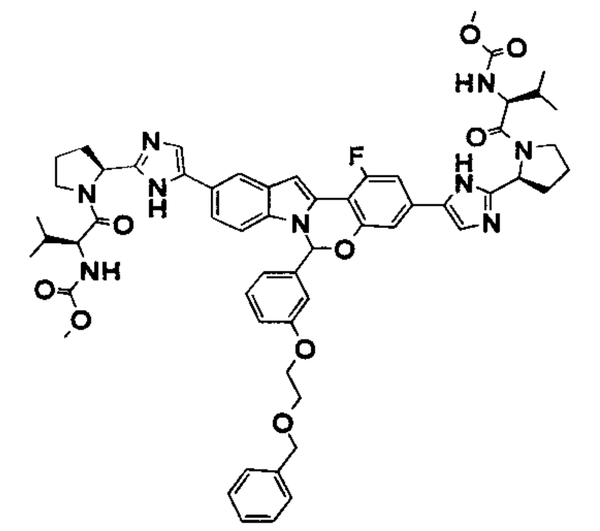
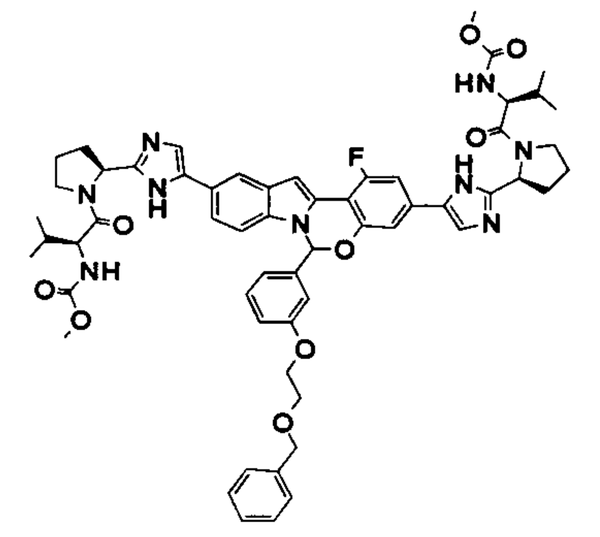
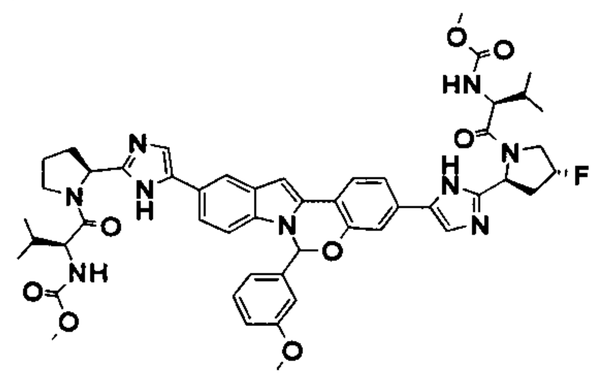
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
387							930.06	931	Single isomer
388							930.06	931	Single isomer
389							926.09	926.9	Single isomer
390							928.07	928.1	Single isomer
391							954.08	955	Mixture of isomers
392							1002.02	1002.9	Mixture of isomers

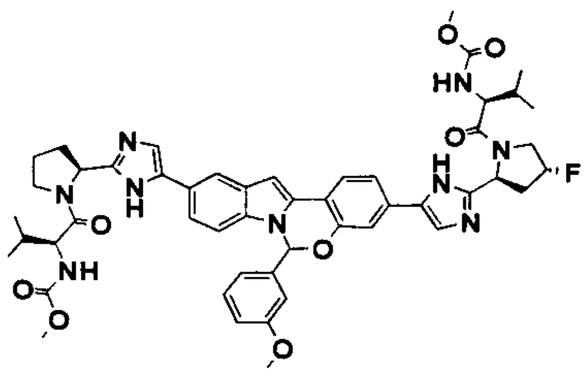
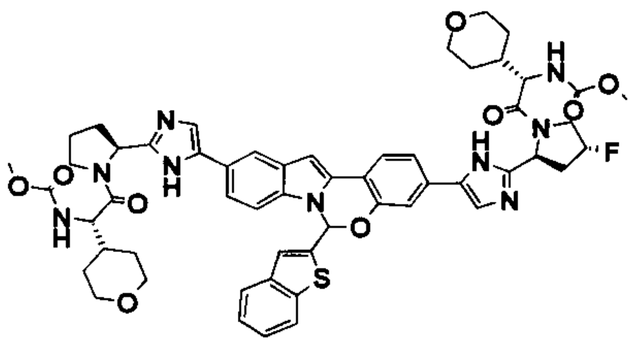
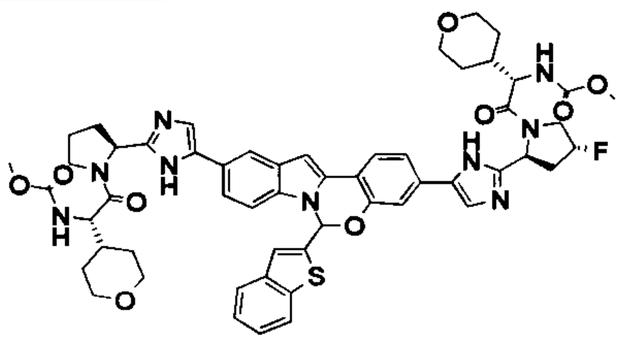
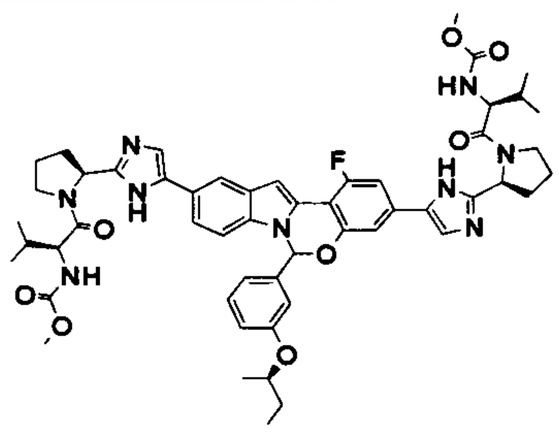
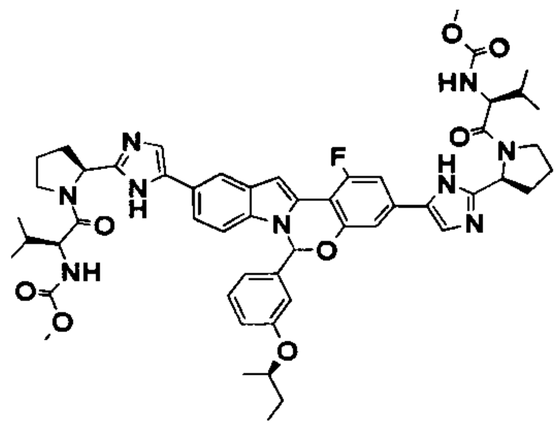
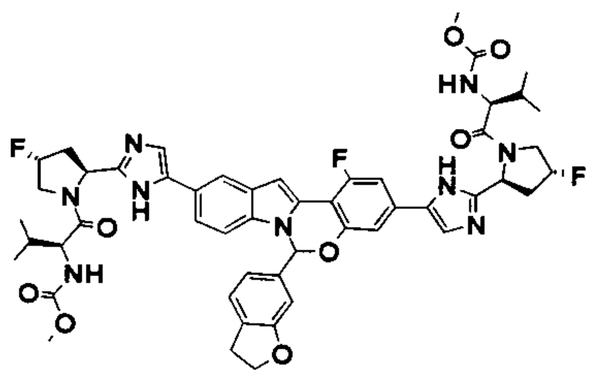
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
393							984.03	985	Mixture of isomers
394							1002.02	1003	Mixture of isomers
395							1002.02	1003	Mixture of isomers
396							944.09	944.8	Single isomer
397							944.09	944.8	Single isomer
398							926.09	927	Single isomer

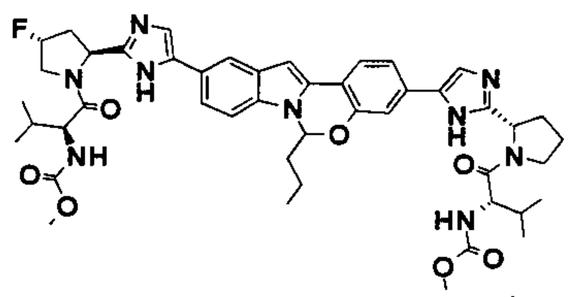
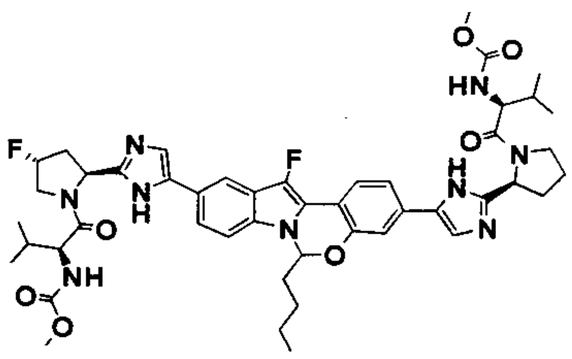
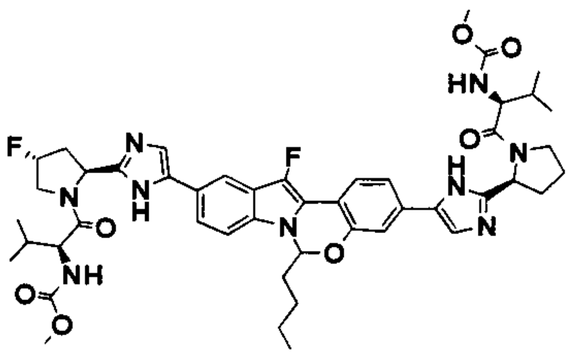
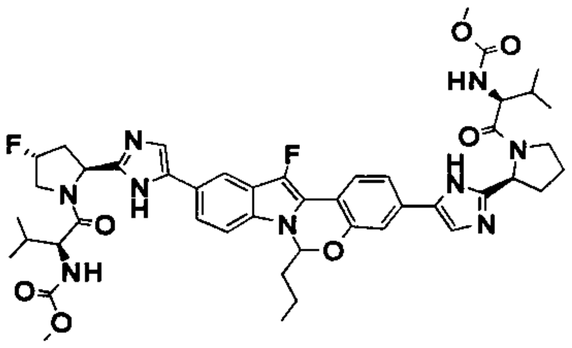
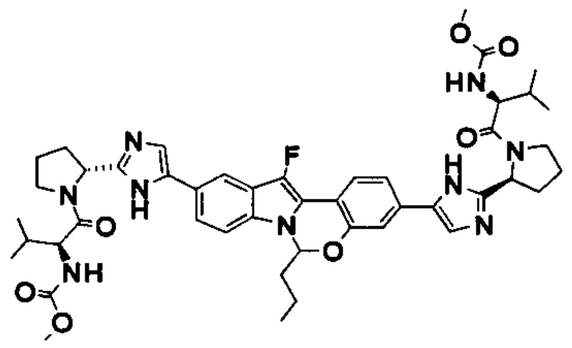
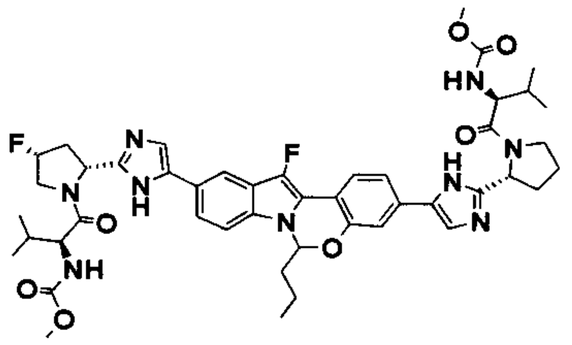
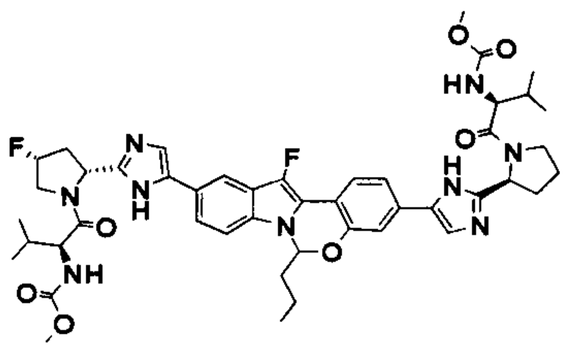
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
399							928.07	929	Single isomer
400							970.15	971	Single isomer
401							970.15	971	Single isomer
402							1006.13	1007	Single isomer
403							1006.13	1007	Single isomer

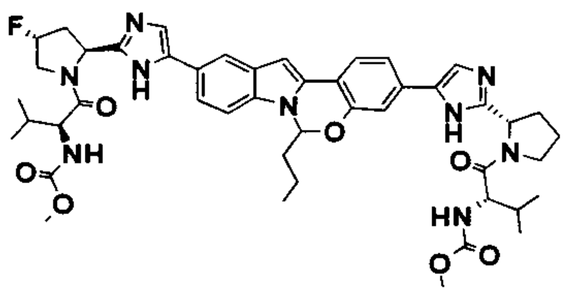
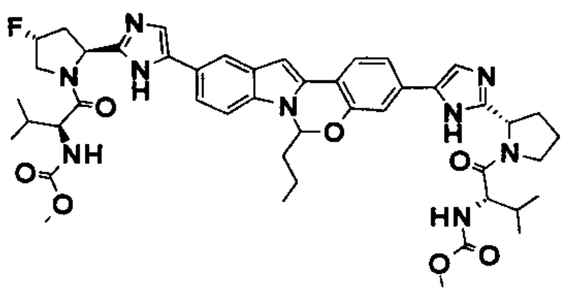
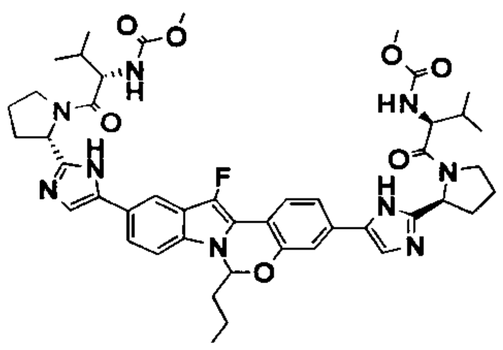
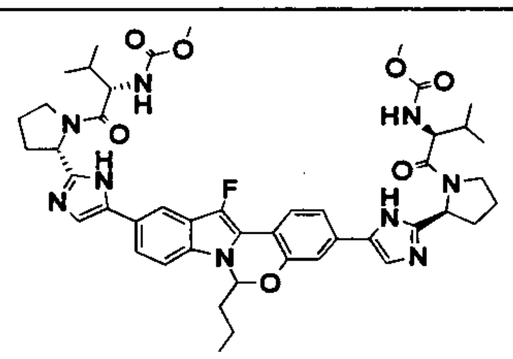
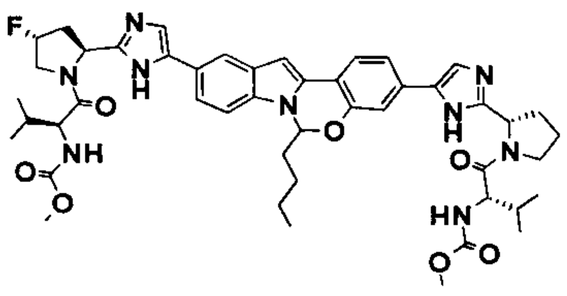
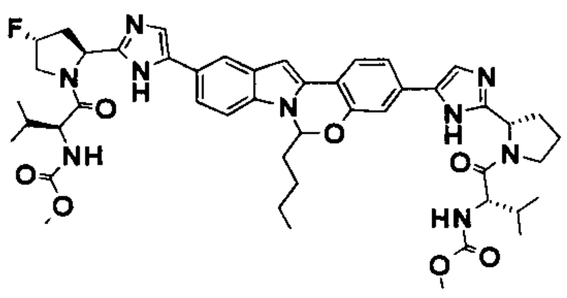
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
404							992.10	992.9	Single isomer
405							992.10	992.9	Single isomer
406							976.10	977	Single isomer
407							976.10	977	Single isomer
408							946.12	947	Single isomer
409							946.12	947	Single isomer

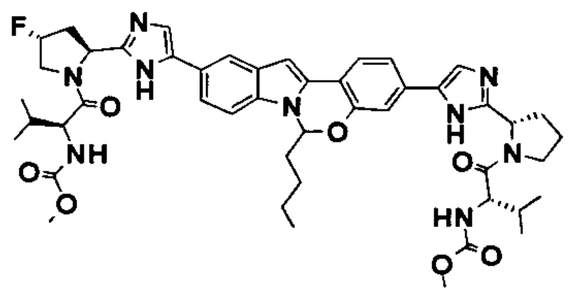
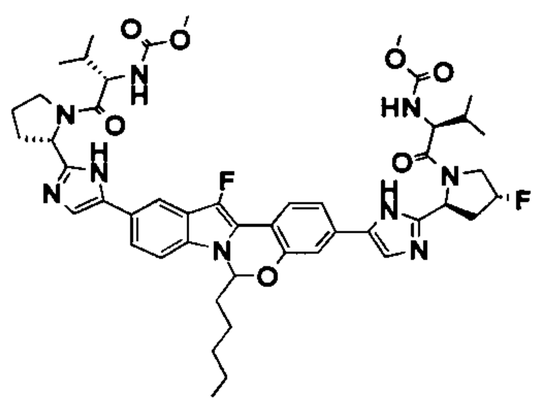
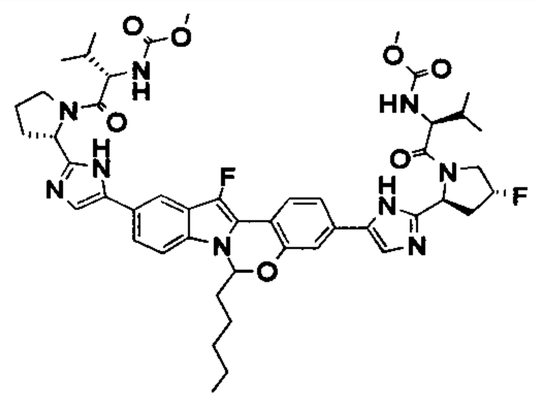
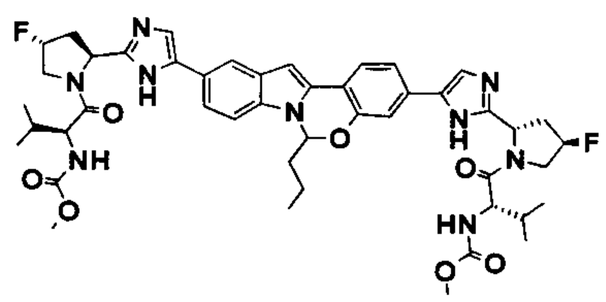
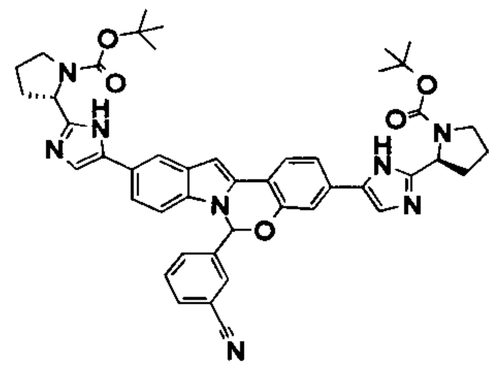
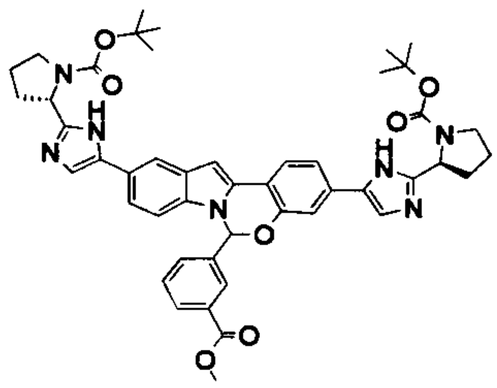
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
410							1020.13	1020.9	Single isomer
411							1020.13	1020.9	Single isomer
412							966.04	967	Single isomer
413							966.04	967	Single isomer
414							954.15	955	Single isomer
415							954.15	955	Single isomer

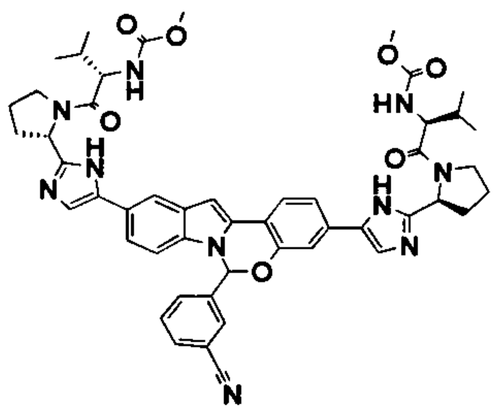
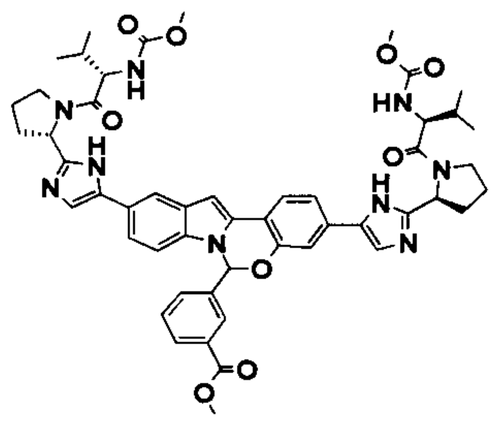
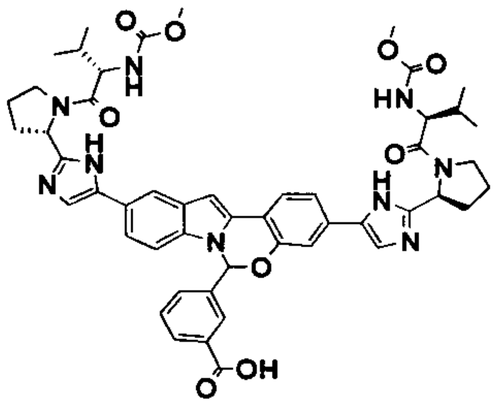
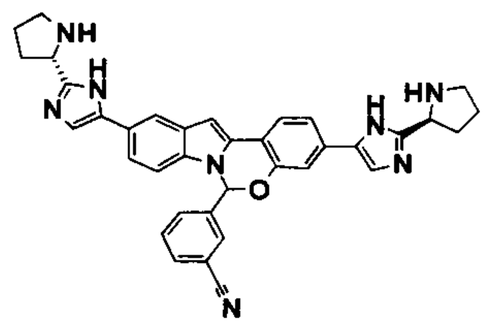
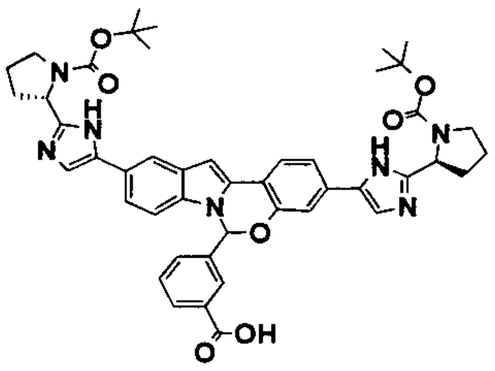
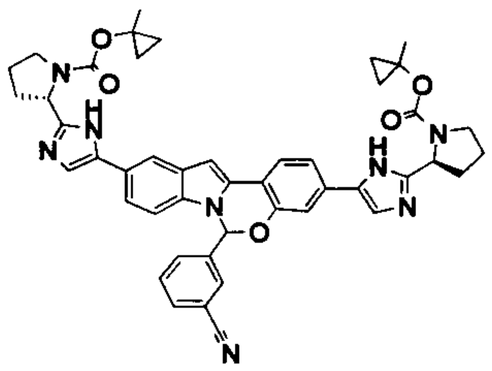
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
416							990.13	990.8	Single isomer
417							990.13	990.8	Single isomer
418							1050.21	1051	Single isomer
419							1050.21	1051	Single isomer
420							930.06	931	Single isomer

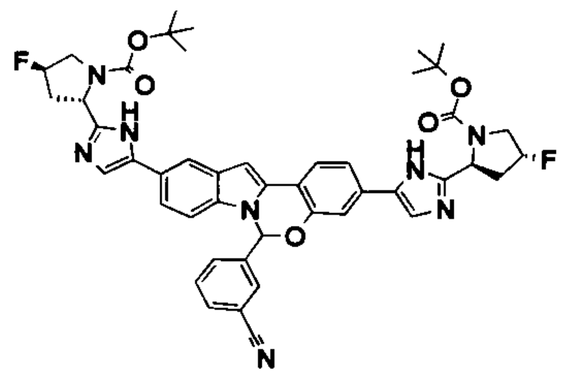
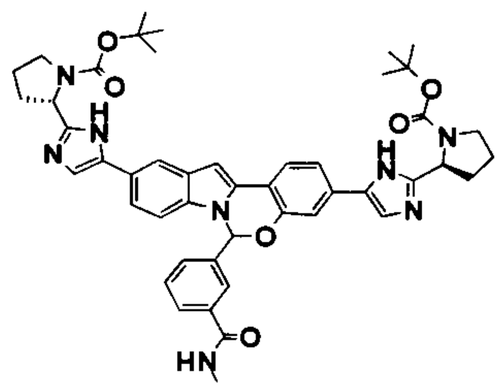
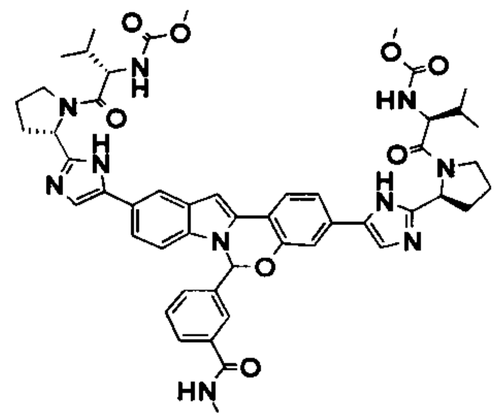
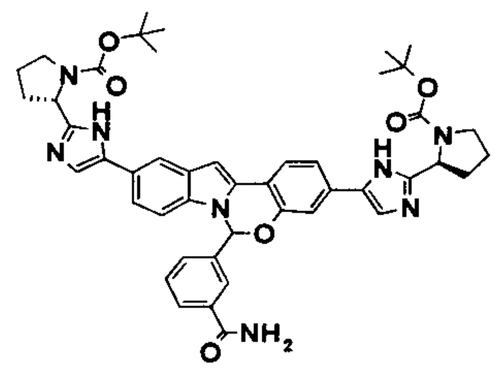
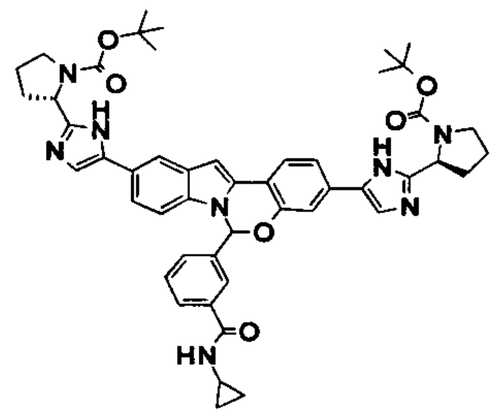
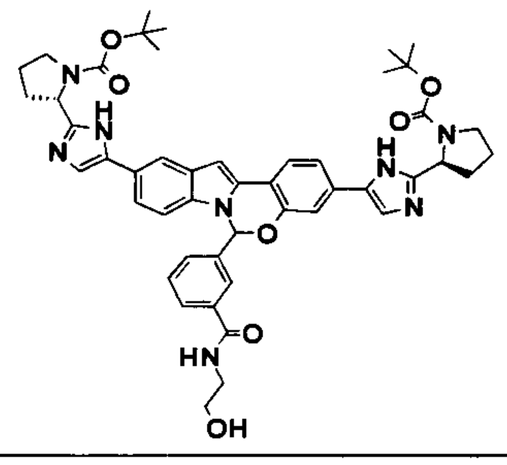
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
421							930.06	931	Single isomer
422							1040.19	1041	Single isomer
423							1040.19	1041	Single isomer
424		0.00389	27	0.6629		6.776	972.14	973.1	Single isomer
425		0.01474	1.047	0.1416		16.74	972.14	973.1	Single isomer
426		0.00649		0.2636		10.16	977.05	978	Single isomer

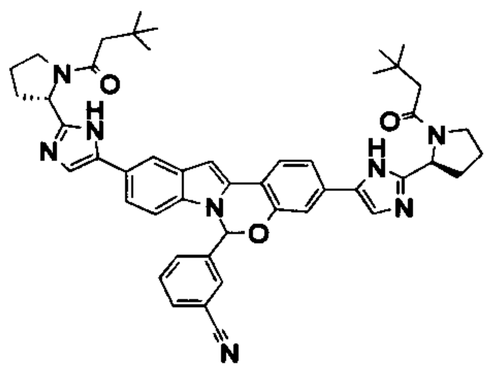
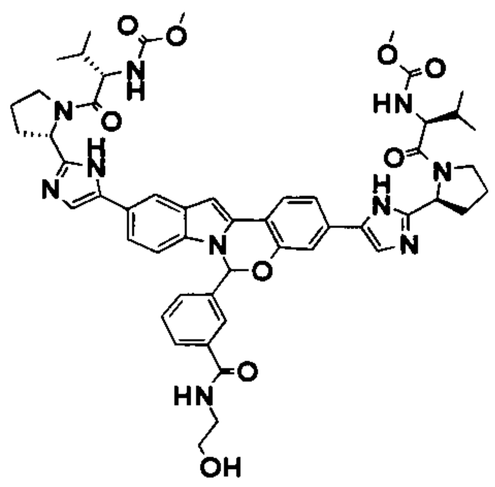
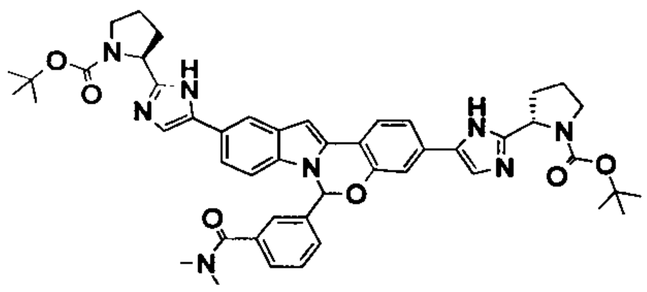
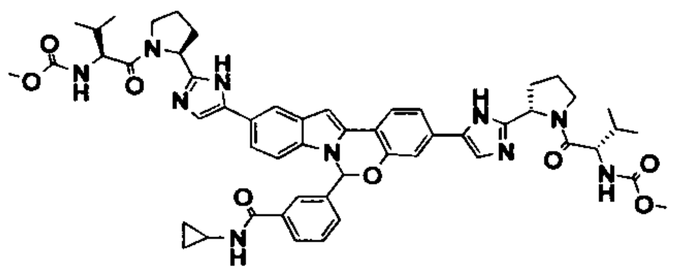
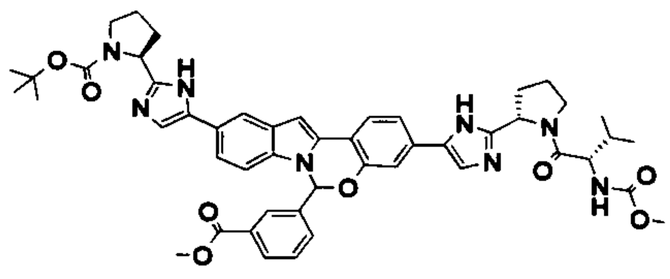
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
427		0.002	3.4	9.8	0.001	44	865.40	866.5	Mixture of isomers
428		0.012	7	5.3	0.001	6	897.40	898.5	Single isomer
429		0.003	0.8	5.9	0.001	41	897.40	898.5	Single isomer
430		0.010	2.7	9.8	0.020	17.1	883.40	883.9	Mixture of isomers
431		0.010	11	0.7	0.020	2.4	865.40	866.2	Mixture of isomers
432		0.004	3.55	2.14	0.001	11	883.40	883.9	Single isomer
433		0.001	0.2	4.86	0.001	69	883.40	884.5	Single isomer

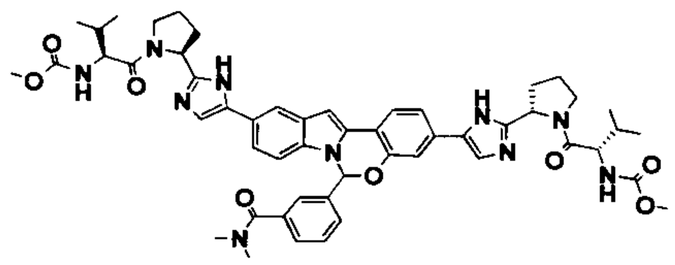
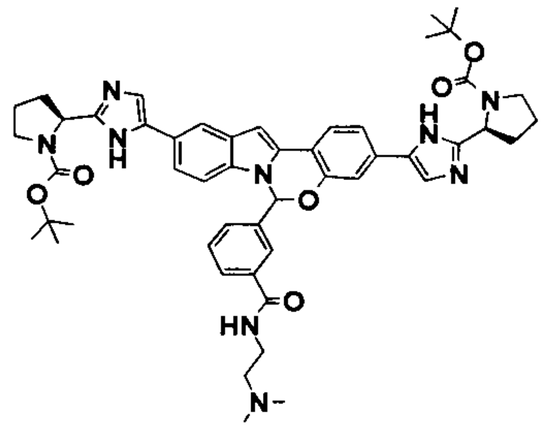
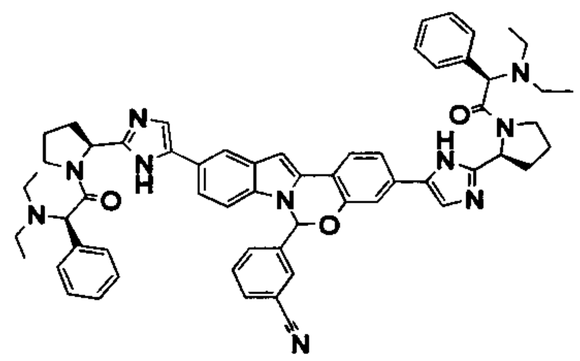
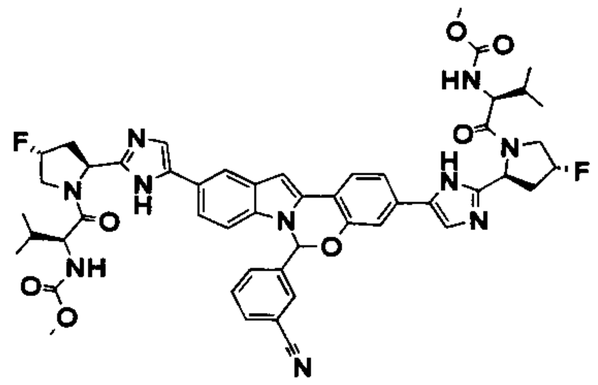
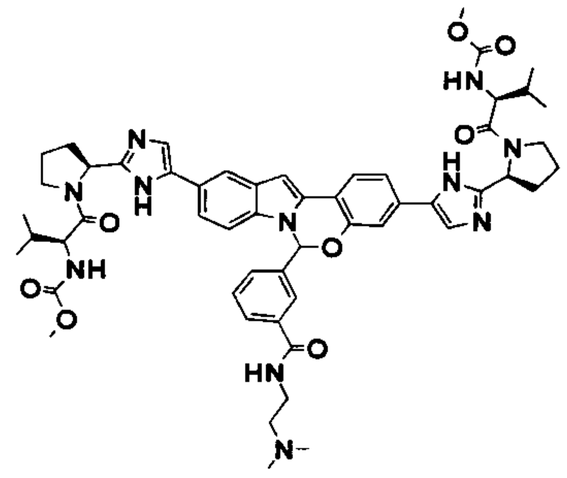
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
434		0.011	4	1	0.001	10	865.40	867.2	Single isomer
435		0.002	0.5	2	0.001	32	865.40	866.5	Single isomer
436		0.002	30	1	0.001	5	865.40	866.5	Single isomer
437		0.003	6	1	0.001	2	865.40	866.5	Single isomer
438		0.008	45.6	10.38	0.003	37.4	879.40	880.5	Mixture of isomers
439		0.014	540.8	7.4	0.002	6.1	879.40	880.7	Single isomer

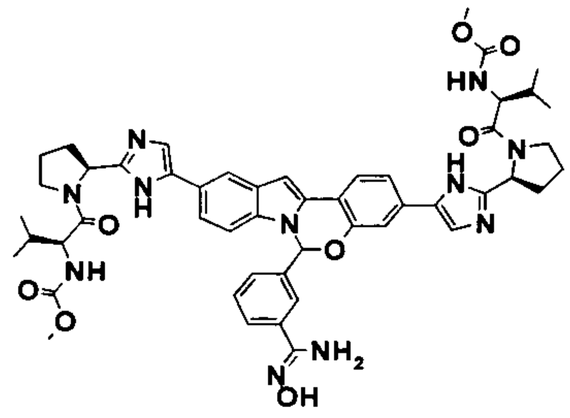
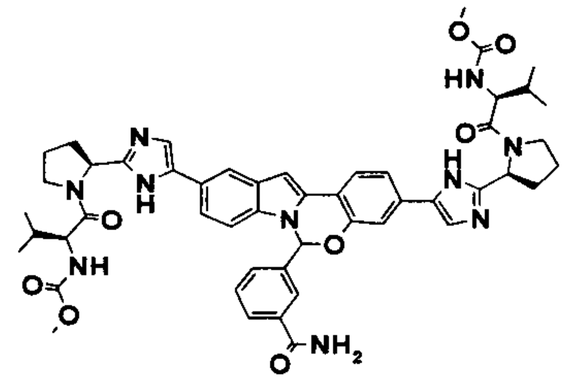
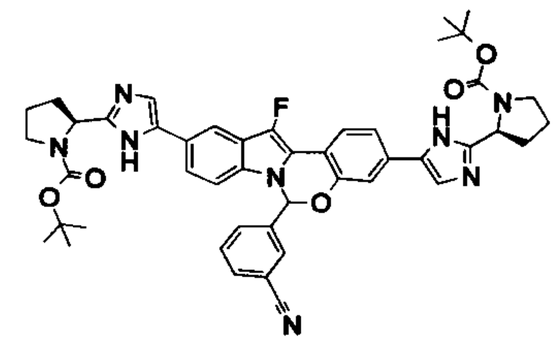
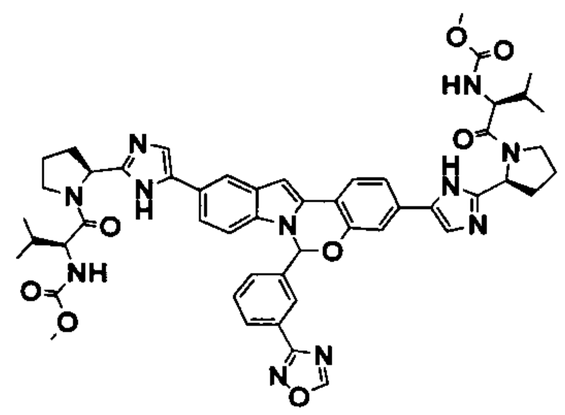
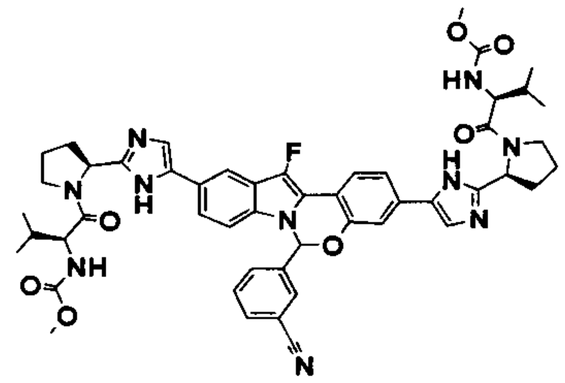
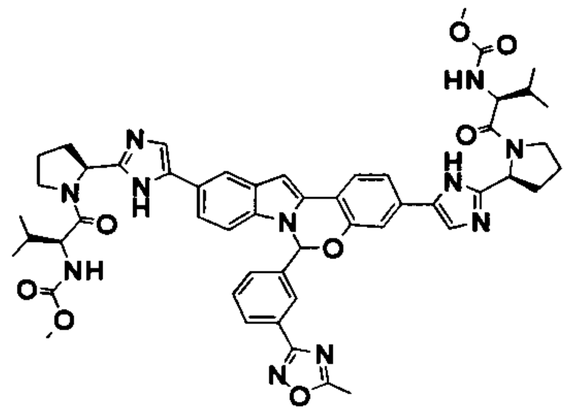
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
440		0.002	24.2	4.05	0.001	52.7	879.40	880.8	Single isomer
441		0.010		14.2	0.020	22.9	911.40	912.7	Single isomer
442		0.010		18	0.020	151.8	911.40	912.7	Single isomer
443		0.019	1.95	42.864	0.008		883.40	884.8	Mixture of isomers
444		1.320	14.582	2.81266	0.792	6.101	792.40	793.4	Mixture of isomers
445		> 10	> 1000	855.866	> 2	682.615	825.40	826.4	Mixture of isomers

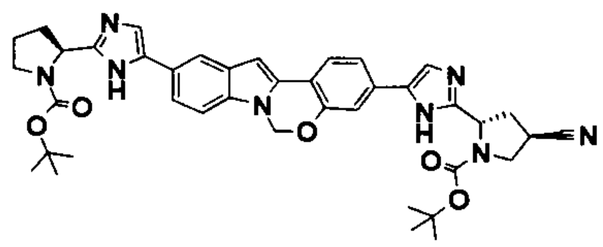
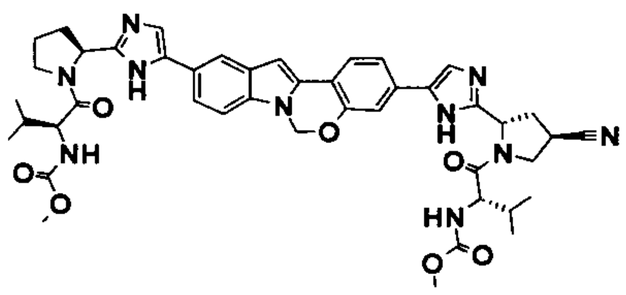
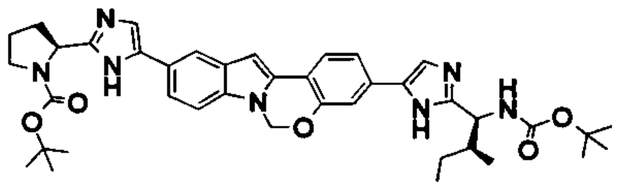
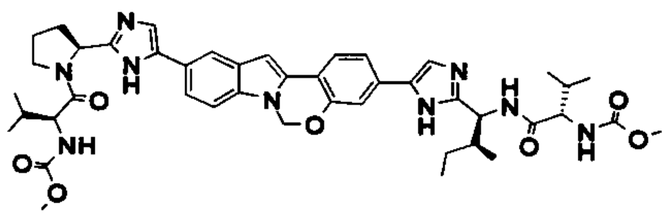
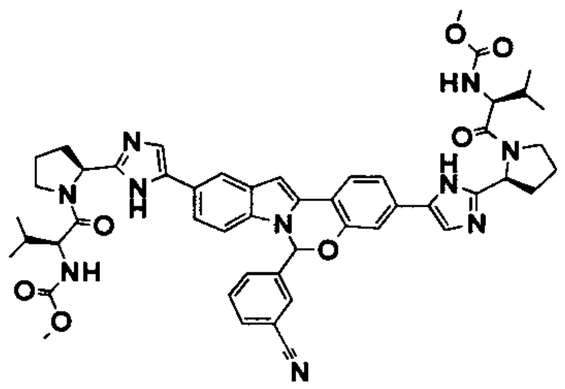
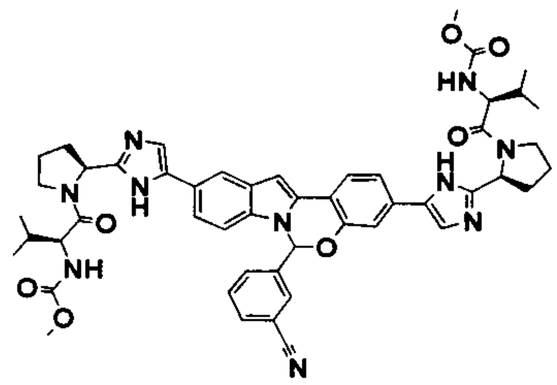
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
446		1.000	4.26	1.95	0.200	2	906.40	907.4	Mixture of isomers
447		1.950	1.95	1.95	0.200	2	939.40	940.4	Mixture of isomers
448		2.830	1000	212.36	2.400	1000	925.40	926.5	Mixture of isomers
449		> 2000	> 5000				592.30	593.3	Mixture of isomers
450		365.116	5099				811.40	812.3	Mixture of isomers
451		131.553	670.918				788.30	789.7	Mixture of isomers

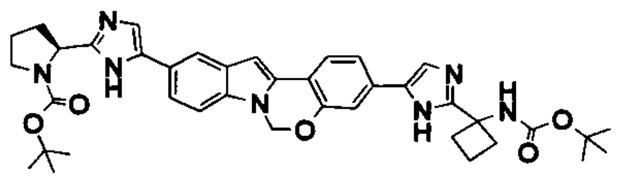
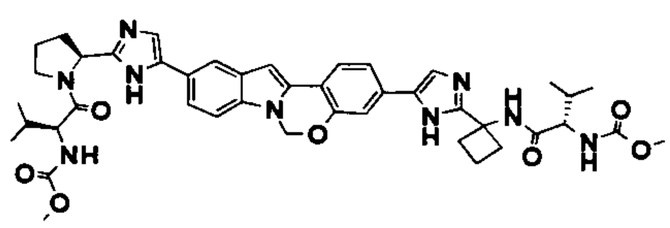
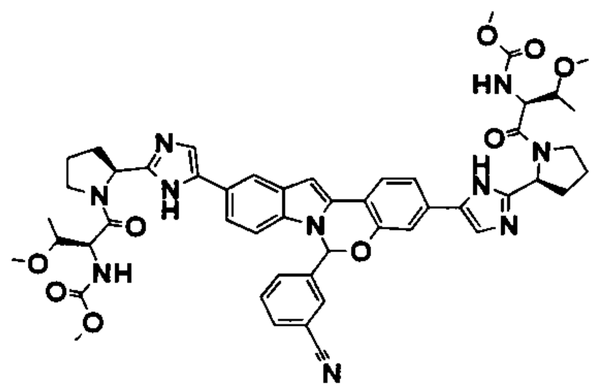
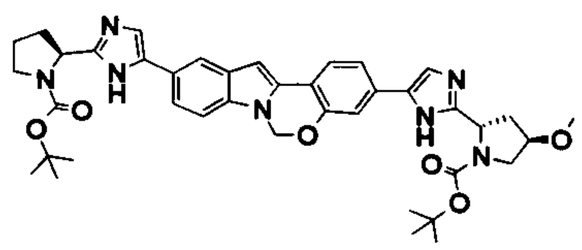
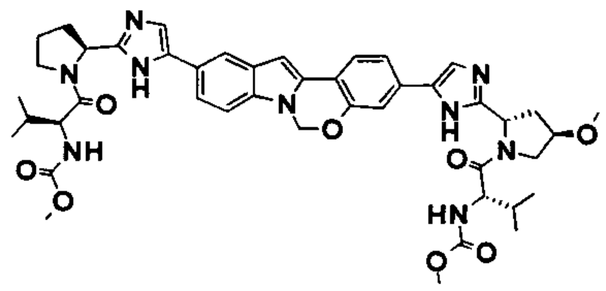
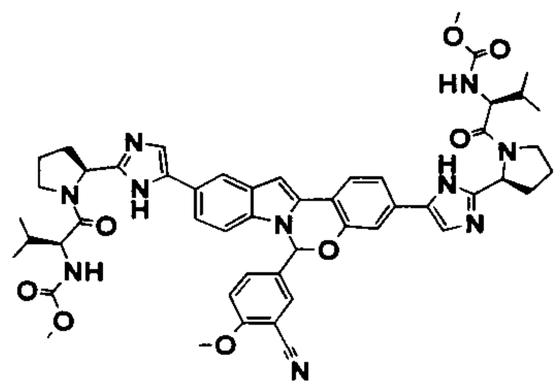
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
452		909.000	> 5000				828.40	829.3	Mixture of isomers
453		294.000	> 5000				824.40	825.4	Mixture of isomers
454		0.064	145	9	0.011	24	938.40	939.3	Mixture of isomers
455		293.000	659.44				810.40	811.4	Mixture of isomers
456		72.699	588.56				850.40	851.4	Mixture of isomers
457		140.477	1225.95				854.40	855.4	Mixture of isomers

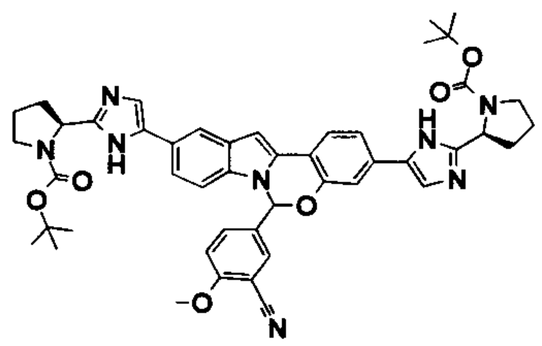
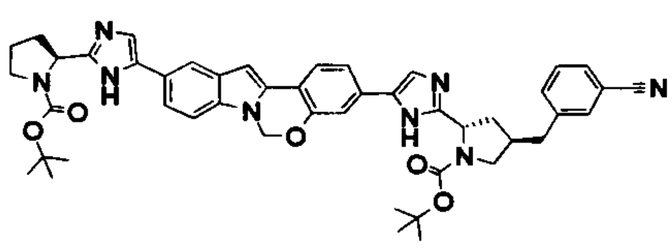
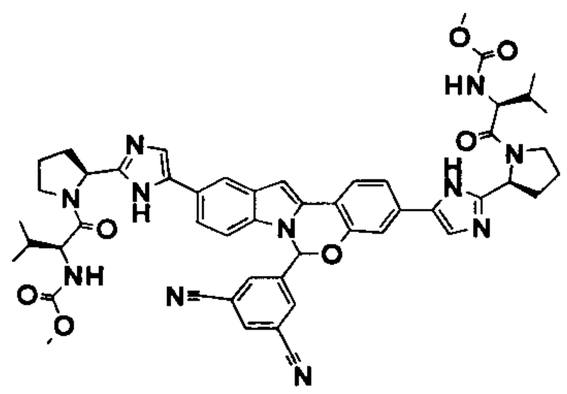
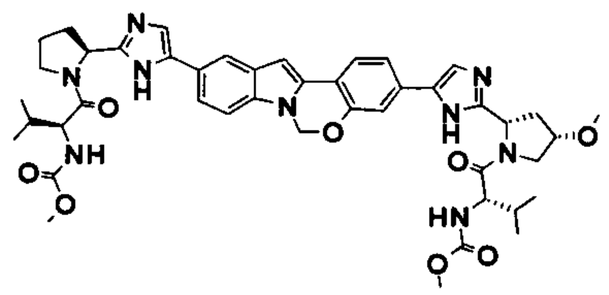
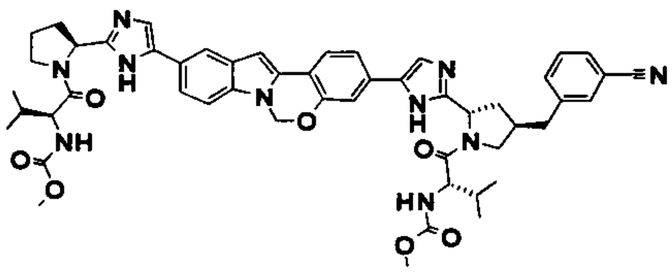
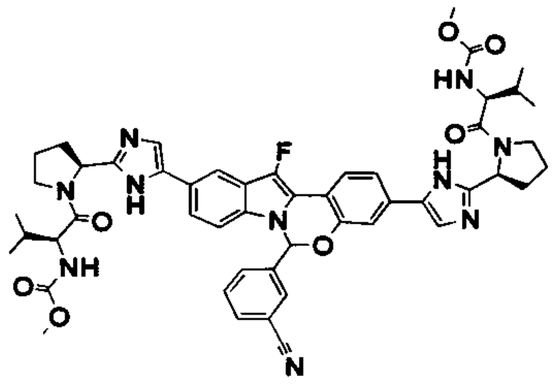
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
458		188.892	227.88				788.40	789.7	Mixture of isomers
459		0.246	19.21	18.4	0.027	200	968.50	968.8	Mixture of isomers
460		512.000	> 20000				838.40	839.4	Mixture of isomers
461		0.097	> 200	14	0.151	99.105	964.50	965.5	Mixture of isomers
462		0.018	> 200	88.9	0.022	76.8	882.40	883.4	Mixture of isomers

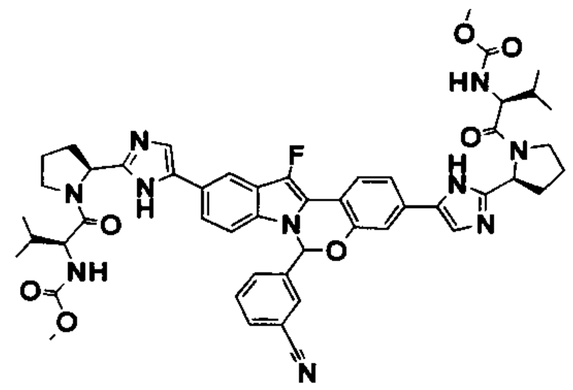
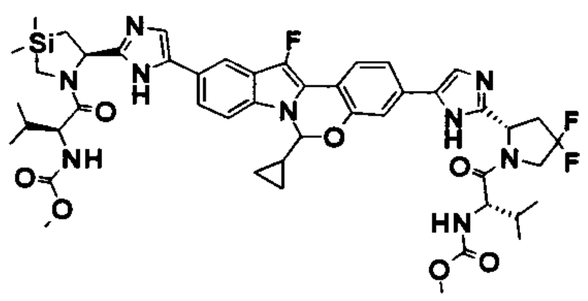
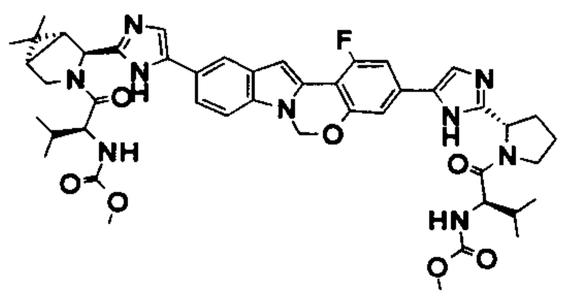
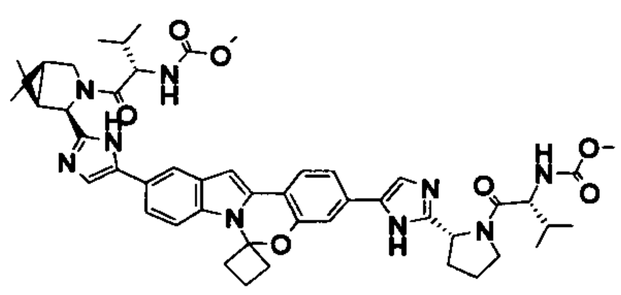
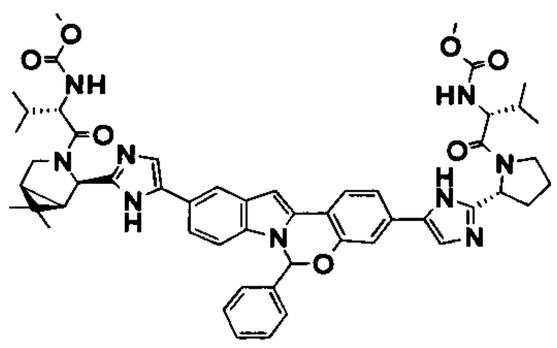
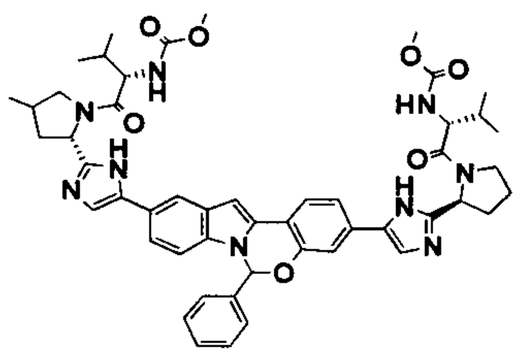
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
463		0.024	> 200	0.4	0.014	41	952.50	953.5	Mixture of isomers
464		485.000	2619				881.50	882.1	Mixture of isomers
465		0.073	> 200	0.27	0.033	0.2	970.50	971.1	Mixture of isomers
466		0.005	0.2	3.2	0.002	49	942.40	943.4	Mixture of isomers
467		>1	>100	>100	0.130	>100	995.50	996.5	Mixture of isomers

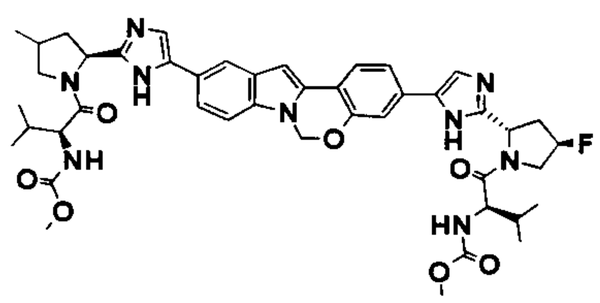
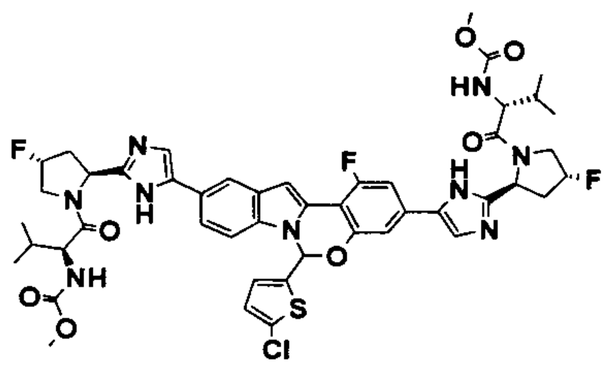
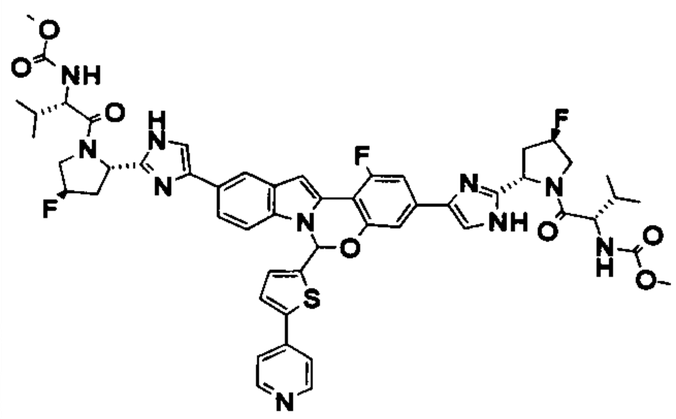
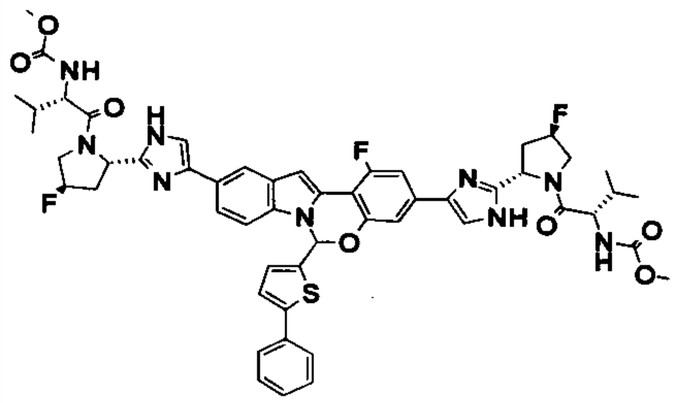
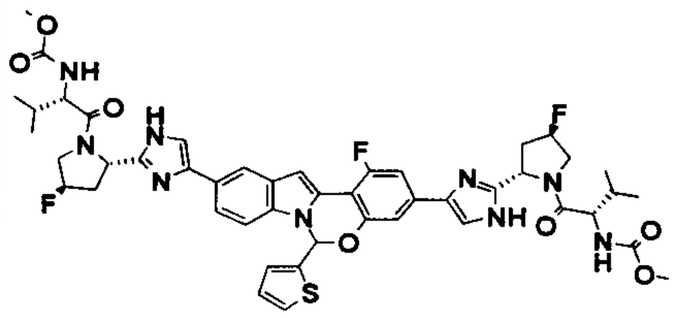
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
468		0.073	24.86	1	0.063	26.5	939.40	940.5	Mixture of isomers
469		0.090	18.89	7	0.011	> 100	924.40	925.4	Mixture of isomers
470		177.000	1884				810.40	811.4	Mixture of isomers
471		0.006	6.2	0.2	0.006	1.9	949.40	950.5	Mixture of isomers
472		0.002	1.31	0.22	0.002	7.5	924.40	925.4	Mixture of isomers
473		0.003	0.88	0.19	0.004	2	963.40	964.5	Mixture of isomers

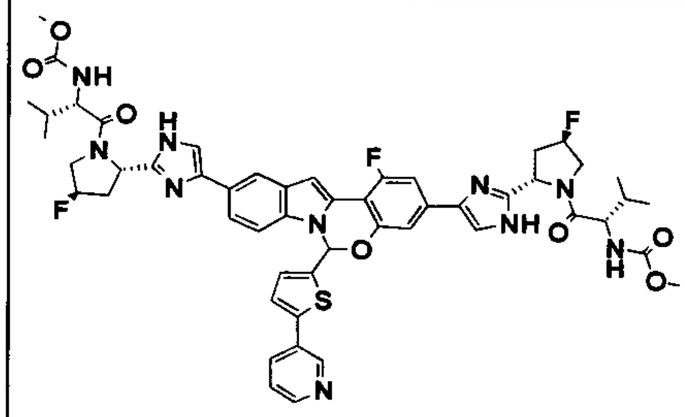
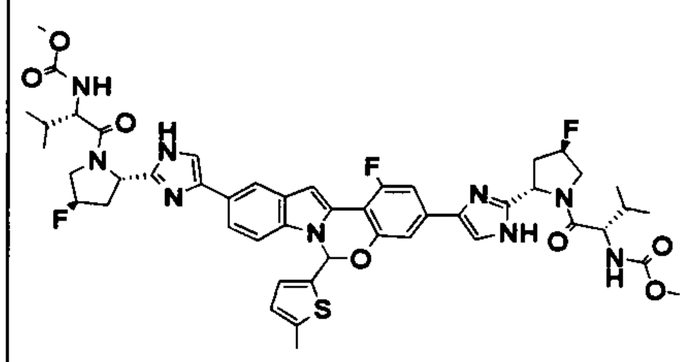
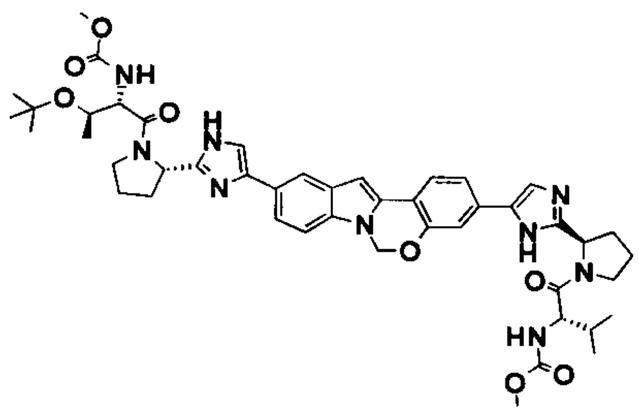
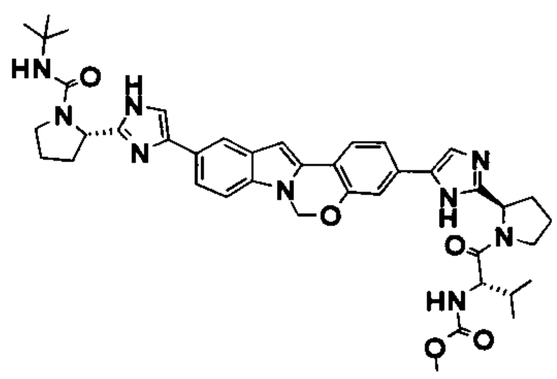
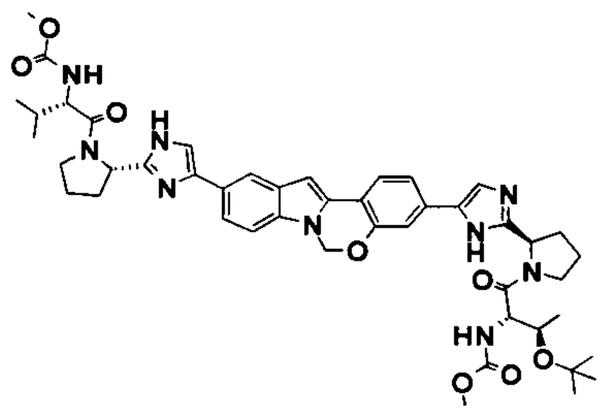
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
474		208.000	19				716.30	717.4	Single isomer
475		0.010	11	0.363	0.003	1.929	830.40	831.4	Single isomer
476		8.400	10000				707.40	709.4	Single isomer
477		0.023	97.1	95	0.013	> 100	821.40	822.5	Single isomer
478		0.004	18	0.41	0.004	4	906.40	908.4	Single isomer
479		0.013	66	> 100	0.005	7.6	906.40	907.4	Single isomer

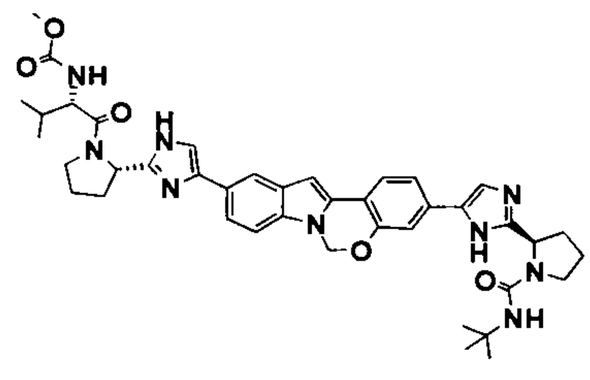
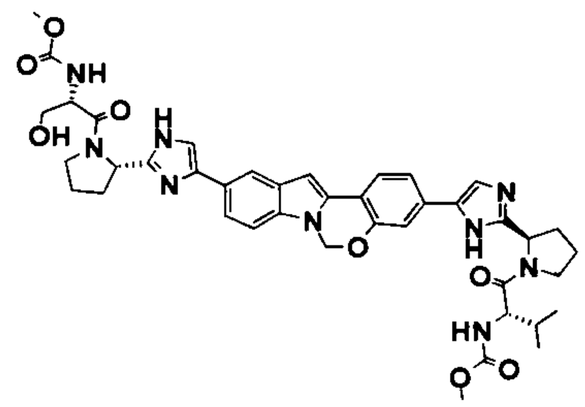
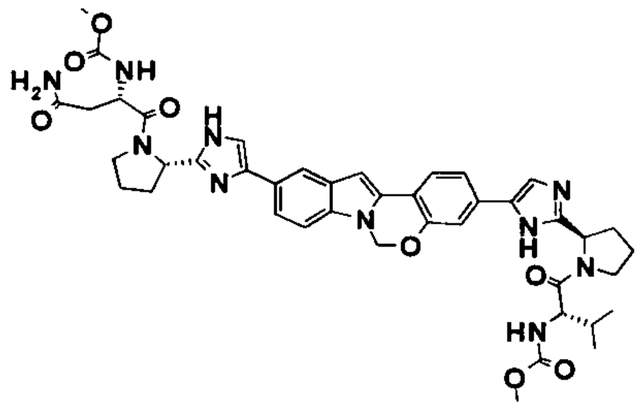
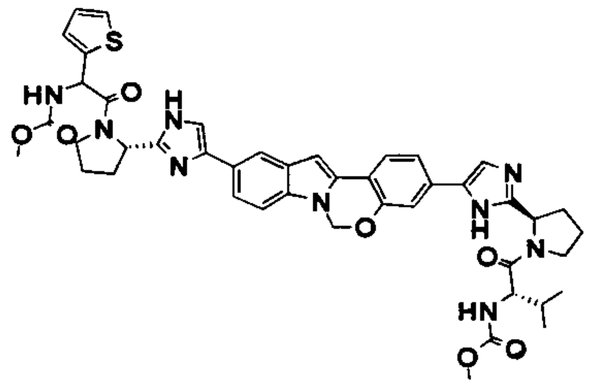
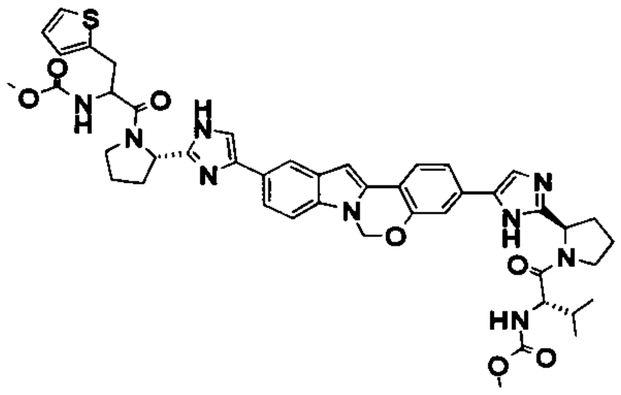
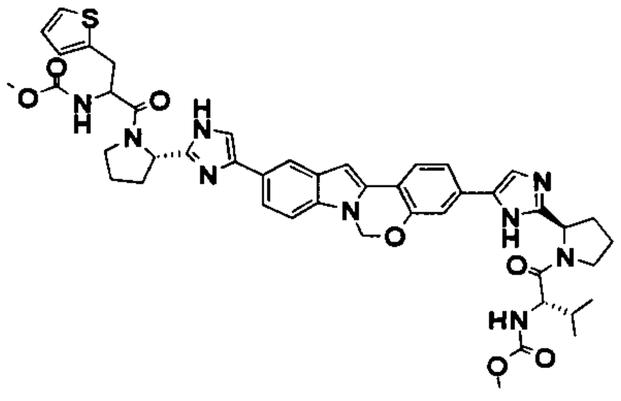
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
480		#######	1227.6				691.30	692.3	Single isomer
481		0.124	62.1	109.9	0.012	110	805.40	806.4	Single isomer
482		0.028		0.382	0.014	2.7	738.40	739.3	Mixture of isomers
483		609.000	>1000				721.40	722.3	Single isomer
484		0.026	11.9	17.3	0.019	> 100	835.40	836.4	Single isomer
485		0.012	22.58	0.23		4.35	936.40	937.4	Mixture of isomers

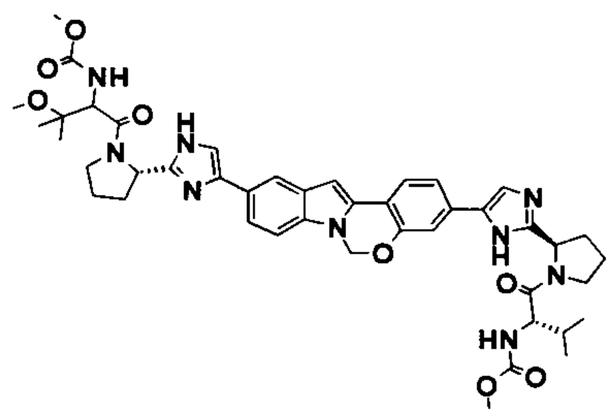
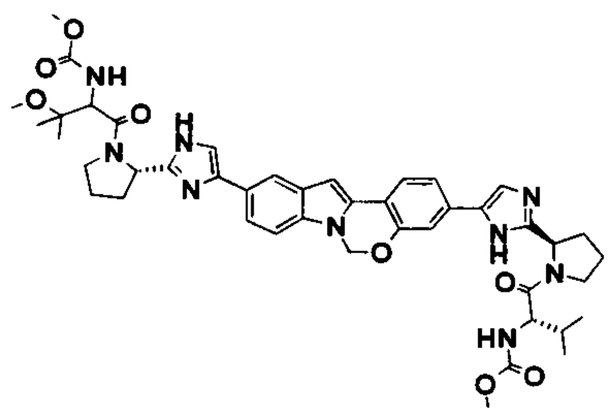
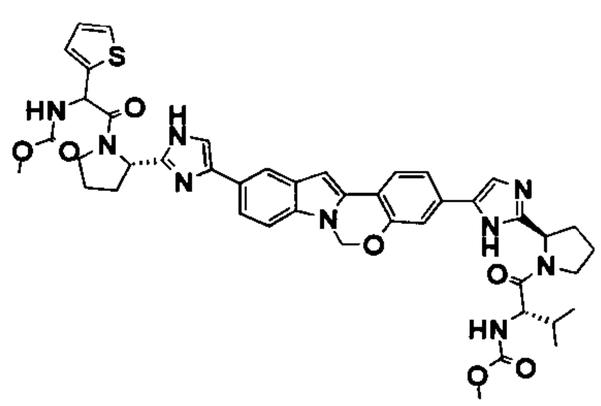
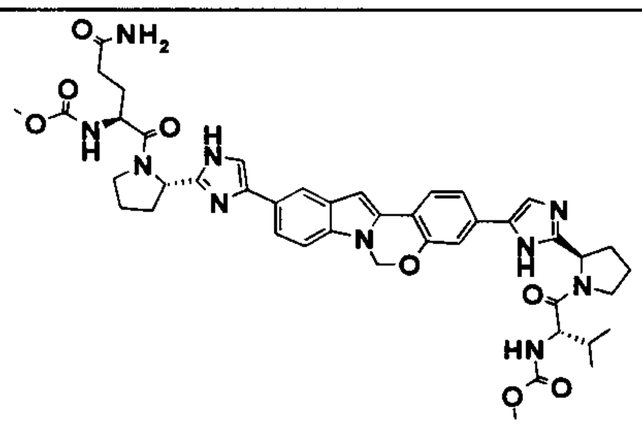
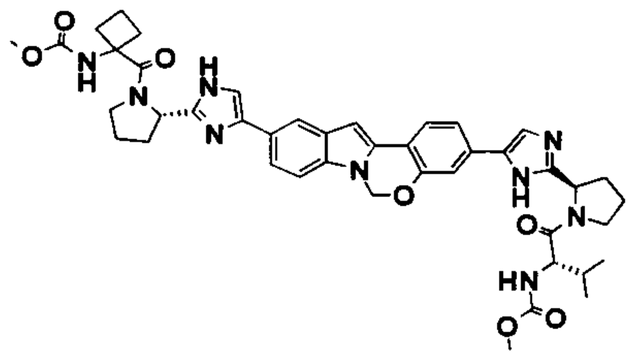
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
486		934.400	>1000				822.40	823.4	Mixture of isomers
487		605.000	>1000				806.40	808.3	Single isomer
488		0.011	114.2	1.62		35.93	931.40	933.2	Mixture of isomers
489		0.860	115.2	236.2		>1000	835.40	836.3	Single isomer
490		0.090	51	65		234	920.40	921.3	Single isomer
491		0.010	9.02	0.42		10.9	924.40	925.3	Single isomer

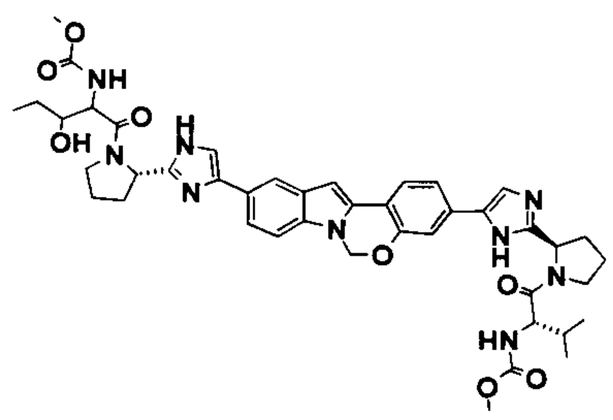
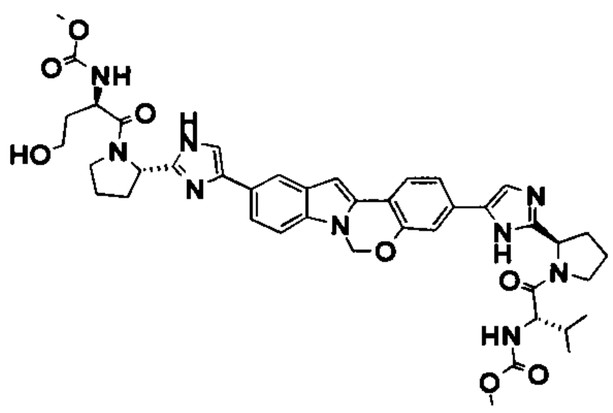
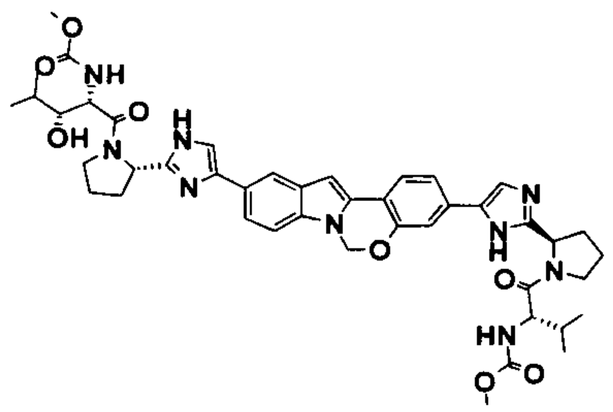
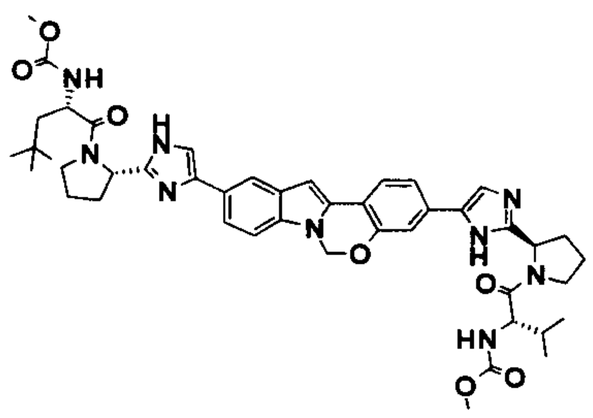
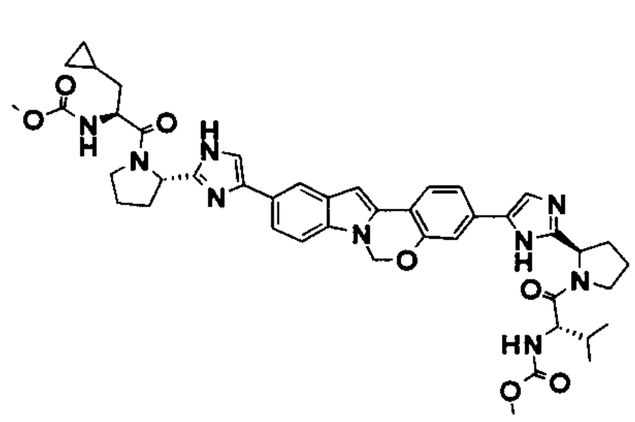
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
492		0.010	21.62	0.17		12.37	924.40	925.3	Single isomer
493		0.006	26	16	0.003	> 200	943.40	944.4	Mixture of isomers
494		0.005	19.2	4.3	0.000	410	863.41	865.4	Single isomer
495		> 0.2	2	5	0.008	973	885.45	886.4	Single isomer
496		0.010	< 100		0.009	233.7	921.45	922.4	Mixture of isomers
497		0.019	5.2	> 2	0.190	227	895.44	896.4	Mixture of isomers

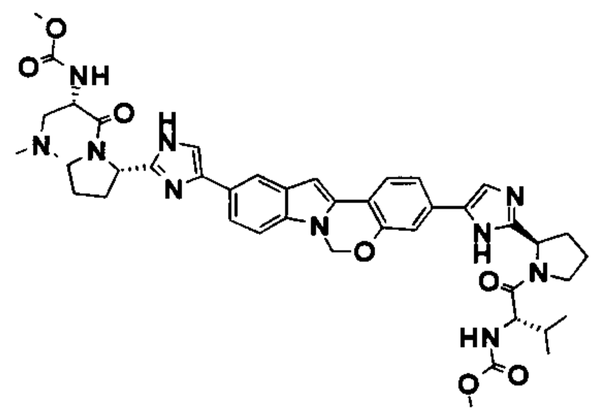
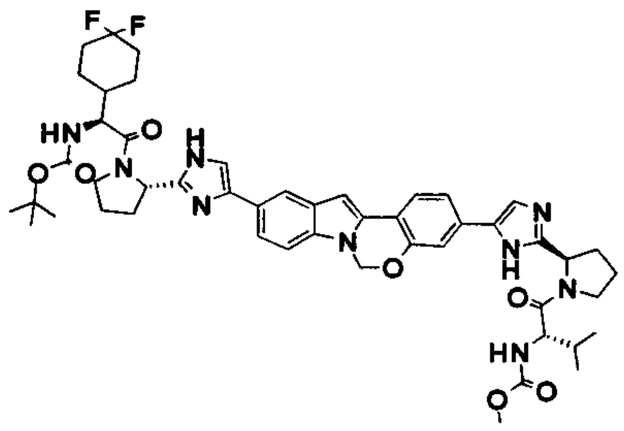
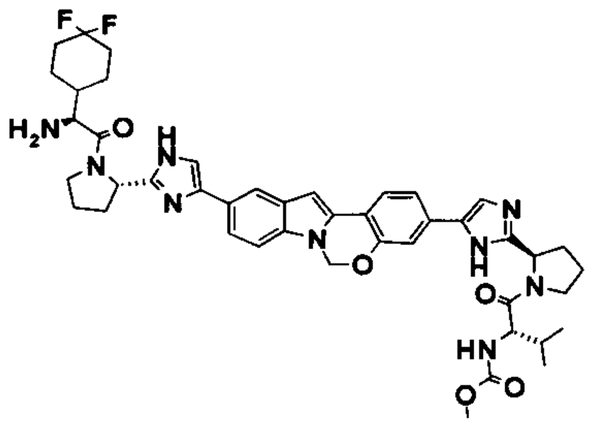
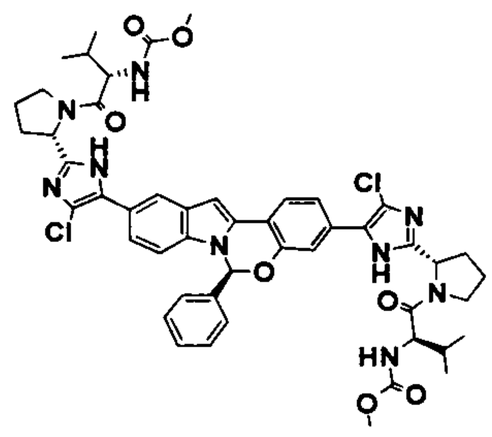
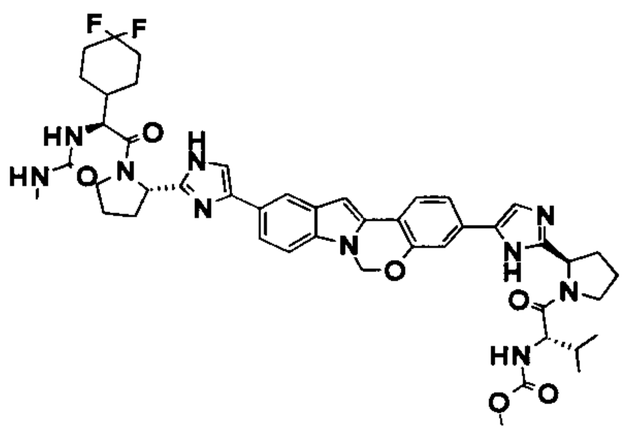
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
498		> 10	> 1000	> 1000	> 2	> 1000	837.40	838.4	Mixture of isomers
499		0.013		1.55	0.005	10	975.30	975.9	Mixture of isomers
500		0.028	0.2	2.826	0.022	50.6	1018.38	1019.0	Mixture of isomers
501		0.007		0.31	0.004	8.3	1017.38	1018.0	Mixture of isomers
502		0.007		1.5	0.005	17.1	941.35	941.9	Mixture of isomers

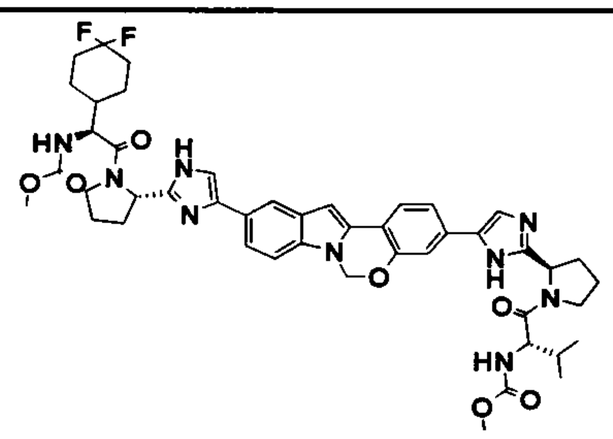
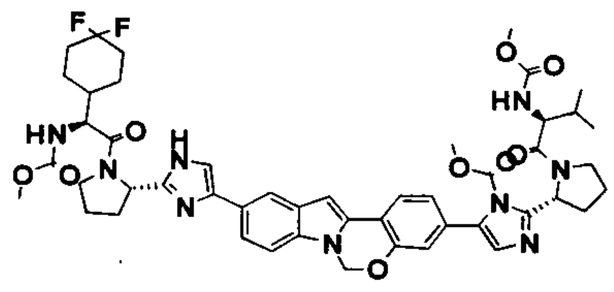
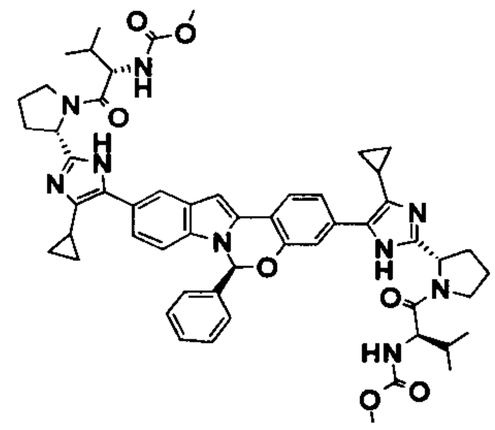
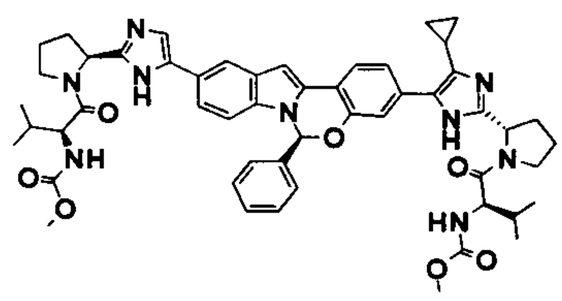
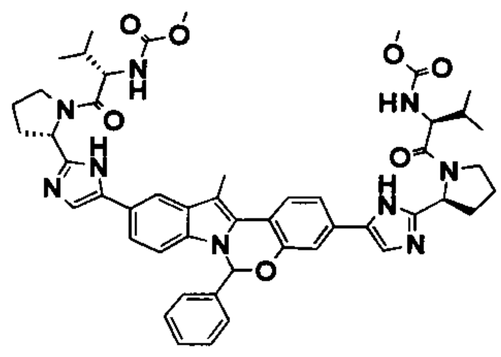
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
503		0.012		1.021	0.007	31.4	1018.38	1019.3	Mixture of isomers
504		0.031		4.391	0.007	33.8	955.37	956.4	Mixture of isomers
505		0.110	> 100	42	0.023		863.43	864.5	Single isomer
506		> 2	109.9	109.9	0.157	110	747.38	748.2	Single isomer
507		0.080	> 100	43	0.029	57.9	863.43	864.2	Single isomer

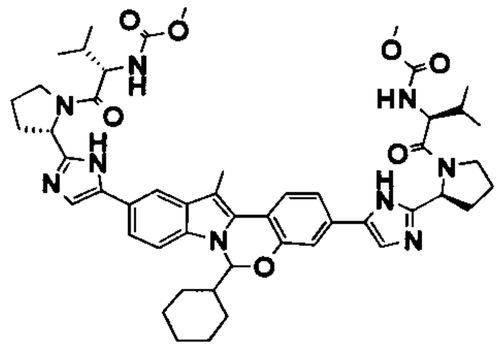
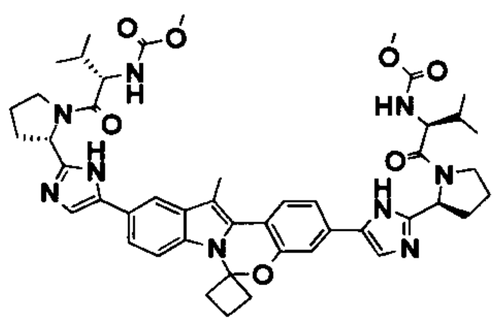
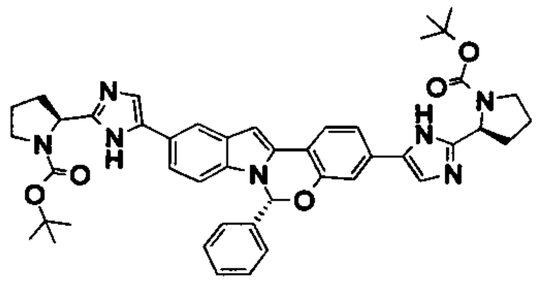
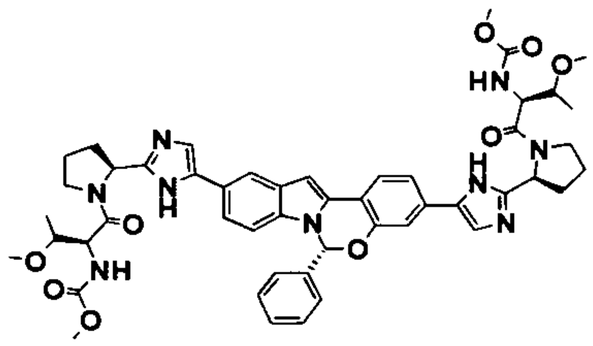
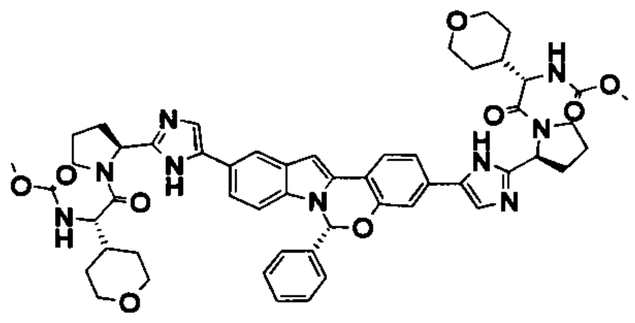
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
508		> 1	> 100	> 100	0.154	> 100	747.39	748.2	Single isomer
509		0.070	> 100	> 100	0.026	> 100	793.35	794.3	Single isomer
510		0.015	> 100	25	0.017	99.5	820.37	821.4	Single isomer
511		0.020	110	50	0.015	69.3	845.33	846.3	Single isomer
512		0.043	109.9	44.71	0.020	110	859.35	860.4	Single isomer
513		0.140	109.9	109.9	0.030	110	859.35	860.4	Single isomer

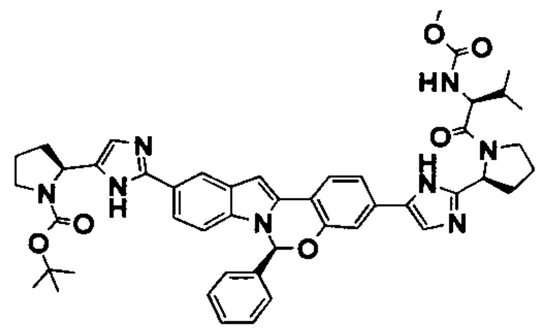
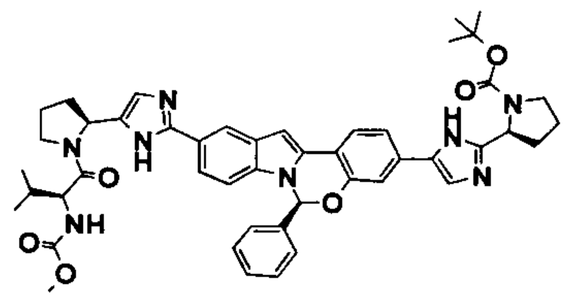
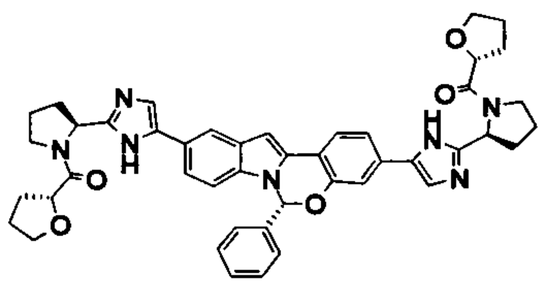
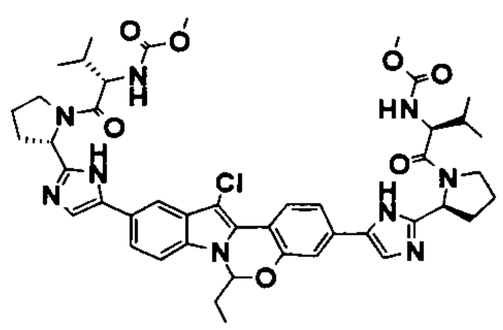
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
514		0.040	109.9	15.53	0.022	110	835.40	836.4	Single isomer
515		0.088	109.9	40.23	0.060	110	835.40	836.4	Single isomer
516							845.33	846.3	Mixture of isomers
517		> 1	> 100	51.2	0.118	> 100	834.38	835.4	Single isomer
518		0.314	> 100	> 100	0.067	> 100	803.38	804.5	Single isomer

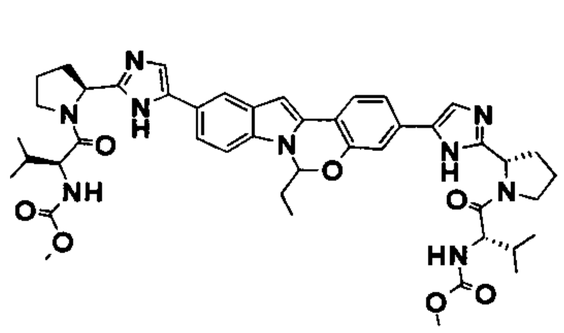
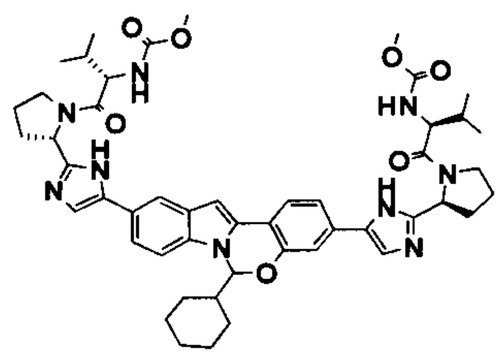
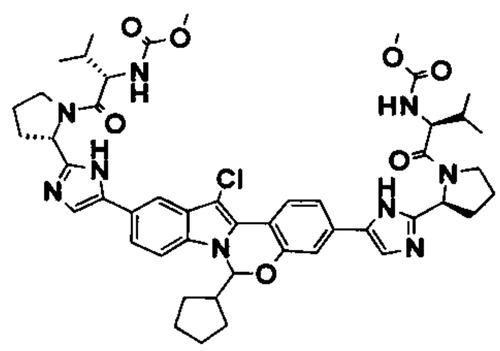
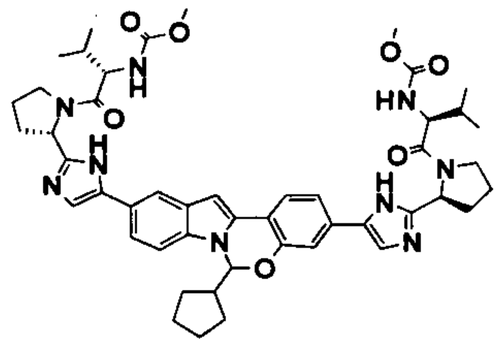
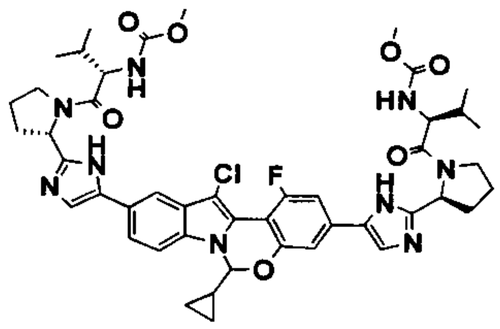
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
519		0.038	> 100	8.7	0.034	> 100	821.39	822.4	Mixture of isomers
520		0.165	1.6		0.082	> 100	807.37	808.4	Single isomer
521		0.044	> 100	4.6	0.020	> 100	835.40	836.4	Single isomer
522		0.054	> 100	24.1	0.022	> 100	833.42	834.4	Single isomer
523		0.085	> 100	27.9	0.040	> 100	817.39	818.3	Single isomer

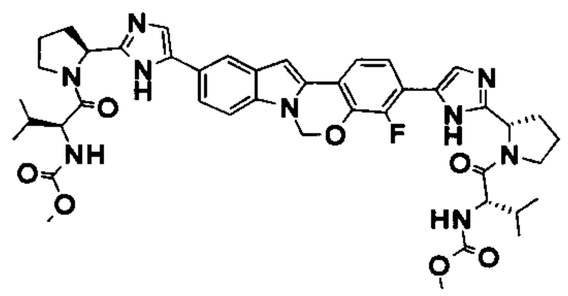
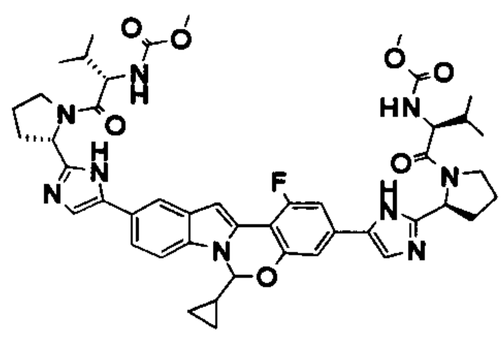
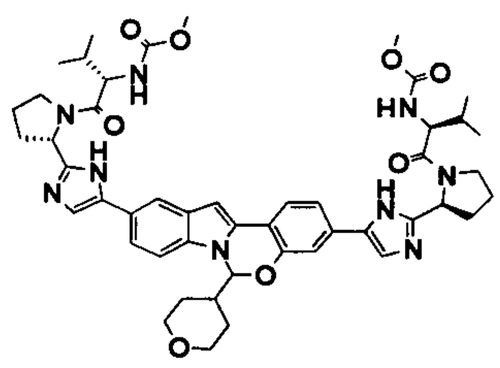
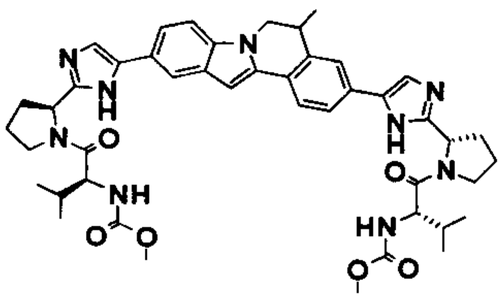
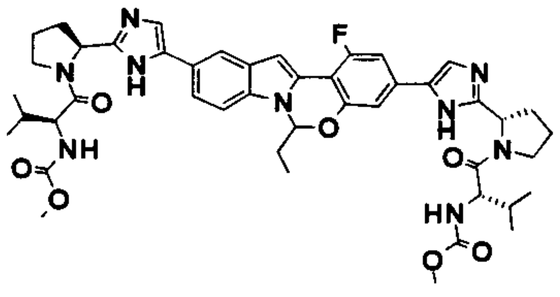
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
524							820.40	NA	Single isomer
525		25.000	1000	592		1000	923.45	924.2	Single isomer
526		1.680	377	195			823.40	824.3	Single isomer
527		0.050	13	0.7		15	949.34	950.2	Single isomer
528		0.420	143	108		>1000	880.42	881.7	Single isomer

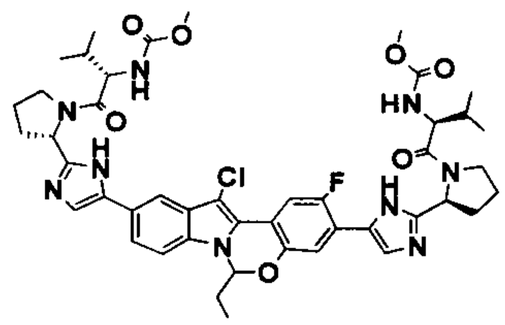
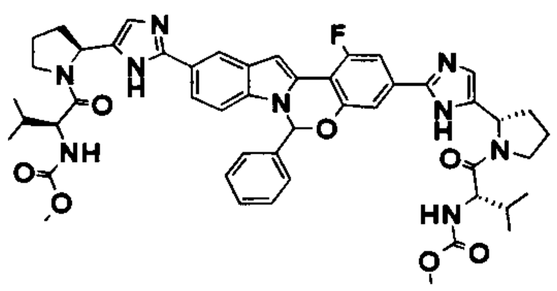
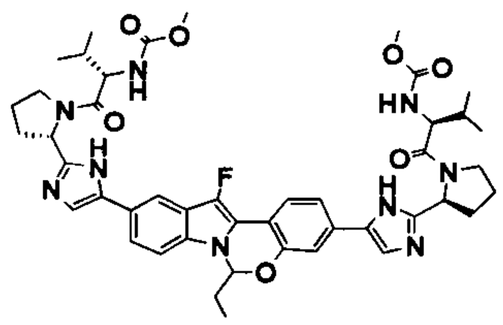
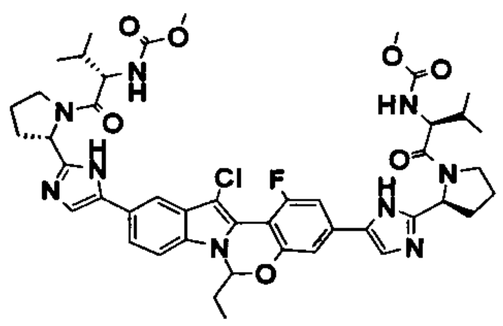
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
529		0.057	42	11		246	881.40	881.7	Single isomer
530		0.060	69	29		210	939.41	940.6	Single isomer
531							961.49	962.5	Single isomer
532							921.48	922.5	Single isomer
533		0.001	8.4	0.2	0.001	7	895.4	896.4	Mixture of isomers

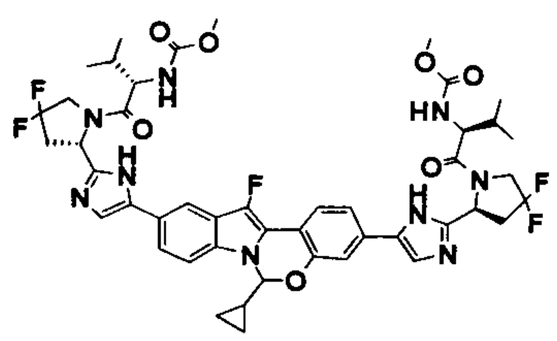
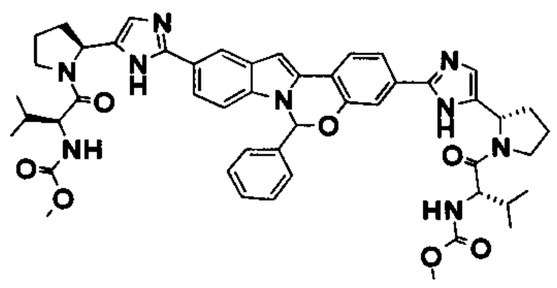
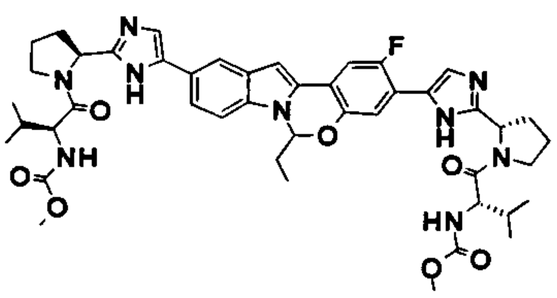
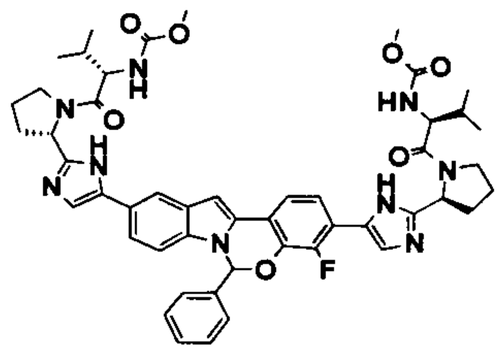
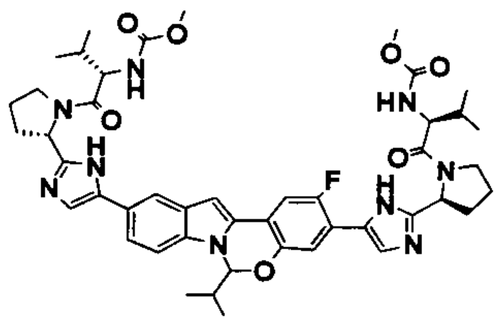
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
534		0.013	12	9.11	0.005	9	901.5	901.8	Mixture of isomers
535		0.020	27.82	1.1	0.002	111	859.4	859.9	Single isomer
536		890.530	10000				767.4	768.4	Single isomer
537		0.013	109.9			18	914	915.5	Single isomer
538		0.006	0.9		0.020	0.2	965.4	966.4	Single isomer

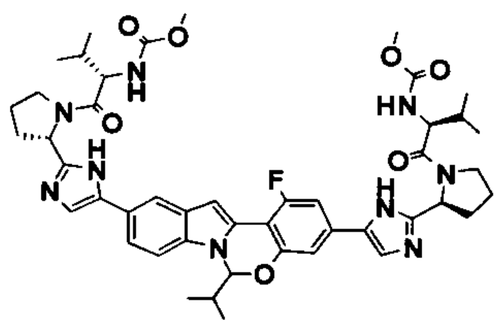
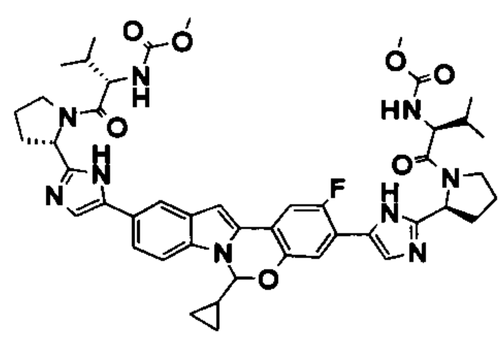
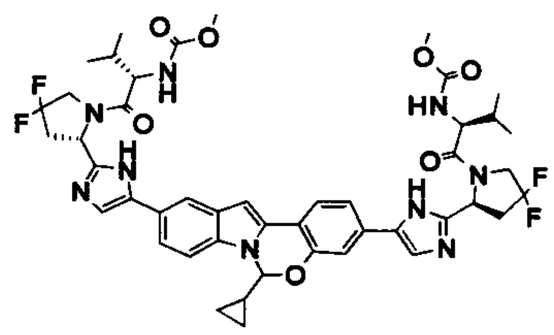
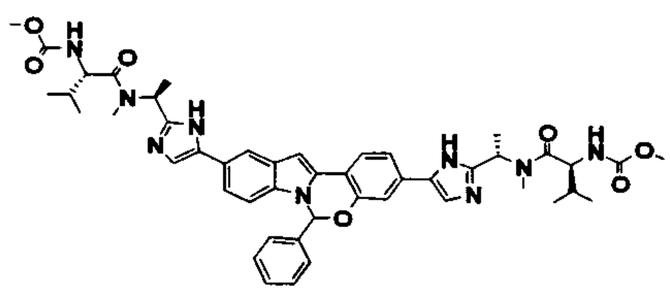
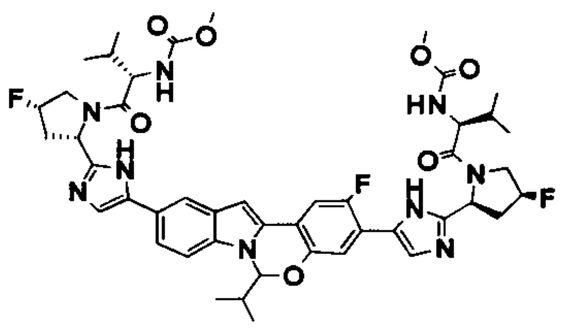
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
539		0.180	>100	93	>1		824.4	825.4	Single isomer
540		0.500	>100	71	>1		824.4	825.2	Single isomer
541		478.000	>1000	>1000	360.000		763.40	765.0	Single isomer
542		0.003	19.19	1.815	0.002	44.5	868.4	869.6	Mixture of isomers

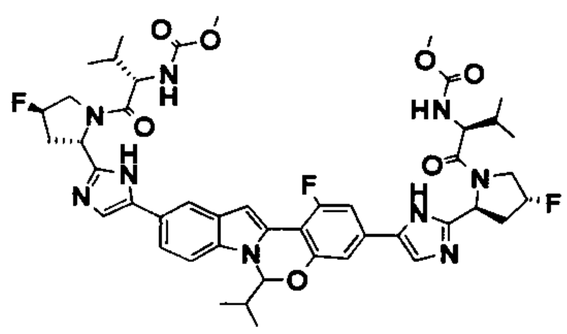
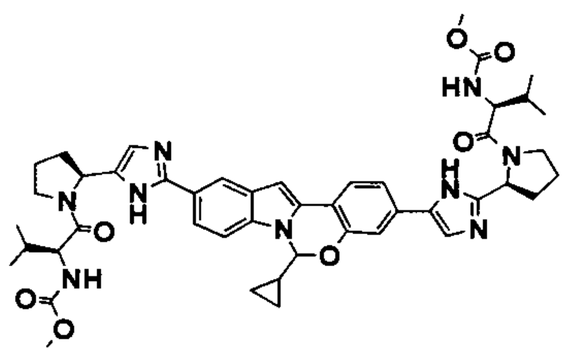
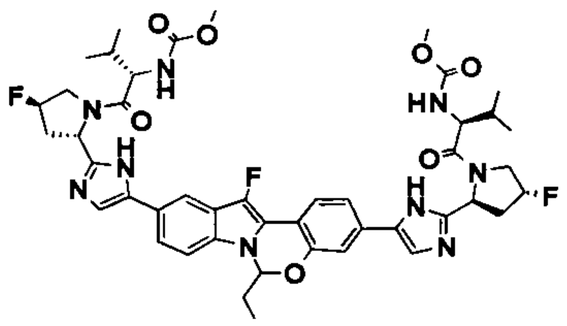
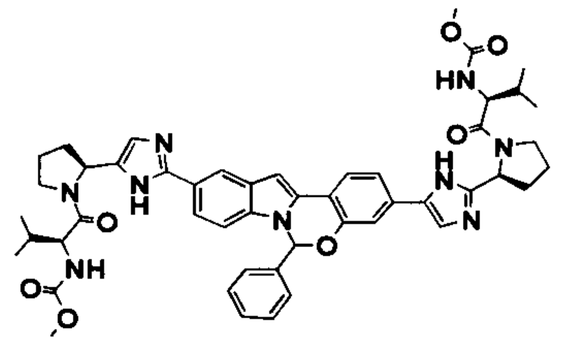
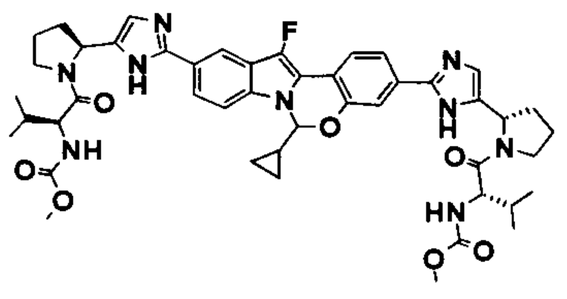
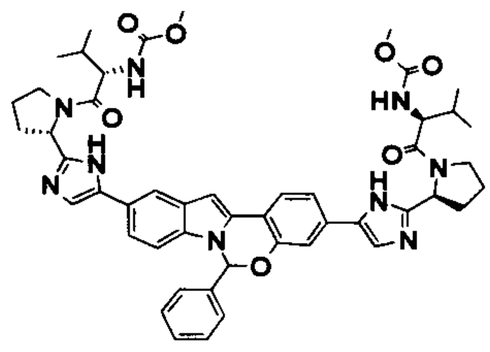
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
543		0.005	12.18	4.748	0.004	3	834.0	834.7	Mixture of isomers
544		0.005	2.26	1.724	0.002	1.1	888.1	889	Single isomer
545		0.004	4.69	0.5041	0.002	1	908.5	909.6	Mixture of isomers
546		0.006	19.64	0.6745	0.003	1.3	874.1	875	Mixture of isomers
547		0.005	16.84	0.619	0.002	8.7	898.4	899.4	Mixture of isomers

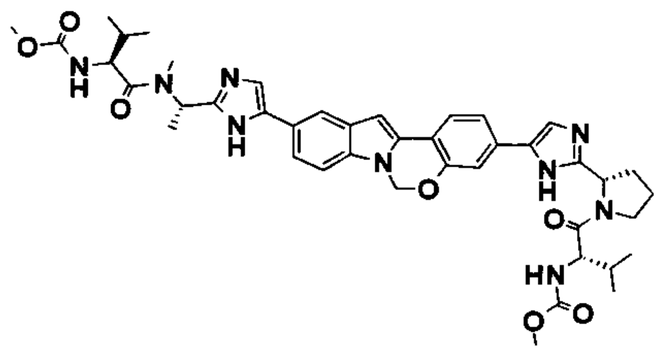
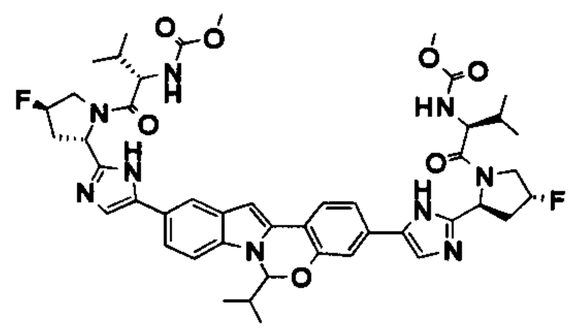
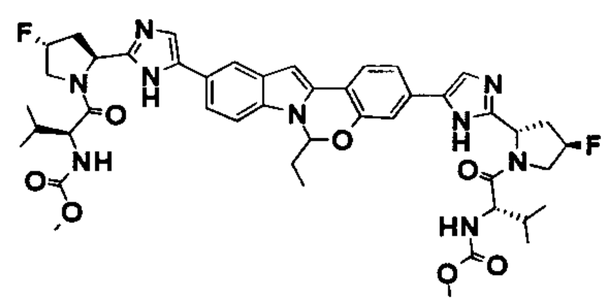
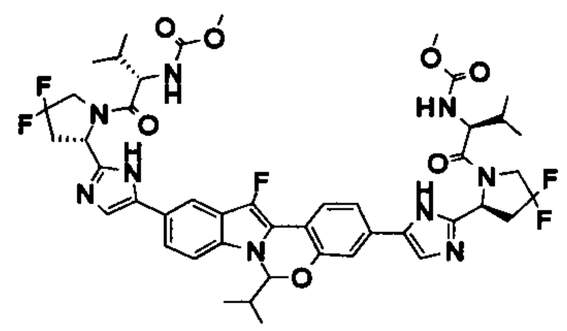
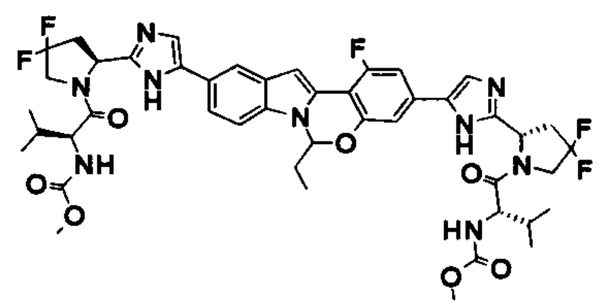
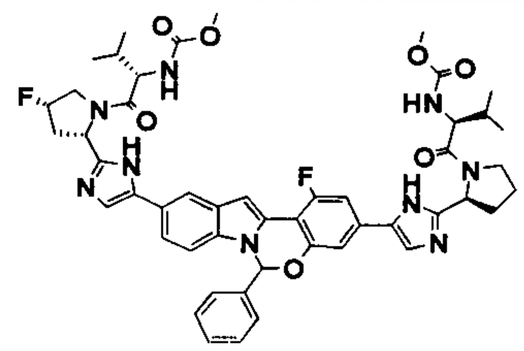
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
548		0.013	31.05	2.474	0.003	> 100	823.9	824.8	Mixture of isomers
549		0.003	1.97	0.9988	0.003	1.3	864.0	865	Mixture of isomers
550		0.009	66.79	1.92	0.004		890.1	891	Mixture of isomers
551		0.061	7.42	6.055	0.009	> 100	818.0	818.8	Mixture of isomers
552		0.003	2.15	1.334	0.088	3.1	852.0	852.7	Mixture of isomers

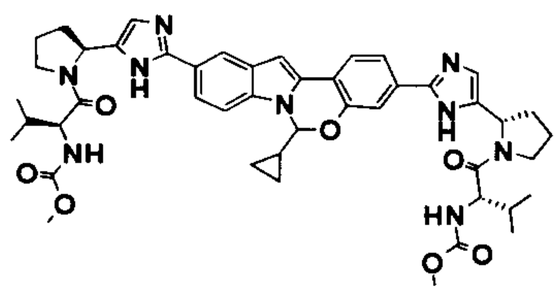
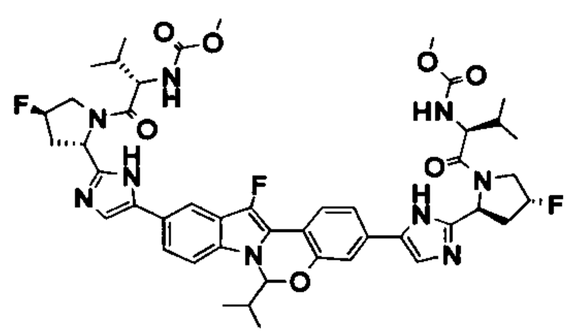
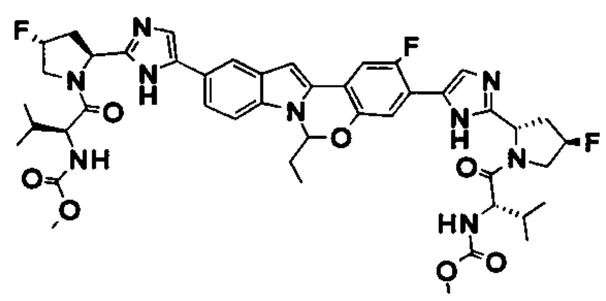
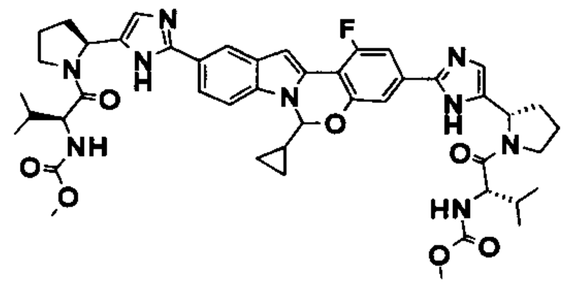
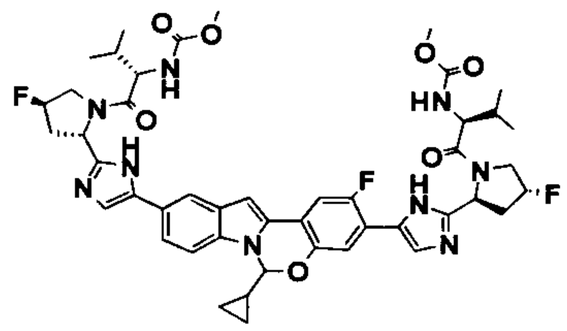
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
553		0.010	101.1	16.66	0.002	78.1	886.4	887.2	Mixture of isomers
554		0.001	27.79	0.767	0.002	7.7	900.0	901	Single isomer
555		0.002	20.77	3.175	0.001	9.8	852.0	852.8	Mixture of isomers
556		0.002	47.82	5.848	0.002	27.7	886.4	887.2	Mixture of isomers
557		0.017	93.26	2.586	0.005	51.2	938.1	938	Single isomer

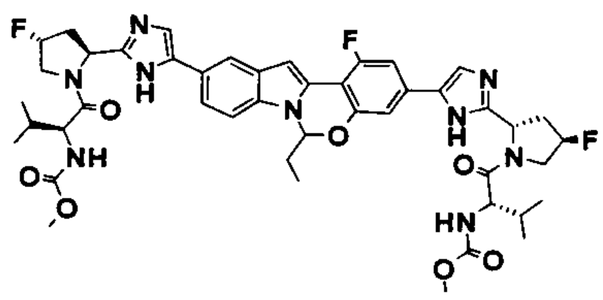
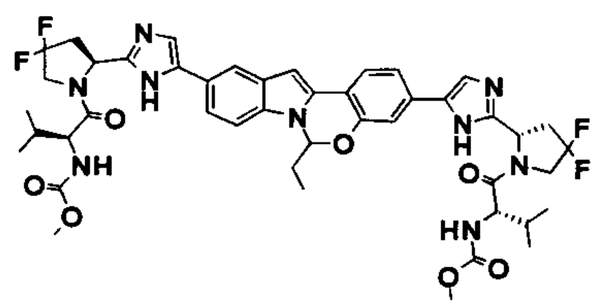
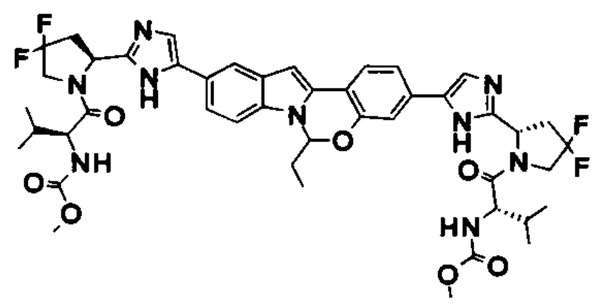
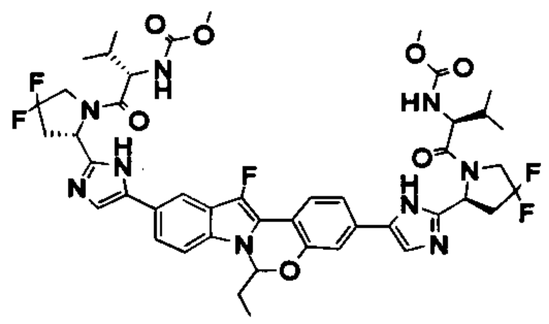
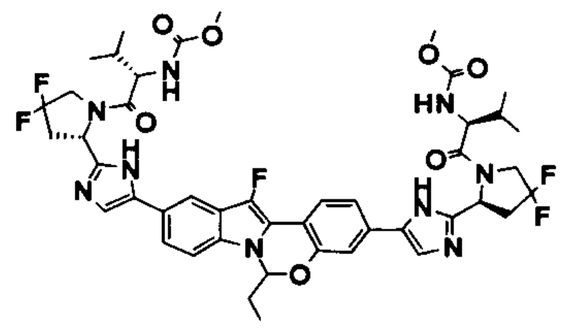
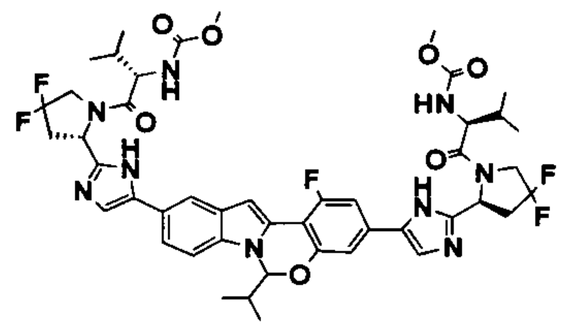
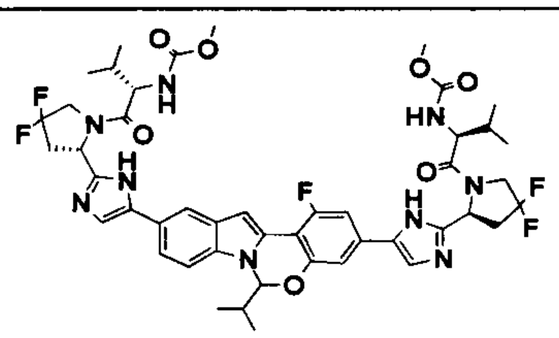
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
558		0.001	3.04	2.004	0.001	33.6	936.0	937	Mixture of isomers
559		0.003	25.61	0.5109	0.001	7.2	882.0	882.9	Single isomer
560		0.007	44.8	13.09	0.002	26.8	852.0	852.8	Mixture of isomers
561							900.0	900.8	Mixture of isomers
562		0.012	167.4	10.22	0.005	13.6	866.0	866.8	Mixture of isomers

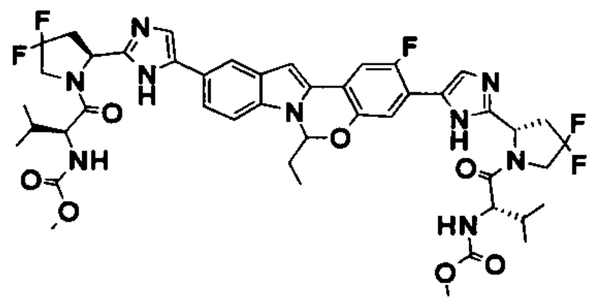
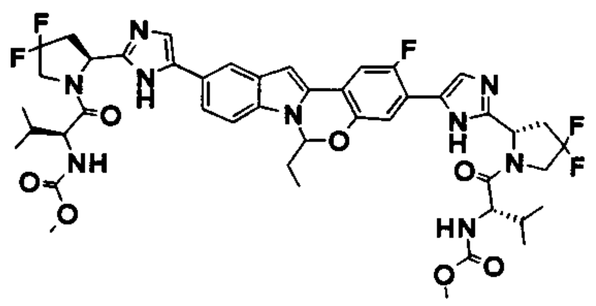
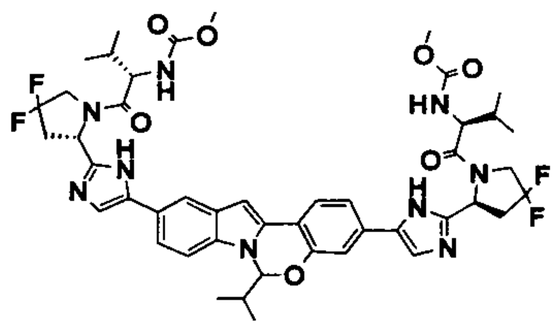
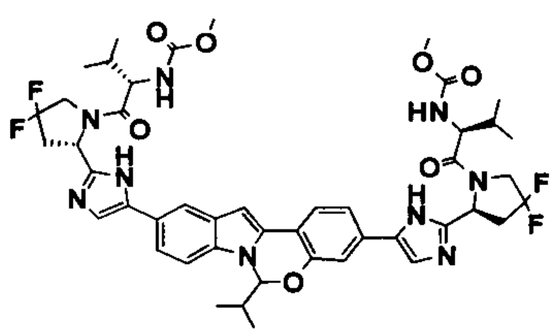
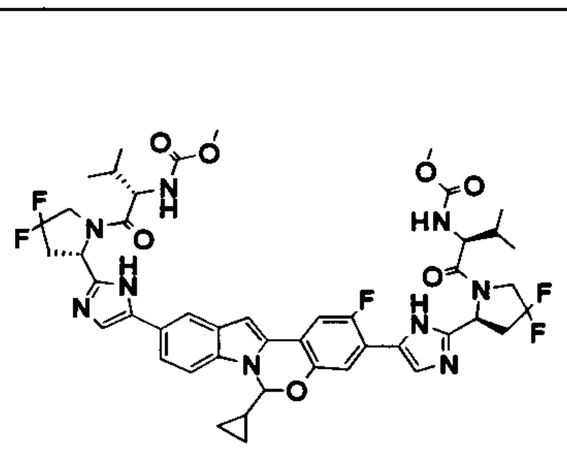
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
563		0.001	12.15	1.339	0.001	4.5	866.0	866.8	Mixture of isomers
564		0.005	48.97	11.08	0.002	17.9	864.0	865	Mixture of isomers
565		0.002	0.93	1.06	0.001	61.1	918.0	919	Mixture of isomers
566		0.022	> 100	33.97	0.006	> 100	858.0	858.7	Single isomer
567		0.033	> 100	12.3	0.003	> 100	902.0	903	Mixture of isomers

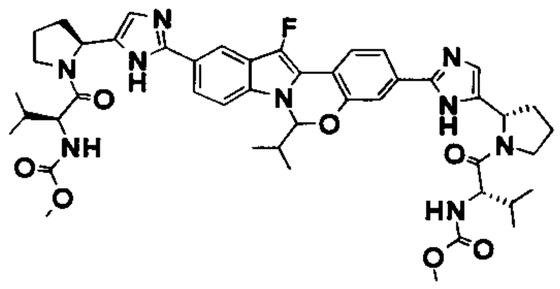
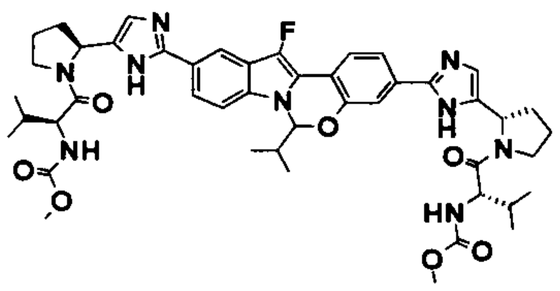
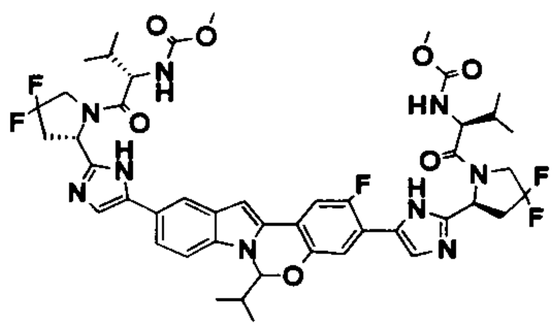
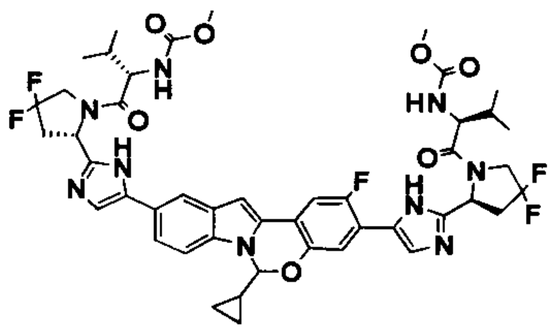
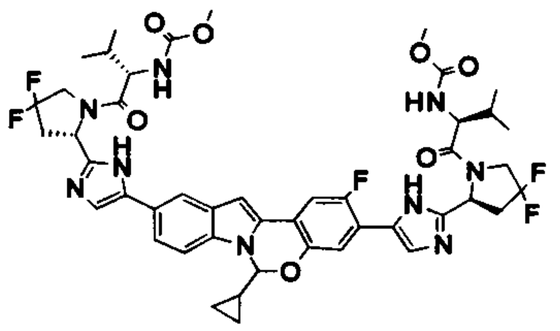
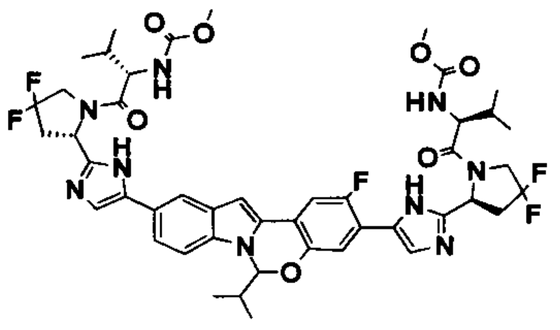
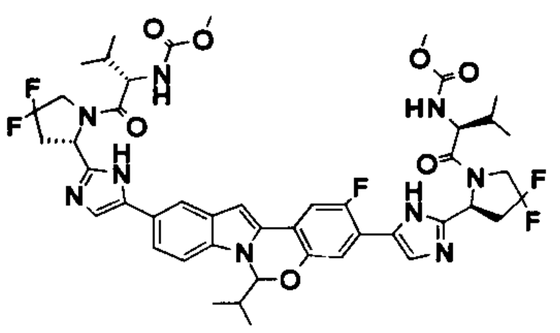
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
568		0.011	0.22	11.63	0.001	43.7	902.0	903	Mixture of isomers
569		0.023	> 100	11.76	0.010	60.5	846.0	846.8	Mixture of isomers
570		0.012	0.2	12.86	0.001	76	888.0	888.8	Mixture of isomers
571		0.001	4.02	0.3006	0.001	3.7	882.0	882.6	Single isomer
572		0.003	22.65	1.359	0.001	2.6	864.0	865	Single isomer
573							882.0	883	Single isomer

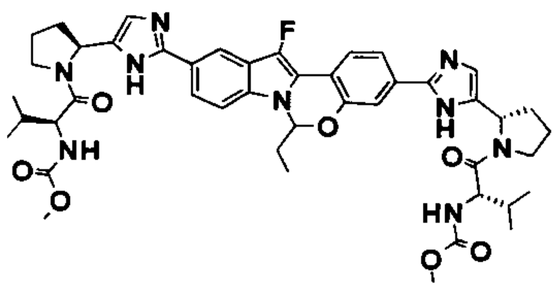
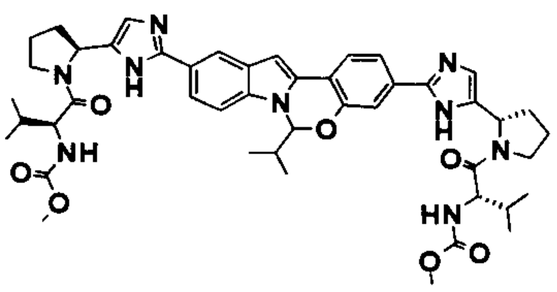
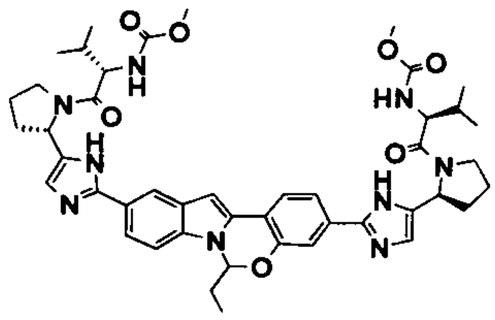
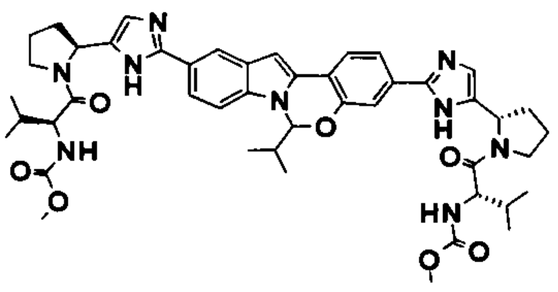
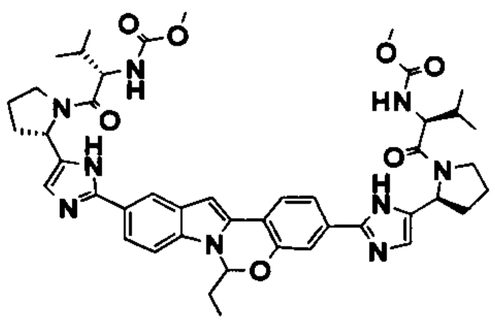
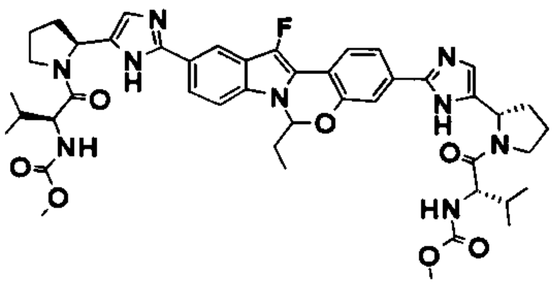
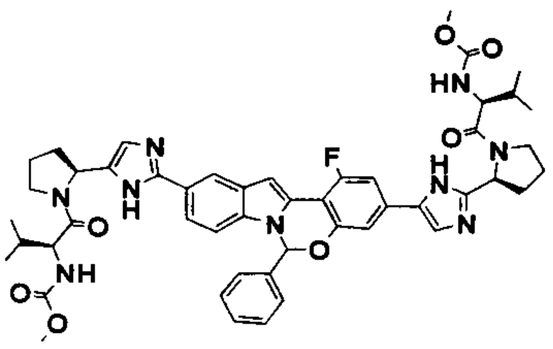
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
574		0.010	> 100	43.2	0.001	336.4	793.9	794.5	Single isomer
575		0.019	0.81	19.86	0.002	44	884.0	884.6	Single isomer
576		0.011	0.41	45.42	0.001	90.8	870.0	870.7	Single isomer
577		0.004	5.64	1.526	0.001	104.4	938.0	938.6	Single isomer
578		0.002	1.09	5.191	0.001	102.9	923.9	925	Single isomer
579		0.011	26.56	2.158	0.009		918.0	919	Single isomer

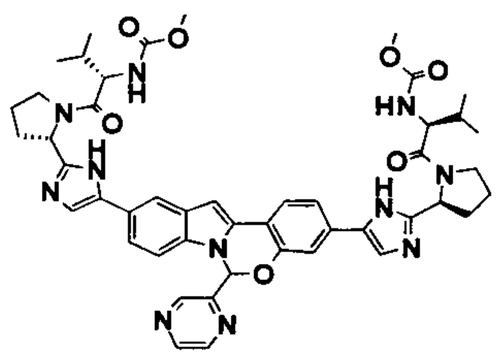
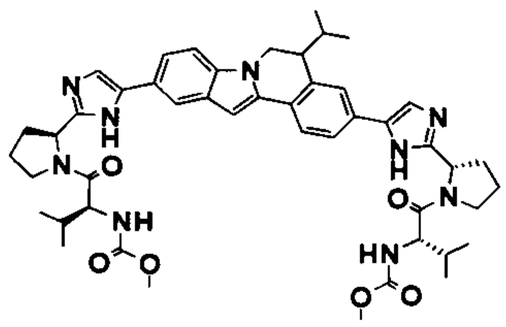
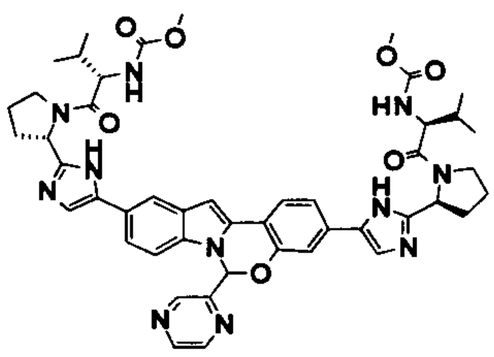
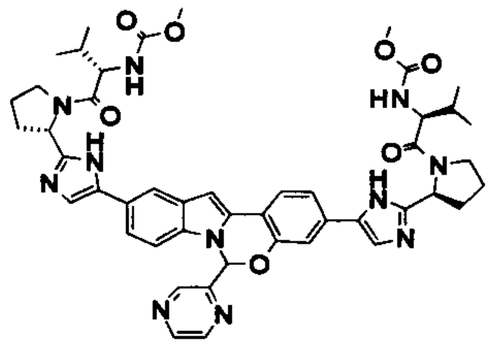
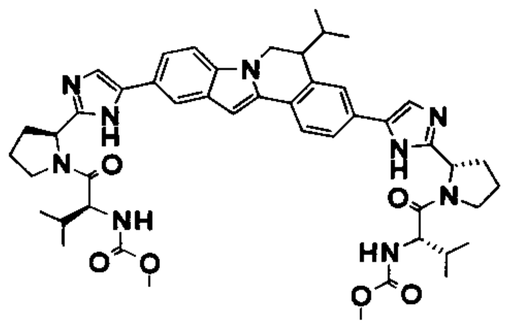
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
580		0.005	60.12	5.531	0.002	2.2	846.0	846.8	Single isomer
581		0.020	0.39	11.49	0.001	70.5	902.0	902.8	Single isomer
582		0.013	1.11	83.06	0.002	93.9	888.0	889	Single isomer
583							864.0	865	Single isomer
584							900.0	900.8	Single isomer

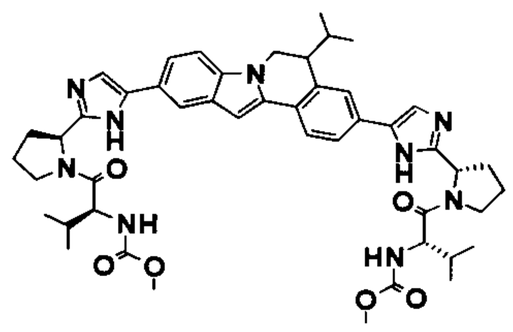
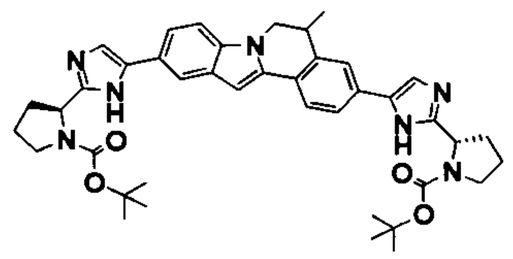
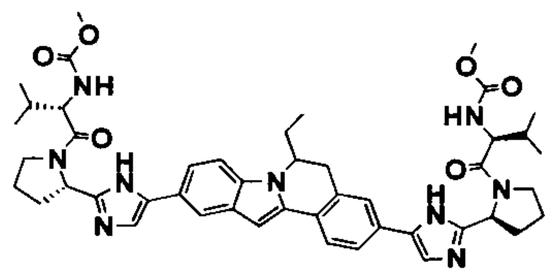
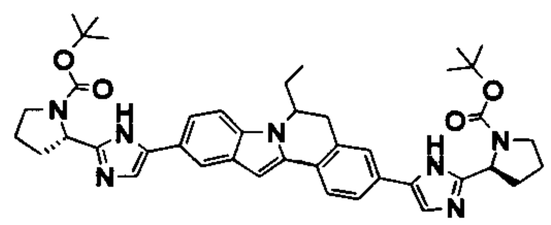
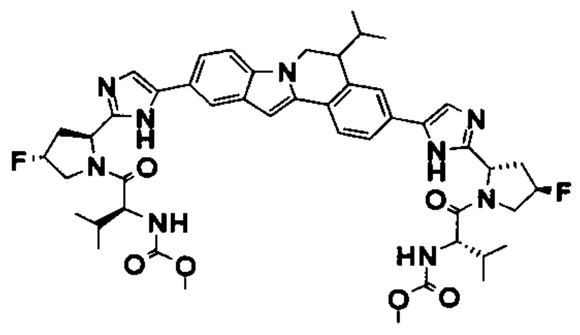
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
585		0.014	0.2	23.5	0.007	64	888.0	888.8	Single isomer
586		0.002	4.2	1.4	0.001	41.7	906.0	906.7	Single isomer
587		0.001	14.82	2.6	0.001	95.4	906.0	906.7	Single isomer
588		0.002	7.68	1	0.001	41.4	923.9	924.7	Single isomer
589		0.001	14.23	2.5	0.001	158.6	923.9	924.7	Single isomer
590		0.003	24	1.7	0.001	59.4	938.0	938.7	Single isomer
591		0.002	43	1.6	0.001	159.4	938.0	938.7	Single isomer

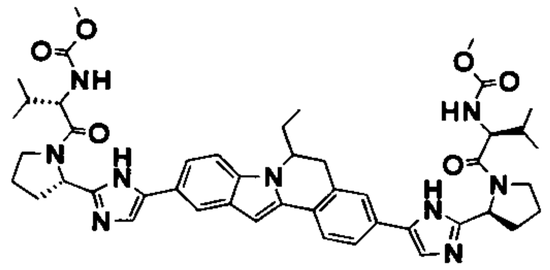
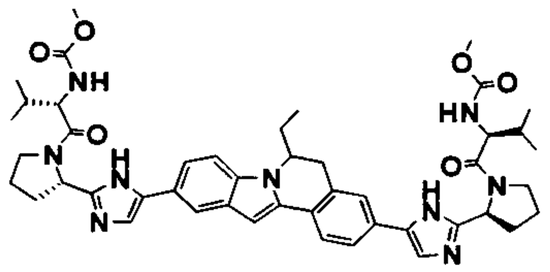
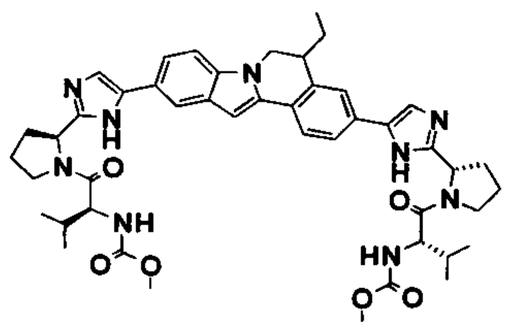
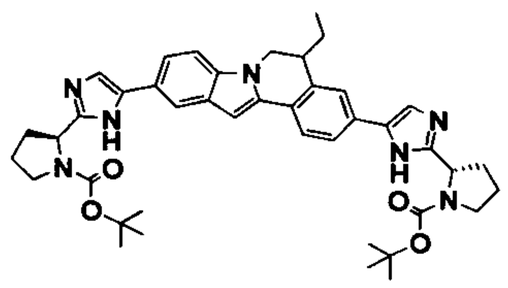
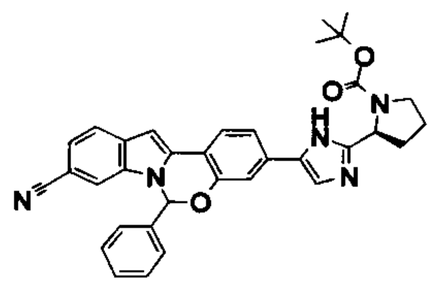
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
592		0.007	53	4	0.001	151.3	923.9	924	Single isomer
593		0.003	59.04	9.4	0.001	209.9	923.9	925	Single isomer
594		0.002	9.6	1.3	0.001	3.1	920.0	921	Single isomer
595		0.001		0.9	0.001	5.4	920.0	920.8	Single isomer
596		0.005		9.18	0.001	134.8	936.0	936.7	Single isomer

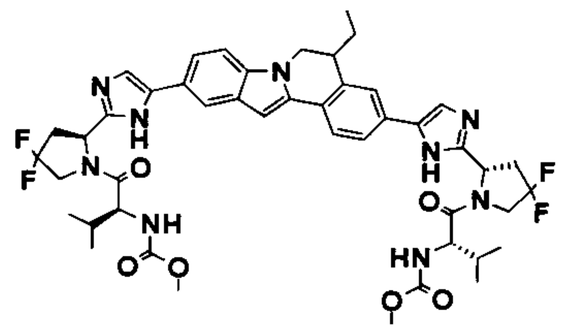
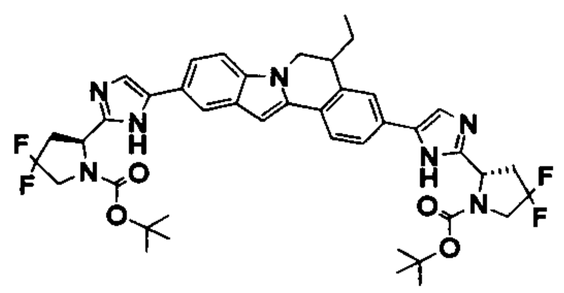
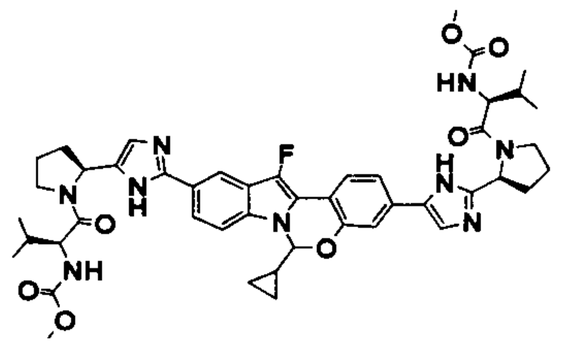
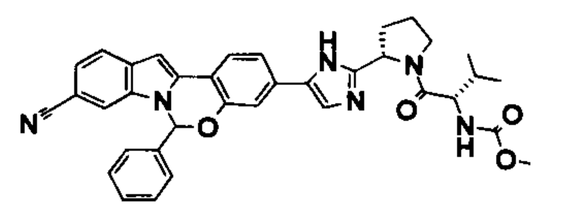
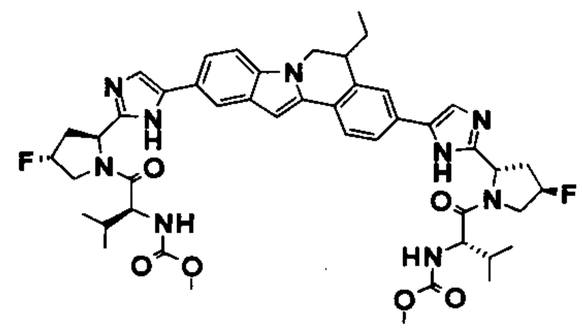
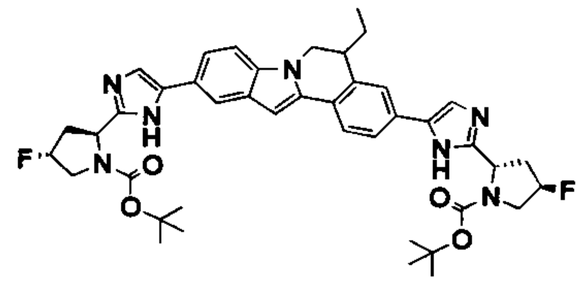
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
597		0.002	31.3	1.18	0.001	5.7	866.0	866.7	Single isomer
598		0.002	35	0.5	0.001	2	866.0	866.7	Single isomer
599		0.020		6.69	0.001	168.7	938.0	938.8	Mixture of isomers
600		0.001		2.53	0.000	111.3	936.0	936.8	Single isomer
601		0.078		6.53	0.001	251.8	936.0	937	Single isomer
602		0.017	19.79	9.6	0.001	58	938.0	939	Single isomer
603		0.013	18.78	7.4	0.002	517	938.0	938.6	Single isomer

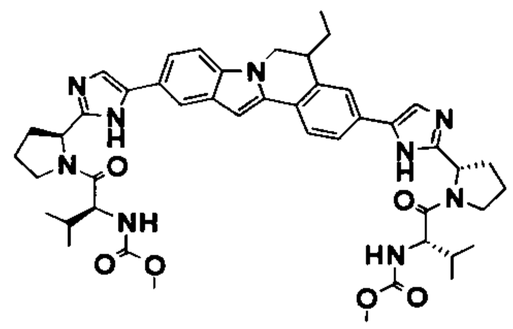
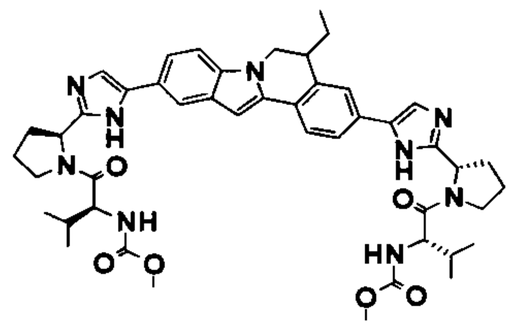
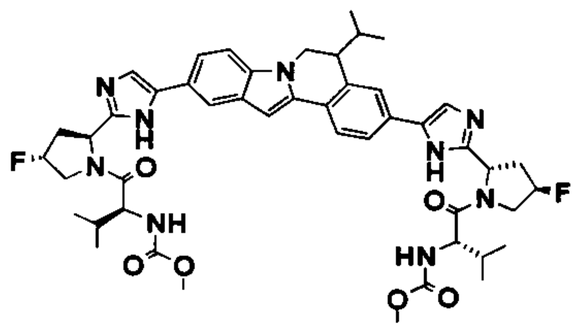
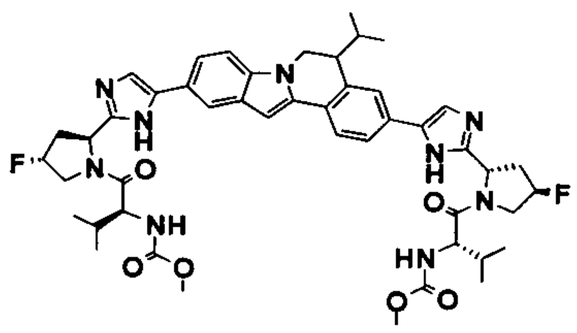
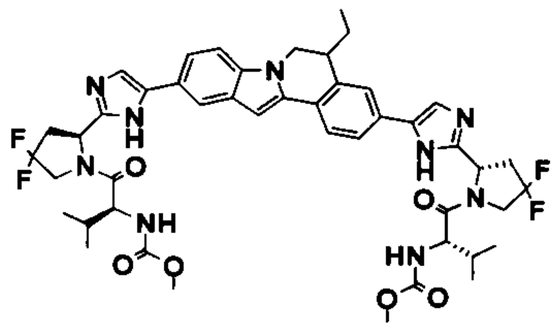
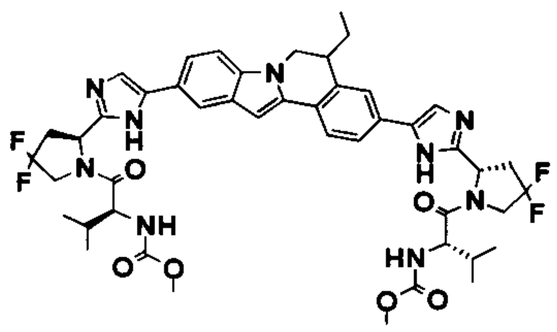
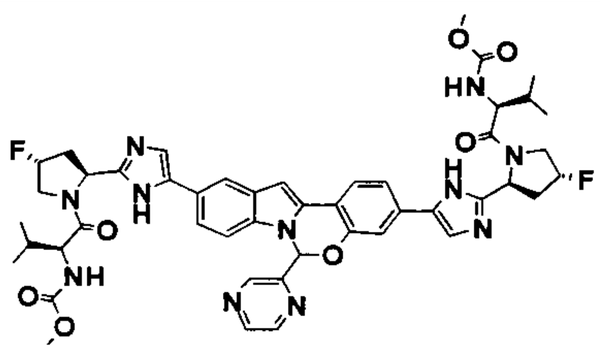
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
604		0.014			0.008		852.0	852.8	Single isomer
605		0.003	21.58	1.9	0.002	2	848.0	848.8	Single isomer
606		0.002	15.22	2.1	0.001	2	834.0	835	Single isomer
607		0.001	16.54	1.7	0.002	7	848.0	849	Single isomer
608		0.002	4.62	3	0.002	12	834.0	834.8	Single isomer
609		0.002	24.89	8.6	0.003	71	852.0	852.8	Single isomer
610		0.009	35	1.4	0.003	3.9	900.0	900.9	Mixture of isomers

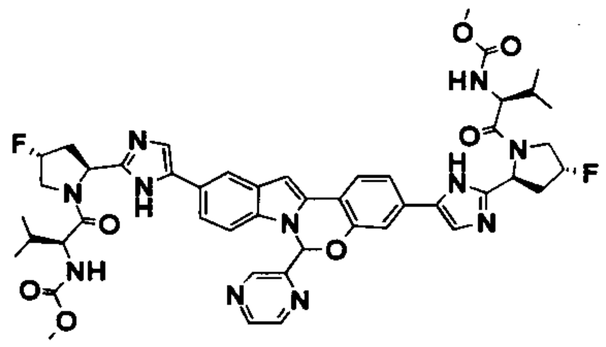
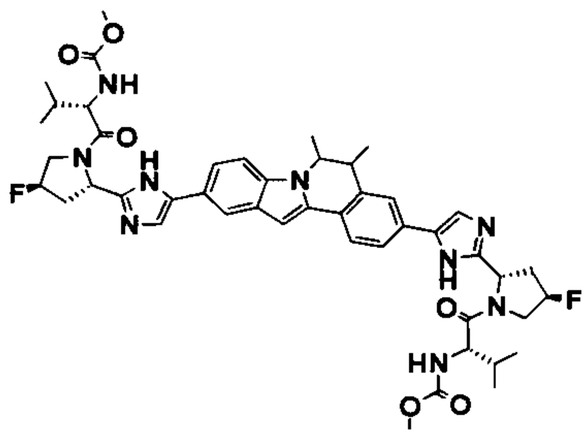
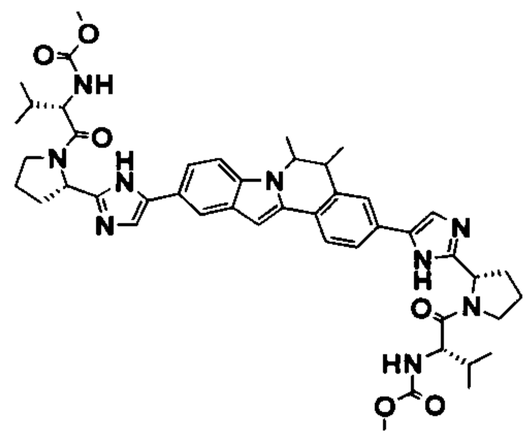
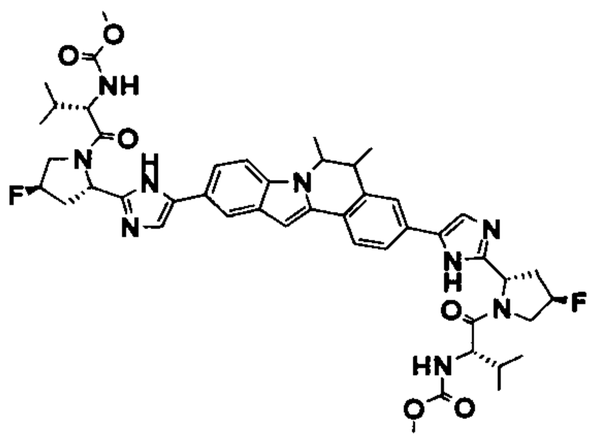
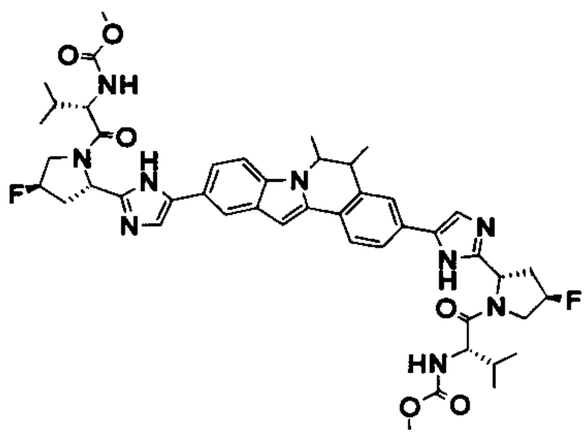
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
611		1.950	27.45	1.95	0.200	12	884.0	885	Mixture of isomers
612		1.950	241.5	7.47	0.200	200	846.1	846.9	Mixture of isomers
613		0.023	359	10		13.2	884.0	885	Single isomer
614		0.004	12	10		9.8	884.0	885	Single isomer
615		0.016	190	9.11	0.003	46	846.1	846.9	Single isomer

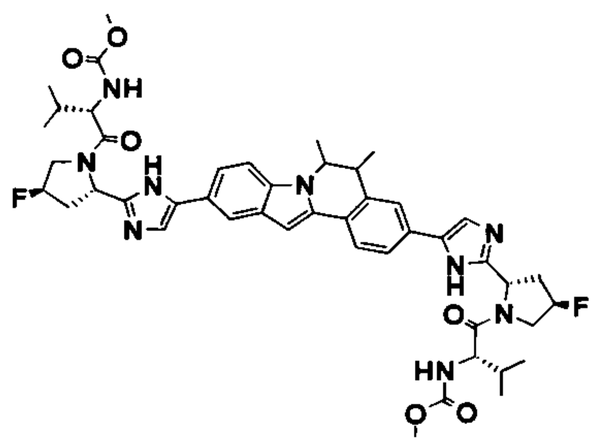
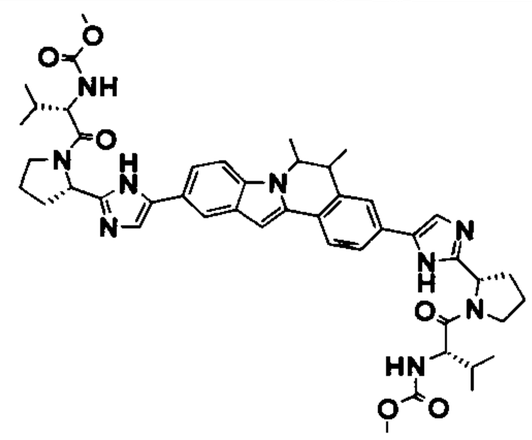
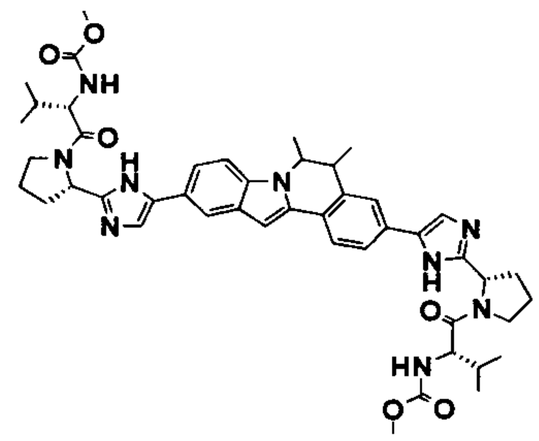
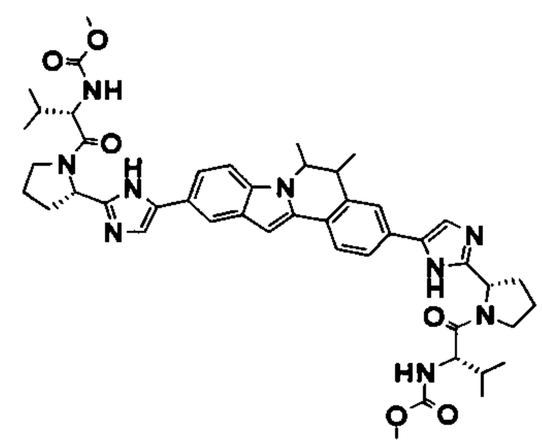
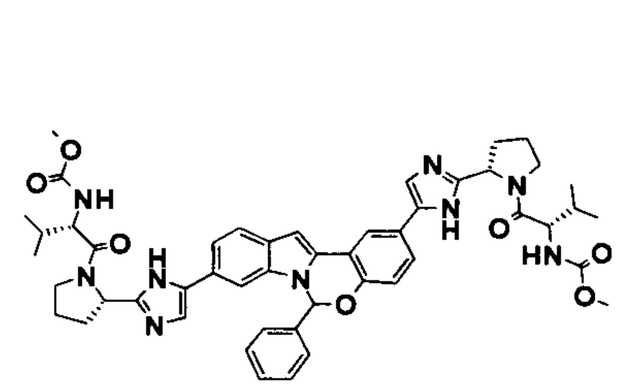
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
616		0.003	23	14.92	0.003	58	846.1	846.9	Single isomer
617							703.9	704.9	Mixture of isomers
618		1.000	152.82				832.0	833	Mixture of isomers
619							717.9	718.9	Mixture of isomers
620		0.024	6.22	32.8	0.003	> 200	882.0	883	Mixture of isomers

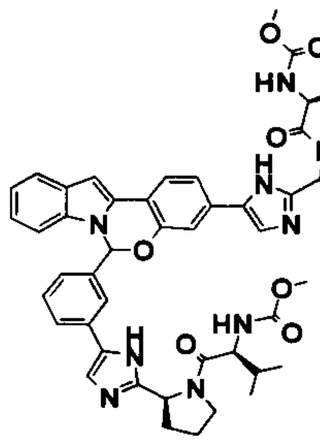
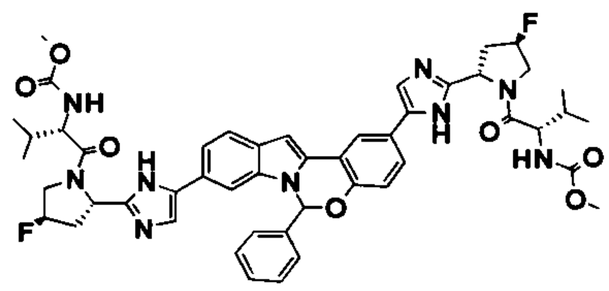
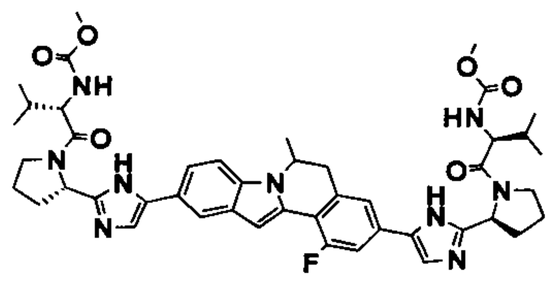
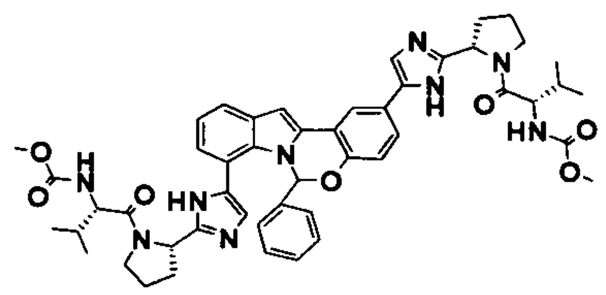
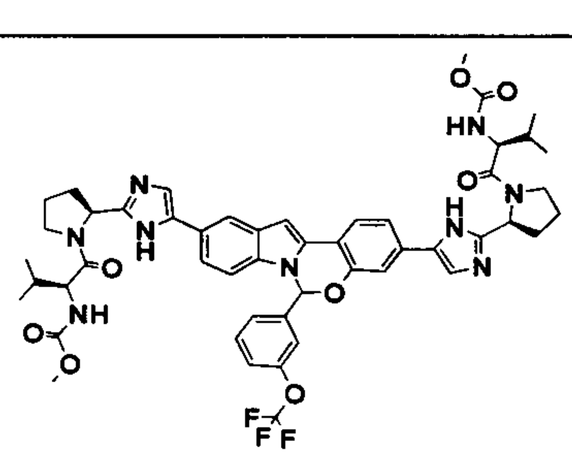
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
621		0.004	34.08	14.7	0.004	43.5	832.0	833	Single isomer
622		0.005	> 200	9.9	0.003	47	832.0	833	Single isomer
623		0.006	> 200	6.6	0.005	92.2	832.0	833	Mixture of isomers
624							717.9	718.9	Mixture of isomers
625		> 2000	> 20000				557.7	559	Mixture of isomers

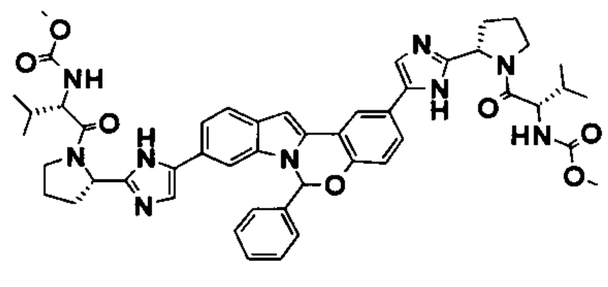
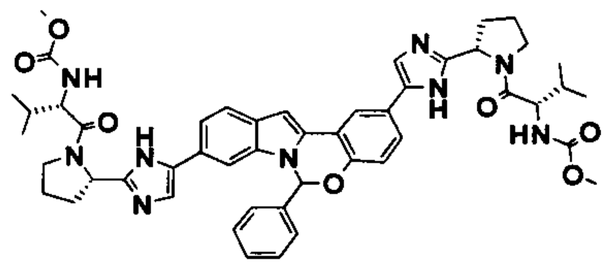
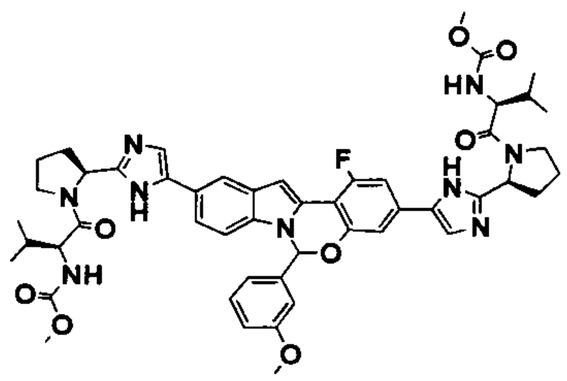
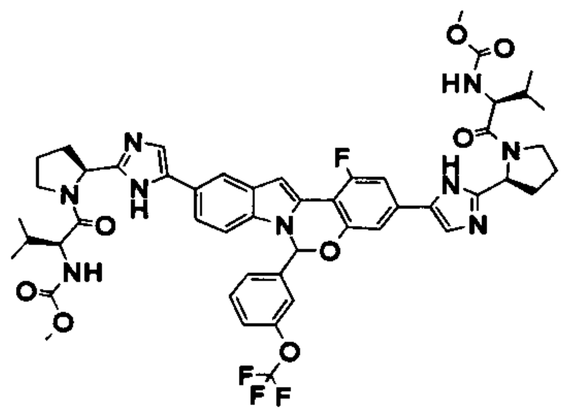
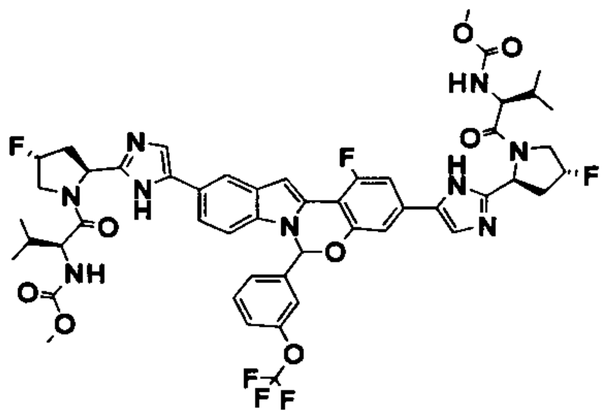
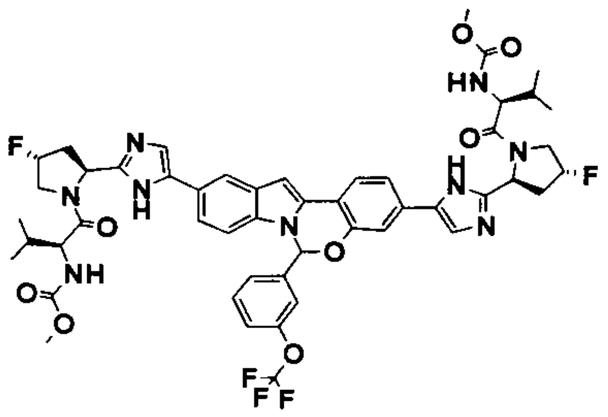
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
626		0.007	41.8	5.3	5.000	> 200	904.0	905	Mixture of isomers
627							789.9	790.9	Mixture of isomers
628		0.296	> 200	29.1	0.066	> 200	864.0	865	Mixture of isomers
629		3.000	1086.62				614.7	615.8	Mixture of isomers
630		0.045	1.45	45.877	0.005	> 200	868.0	869.1	Mixture of isomers
631		> 2	> 200	> 200	> 2	> 200	753.9	755	Mixture of isomers

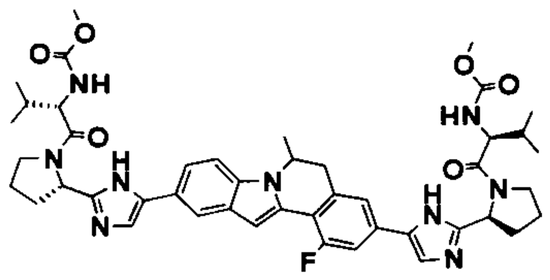
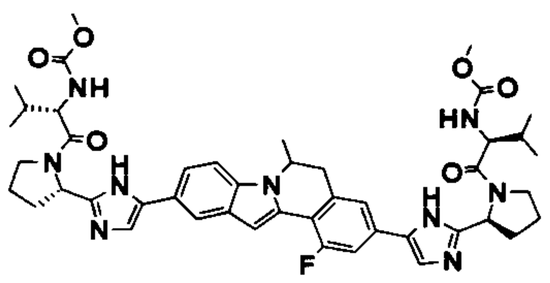
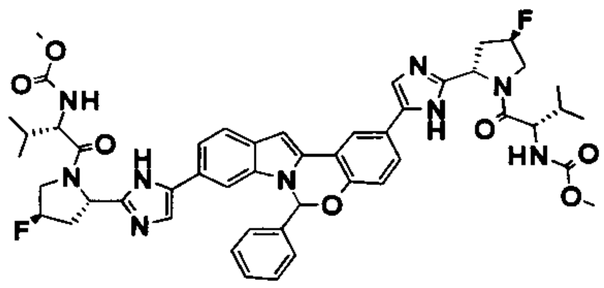
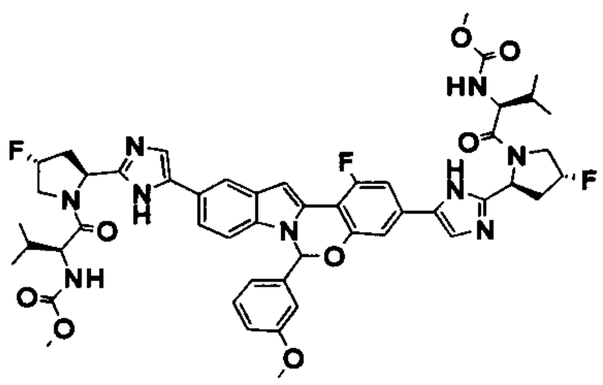
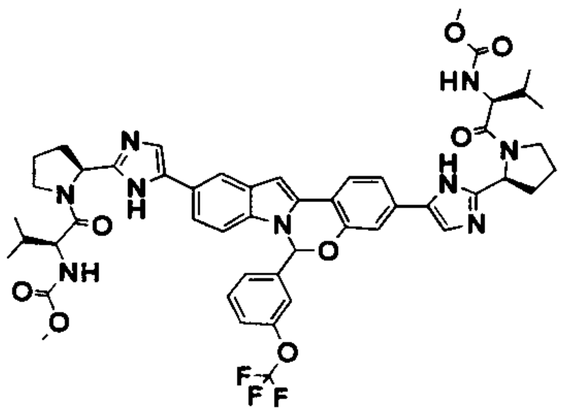
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
632		0.003	> 200	2.1	0.004	54.1	832.0	833	Single isomer
633		0.003	82.89	14.2	0.003	53.1	832.0	832.9	Single isomer
634		0.036	1.87	89.97	0.009	> 200	882.0	882.9	Single isomer
635		0.277	1.26	35.724	0.008	> 200	882.0	882.9	Single isomer
636		0.012	86.77	3.2	0.004	> 200	904.0	904.9	Single isomer
637		0.003	78.42	22.7	0.002	> 200	904.0	905.1	Single isomer
638		0.050	4.6	21.7	0.007	47.6	920.0	921	Single isomer

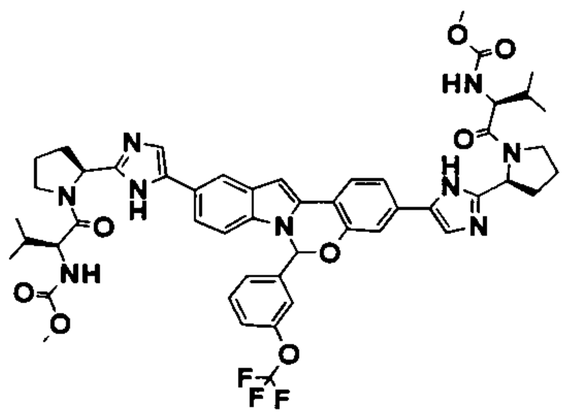
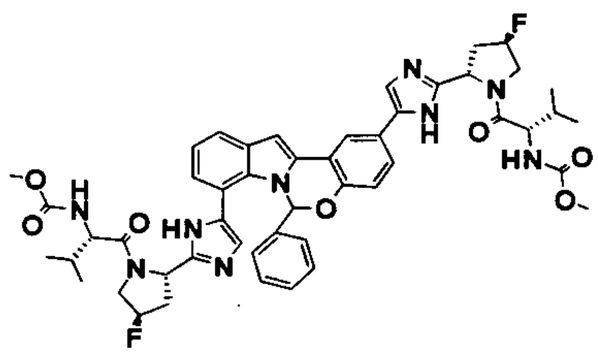
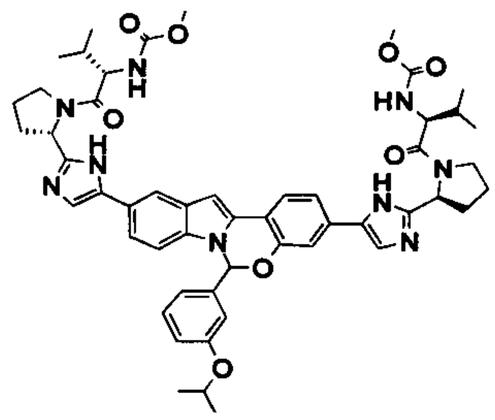
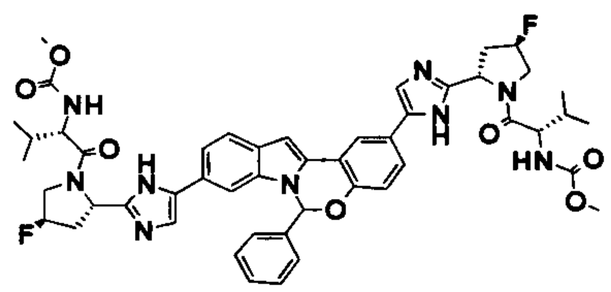
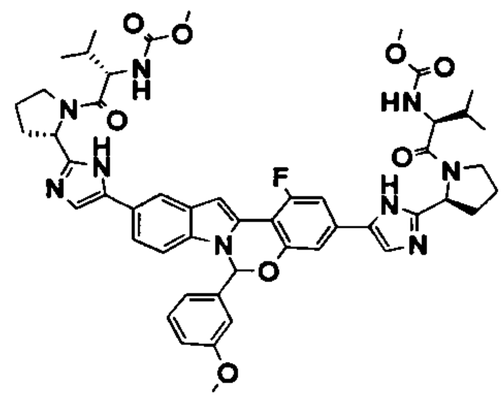
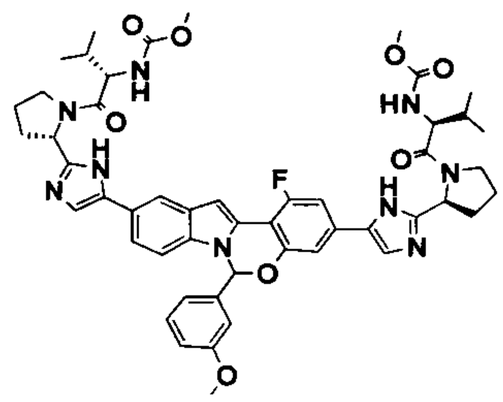
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
639		0.008		26.9	0.005	41.9	920.0	921	Single isomer
640							868.0	868.8	Mixture of isomers
641							832.0	832.9	Mixture of isomers
642							868.0	868.8	Mixture of isomers
643							868.0	868.8	Mixture of isomers

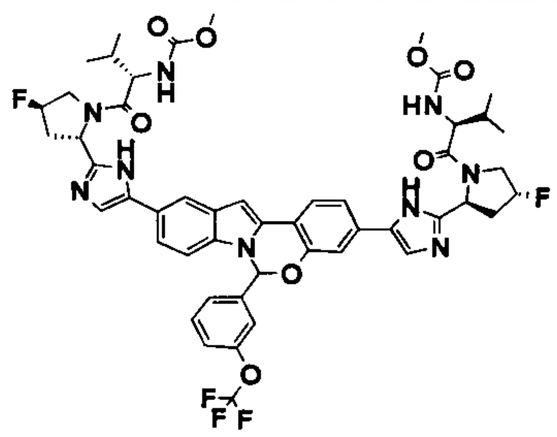
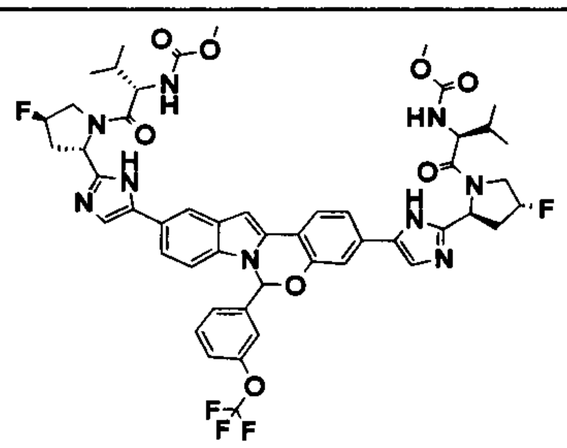
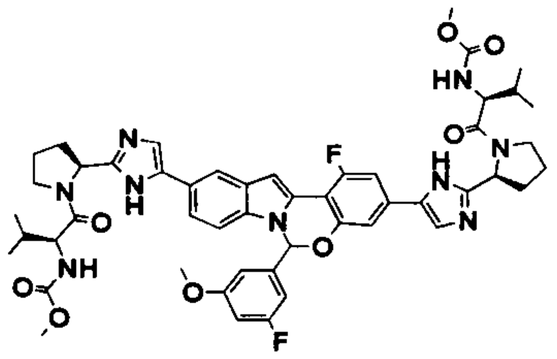
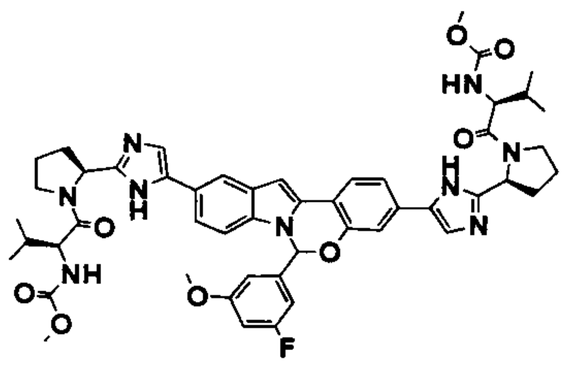
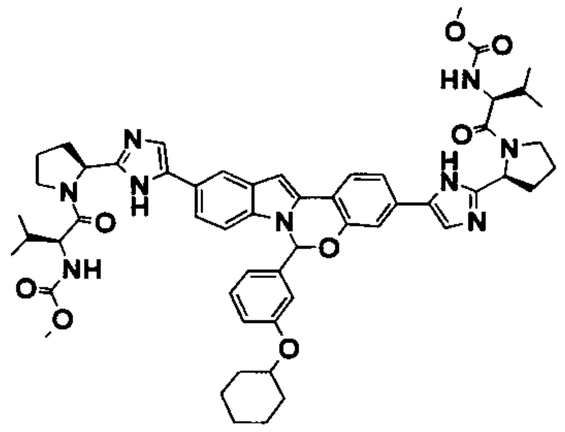
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
644							868.0	868.9	Mixture of isomers
645							832.0	833	Mixture of isomers
646							832.0	833	Mixture of isomers
647							832.0	833	Mixture of isomers
648		0.340	38	34	0.006	67	882.0	883	Mixture of isomers

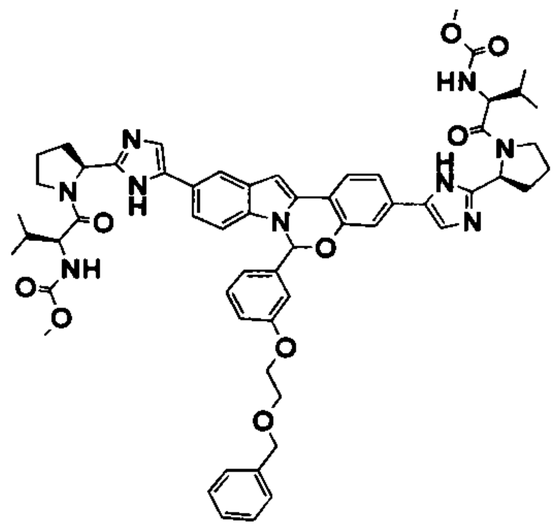
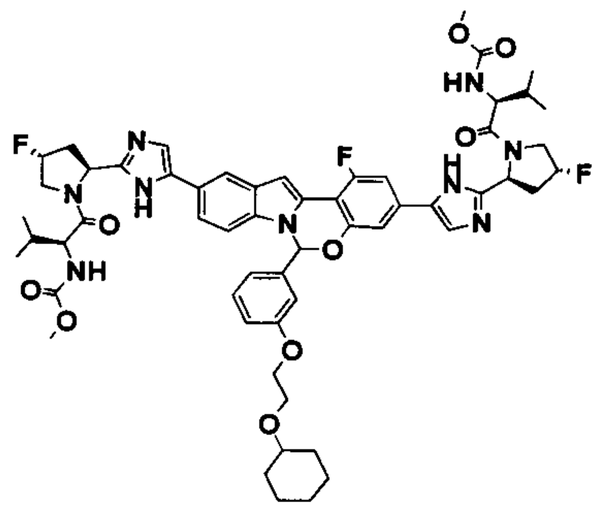
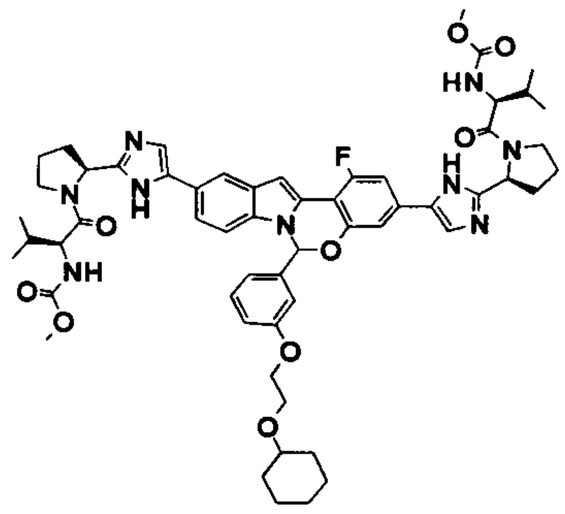
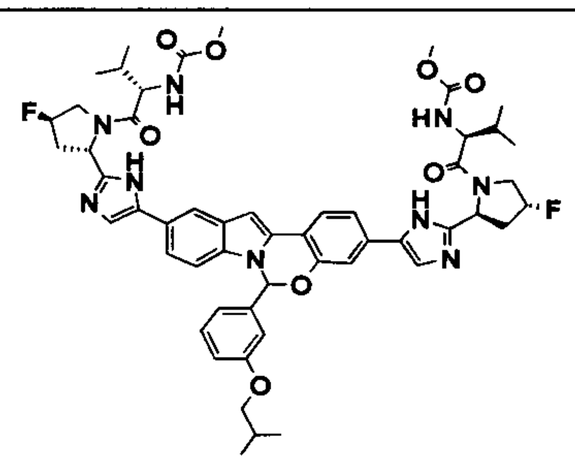
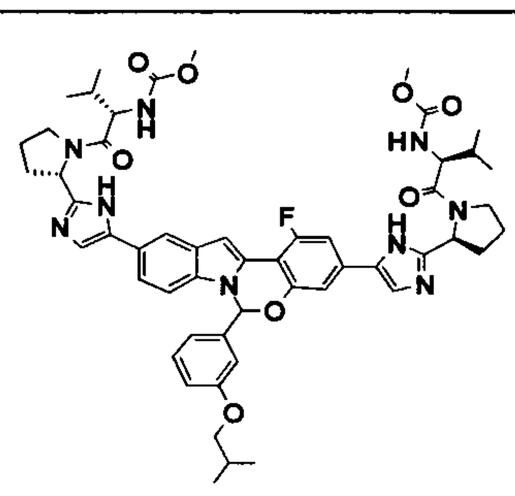
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
649		406.000	2295				882.0	883	Mixture of isomers
650		#######	274				918.0	919.1	Mixture of isomers
651		0.003	2.42	20	0.005	46	836.0	837	Mixture of isomers
652		> 1	> 100	> 100	0.022	> 100	882.0	882.9	Mixture of isomers
653		0.002		0	0.002	4.5	966.0	967	Mixture of isomers

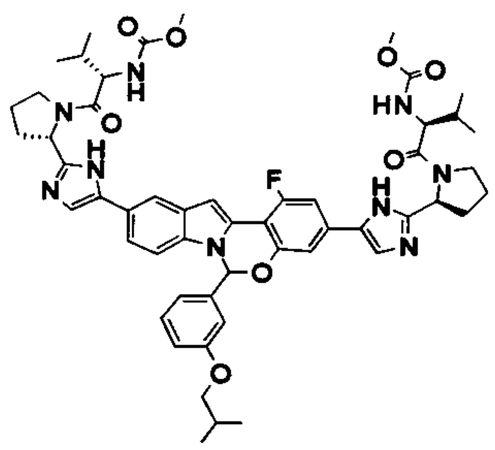
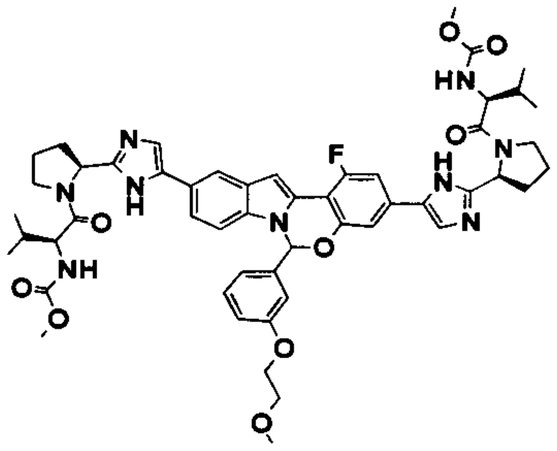
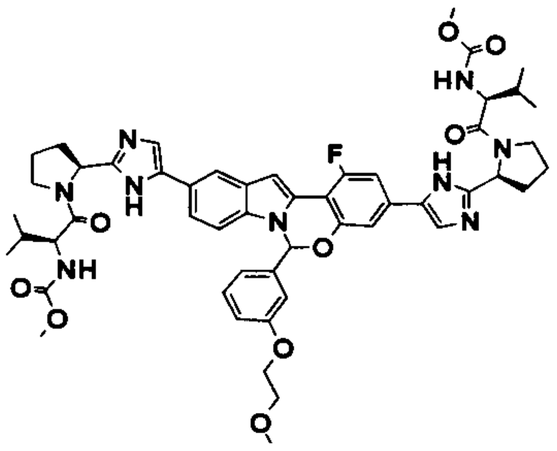
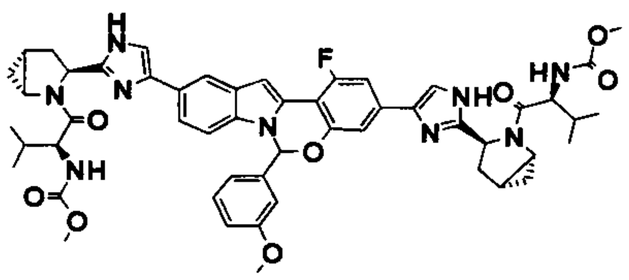
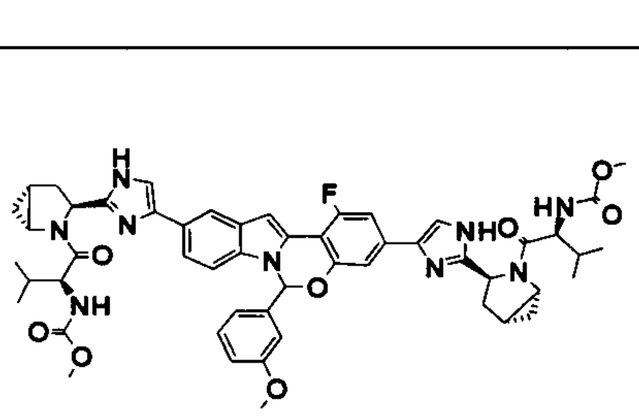
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
654		0.037	> 100	37	0.003	65.2	882.0	882.9	Single isomer
655		0.673	> 100	42	0.011	> 100	882.0	882.8	Single isomer
656		0.006	5	0.2	0.003	1.9	930.1	931	Mixture of isomers
657		0.007	4	0.2	0.004	22.8	984.0	985	Mixture of isomers
658		0.004	0.2	1.6	0.004	30.5	1020.0	1021	Mixture of isomers
659		0.006	1	7	0.002	42.9	1002.0	1003	Mixture of isomers

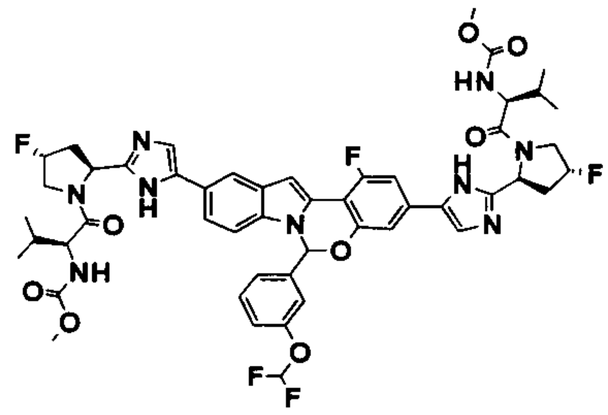
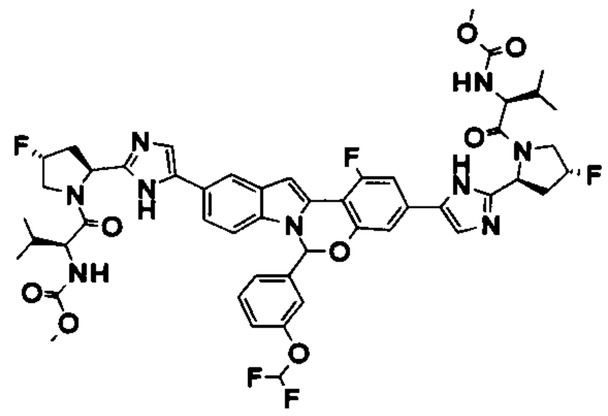
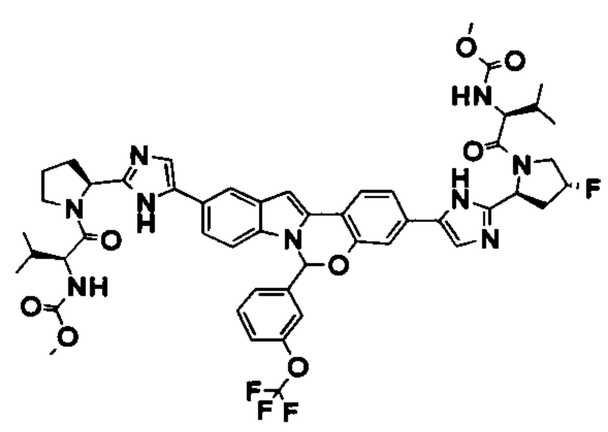
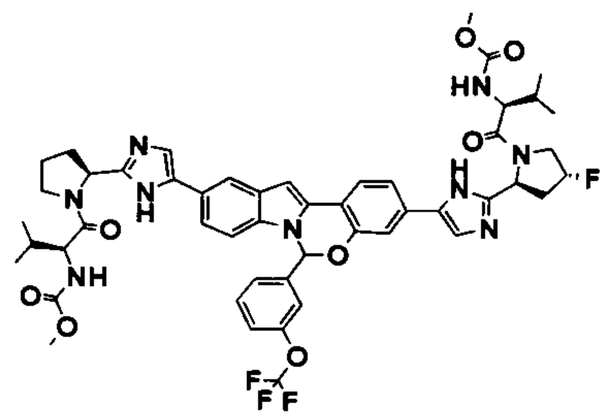
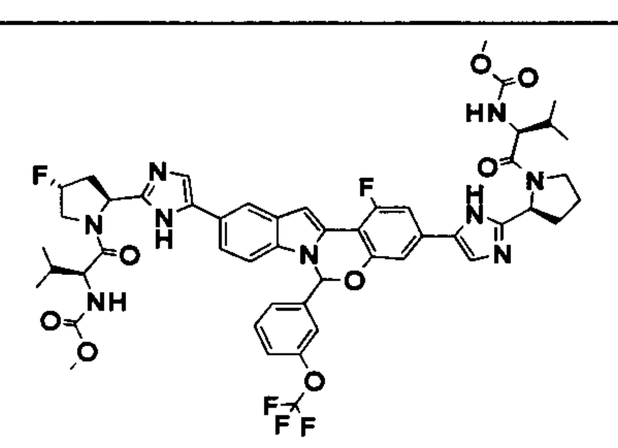
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
660		0.006	8	5.7	0.005	43	836.0	836.9	Single isomer
661		0.004	> 100	11.8	0.004	25.2	836.0	837.1	Single isomer
662		0.260	62	59.6	0.013	> 100	918.0	918.9	Single isomer
663		0.004	1	0.3	0.004	14	966.0	966.9	Single isomer
664		0.002	16	0.2	0.002	8.3	966.0	966.9	Single isomer

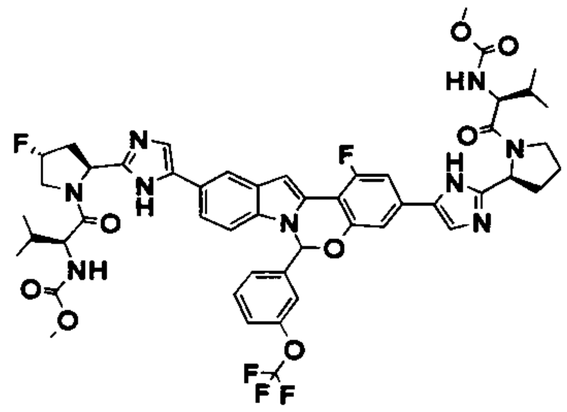
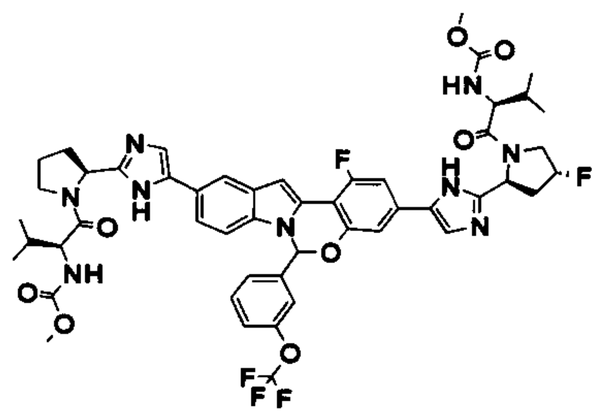
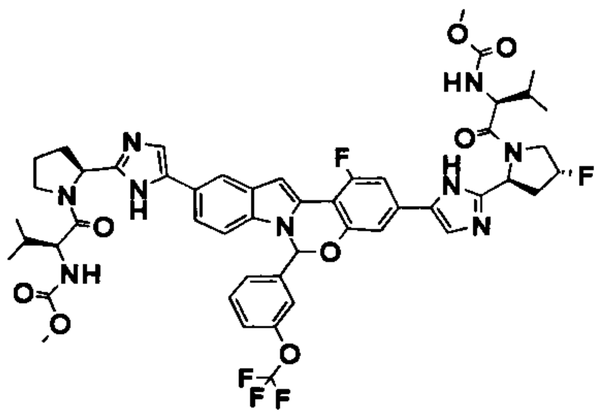
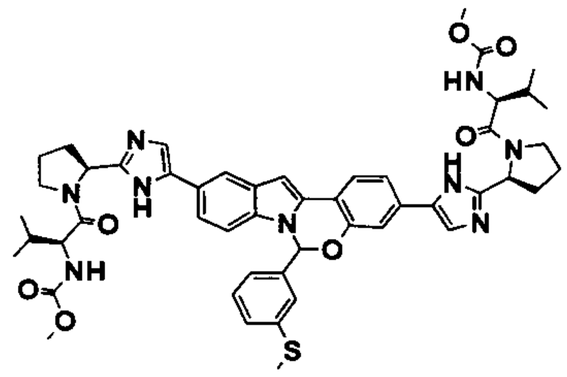
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
665		0.005	6	0.2	0.003	2.9	966.0	966.8	Single isomer
666		1.000	> 100	> 100	0.000	> 100	918.0	918.8	Mixture of isomers
667							940.1	940.9	Mixture of isomers
668							918.0	918.9	Single isomer
669		0.005	0.6	0.2	0.003	0.7	930.1	930.9	Single isomer
670		0.006	5	0.2	0.005	2.9	930.1	931	Single isomer

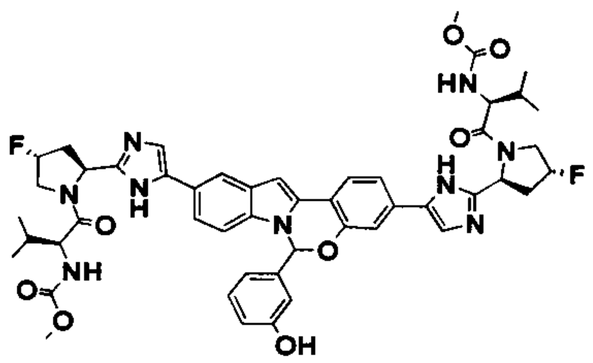
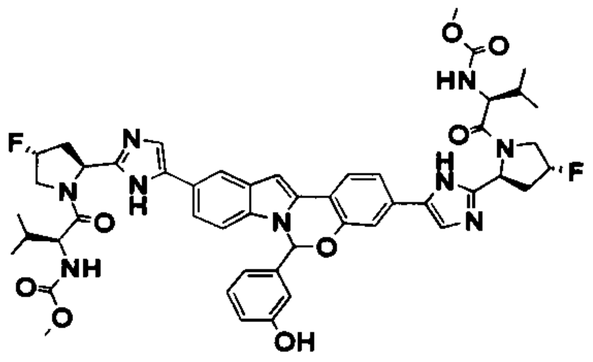
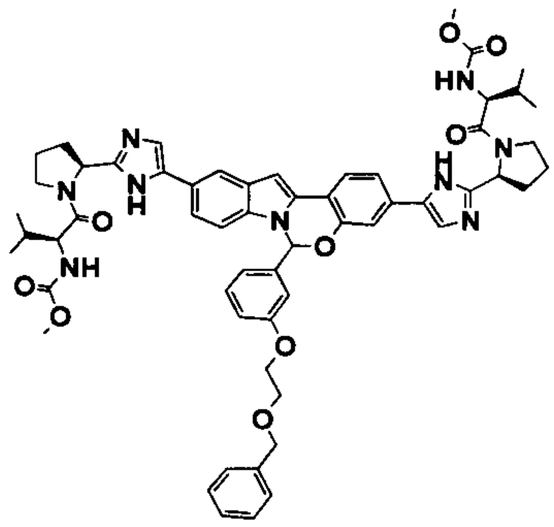
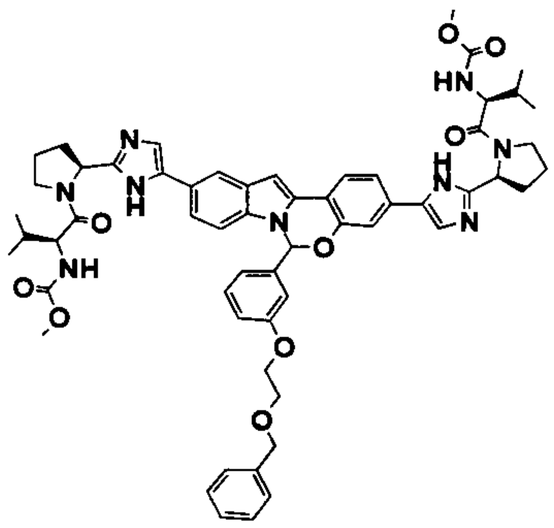
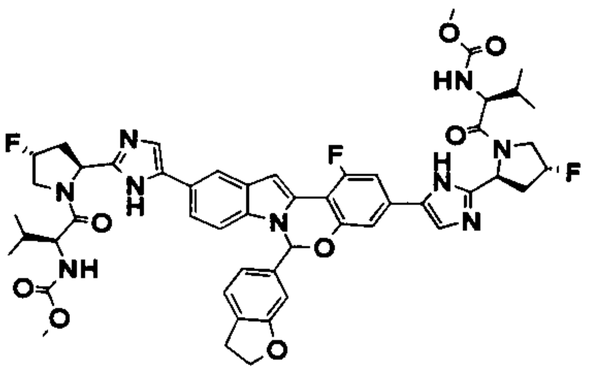
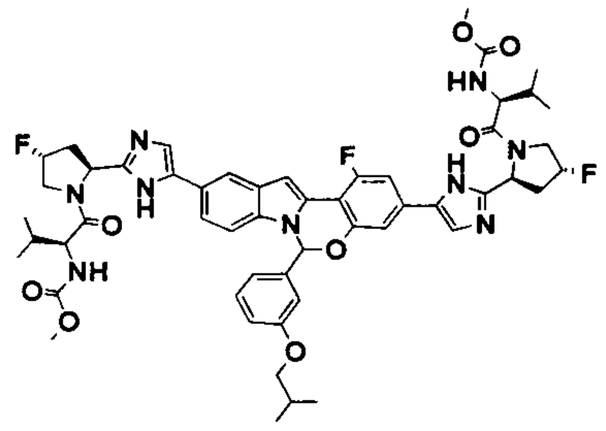
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
671		0.016	0.6	2.4	0.005	52.5	1002.0	1002	Single isomer
672		0.006	0.22	2.1	0.005	26.8	1002.0	1003	Single isomer
673		0.00685	1.4	0.1408			948.0	948.9	Mixture of isomers
674		0.01579	7.862	0.1396			930.1	931	Mixture of isomers
675		0.01313	5.192	0.1423			980.2	981.1	Mixture of isomers

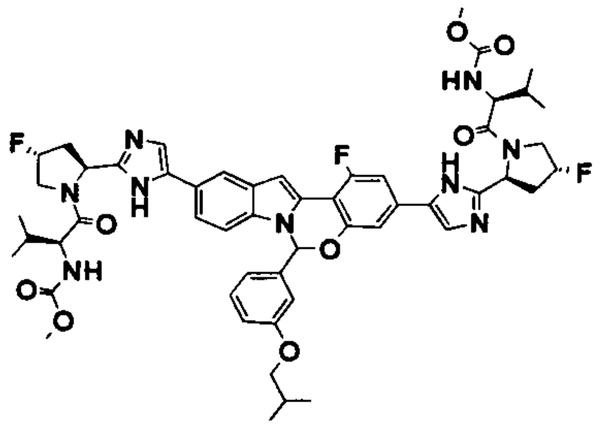
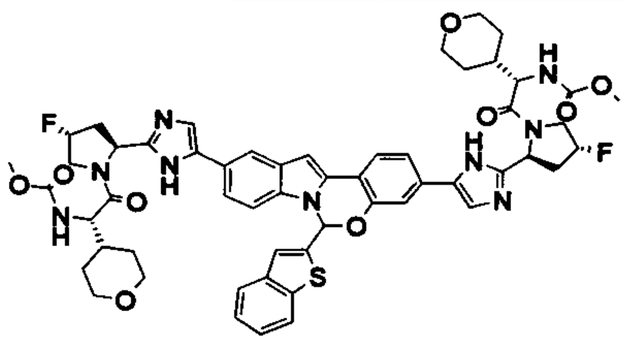
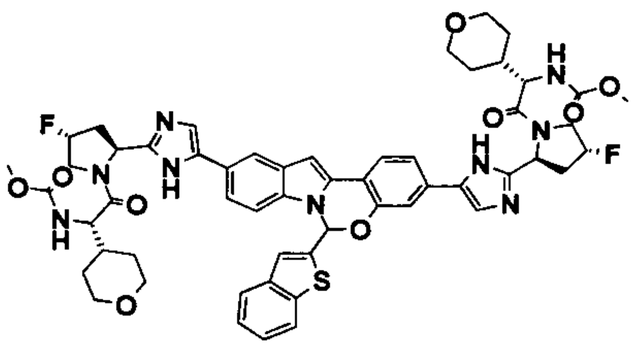
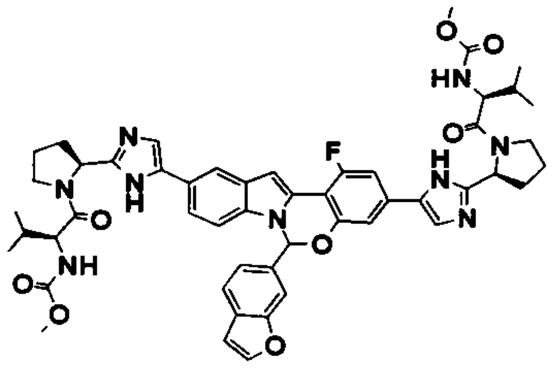
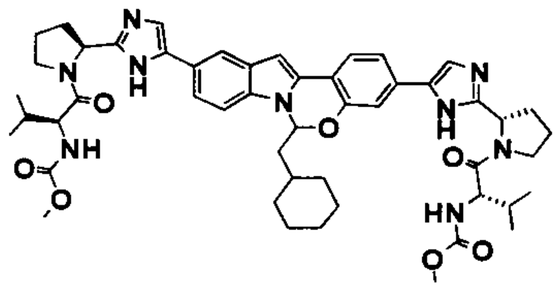
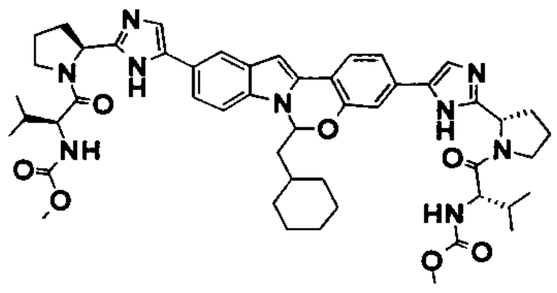
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
676		0.01146	9.211	0.2883			1032.2	1033.2	Mixture of isomers
677		0.02203	0.1319	3.906			1078.2	1079.1	Mixture of isomers
678		0.02197	5.034	0.3629			1042.2	1043.1	Mixture of isomers
679		0.01418	0.1566	2.77			990.1	991	Mixture of isomers
680		0.01	43.4	0.5746			972.1	973	Single isomer

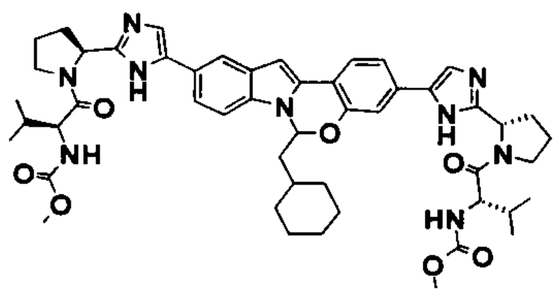
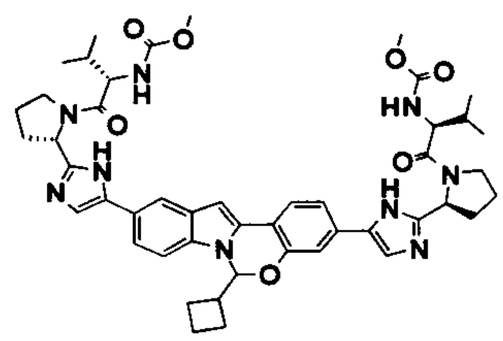
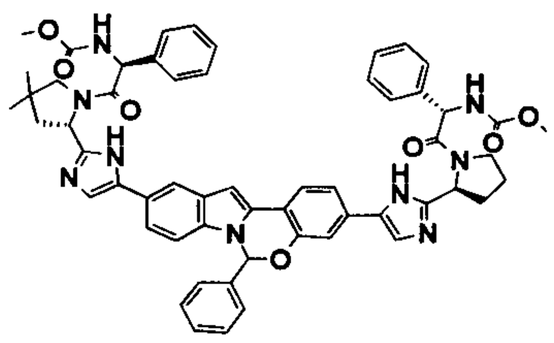
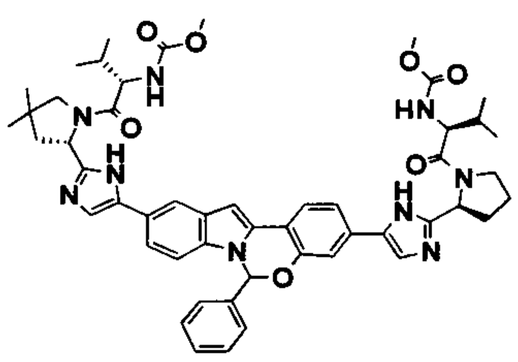
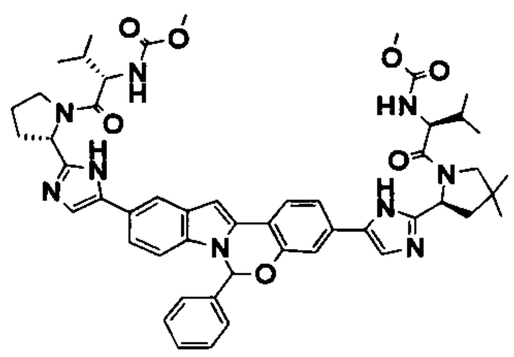
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
681		0.00981	4.784	0.2061			972.1	973	Single isomer
682		0.0088	3.58	0.1225			974.1	975.1	Single isomer
683		0.05331	18.5	0.3538			974.1	975.1	Single isomer
684		0.00554	0.09471	0.02844			954.1	955	Single isomer
685		0.01215	2.5	0.16			954.1	955	Single isomer

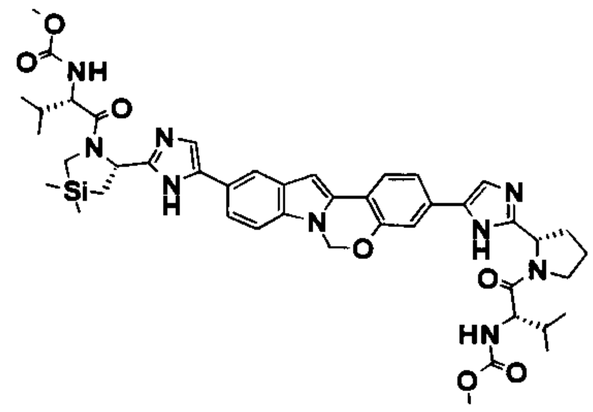
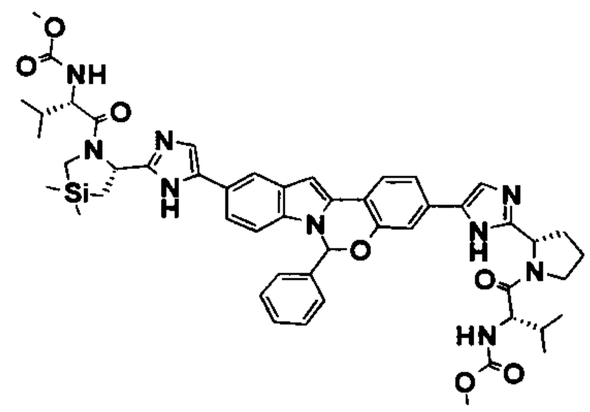
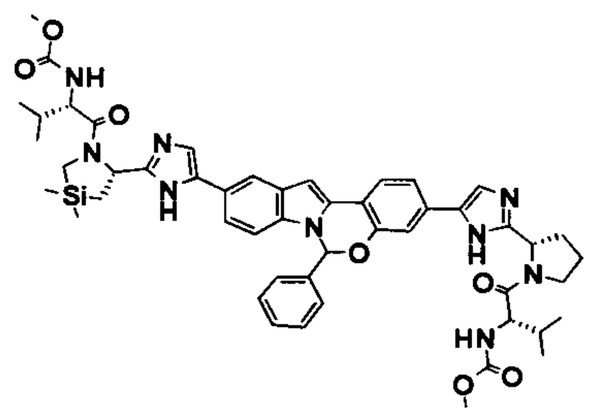
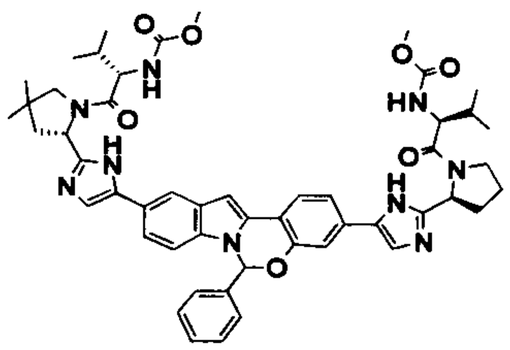
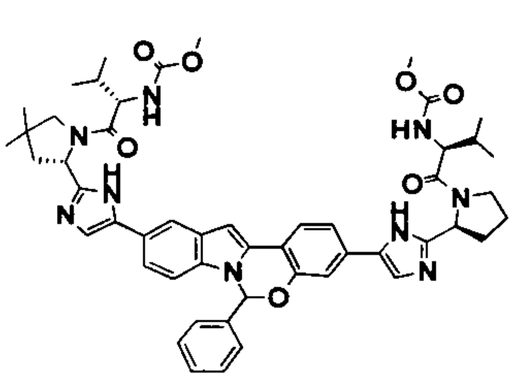
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
686		0.00799	0.01904	1.958			1002.0	1003	Single isomer
687		0.02801	0.197	2.78			1002.0	1003	Single isomer
688		0.00919	15.96	0.9876			984.0	984.8	Single isomer
689		0.00254	1.935	2.455			984.0	984.8	Single isomer
690		0.00529	0.6467	0.9878			1002.0	1003	Single isomer

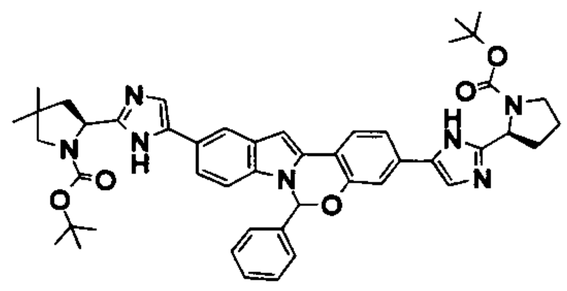
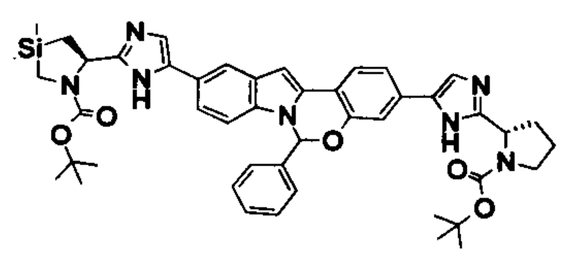
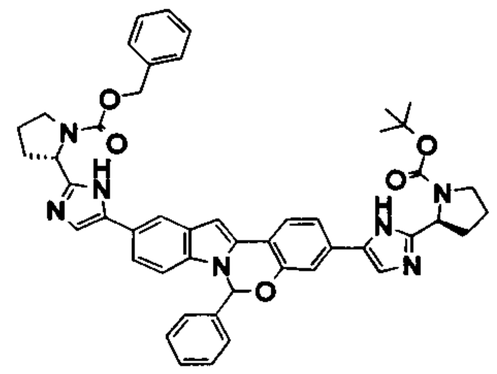
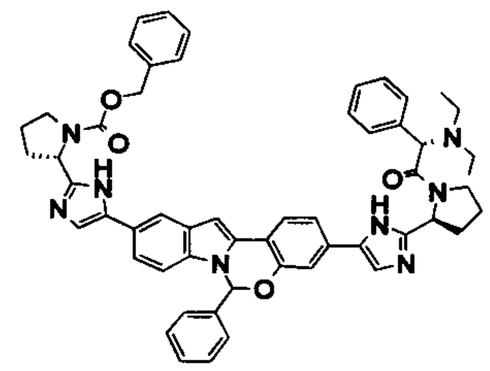
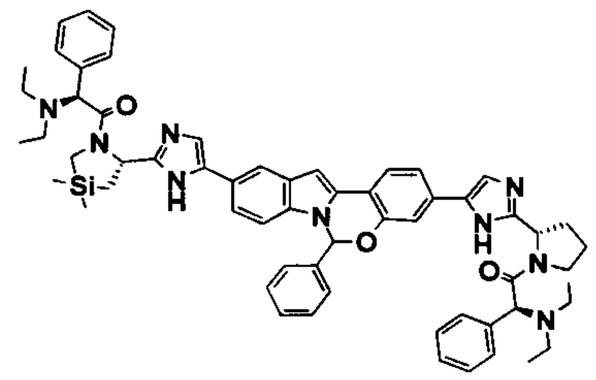
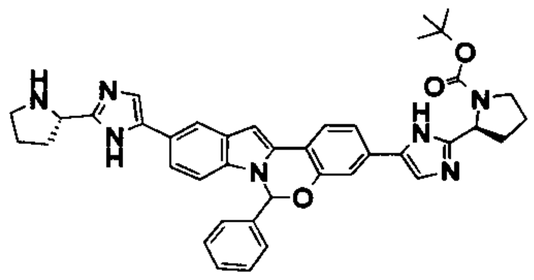
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
691		0.00274	5.758	1.067			1002.0	1003	Single isomer
692		0.01126	0.3635	0.7222			1002.0	1003	Single isomer
693		0.00297	1.13	0.5323			1002.0	1003	Single isomer
694		0.00191	1.68	0.4014			928.1	929.9	Single isomer
695		0.00523	1.498	0.2222			928.1	929.1	Single isomer

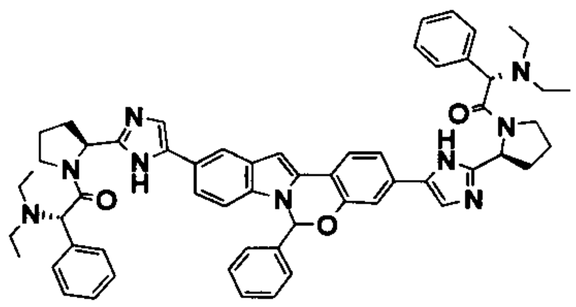
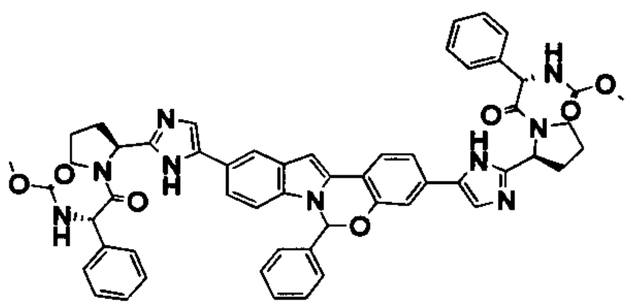
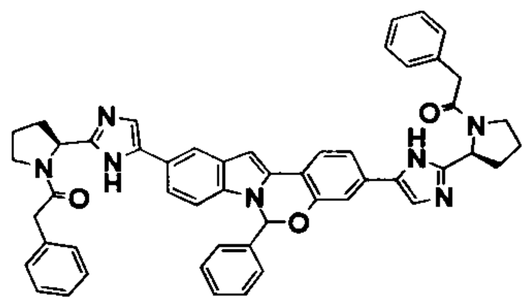
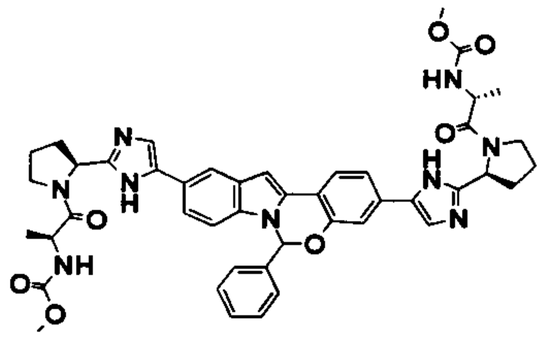
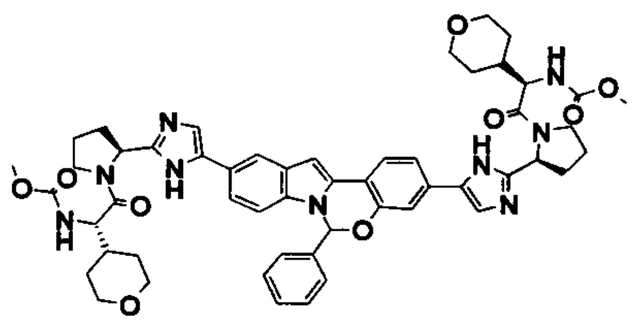
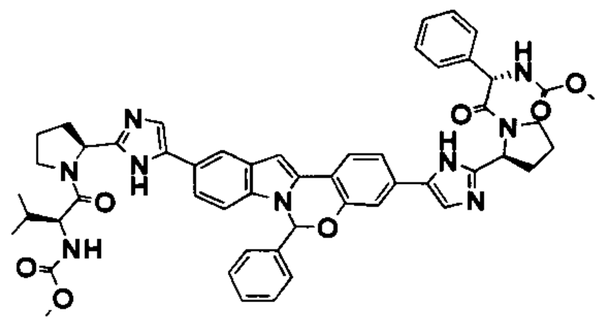
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
696		0.7761	14.77	9.446			934.0	935.1	Single isomer
697		0.2843	0.8465	13.44			934.0	935.1	Single isomer
698		0.02305	48.17	0.1533			1032.2	1033	Single isomer
699		0.02112	11.47	0.229			1032.2	1033	Single isomer
700		0.02385	0.4835	2			978.1	978.9	Single isomer
701		0.02913	0.1689	3.14			1008.1	1008.9	Single isomer

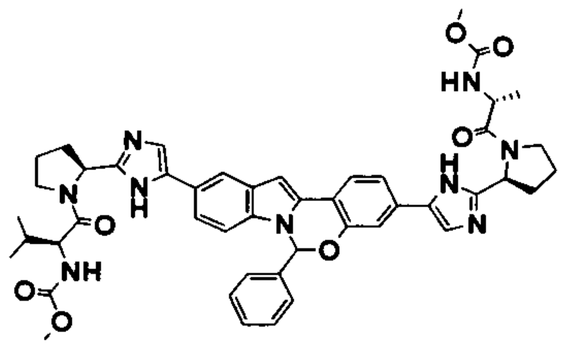
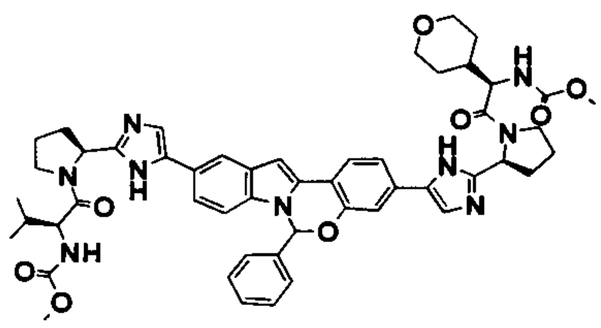
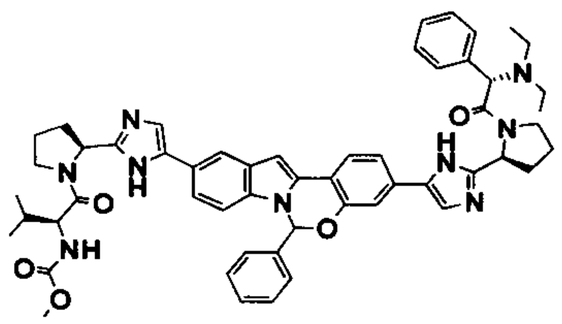
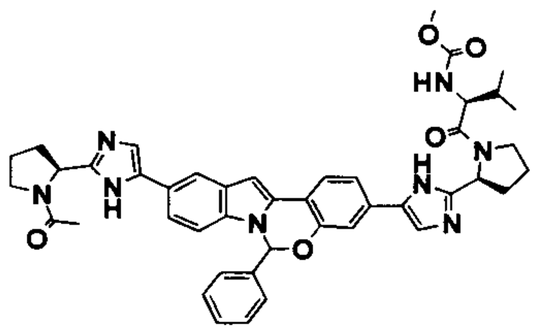
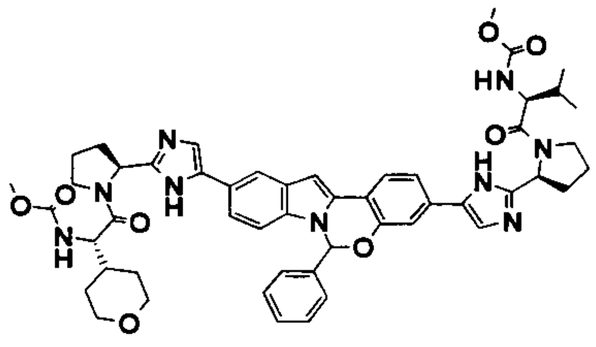
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
702		0.06167	0.06878	1.535			1008.1	1008.9	Single isomer
703		0.130	0.52	0.094			1058.2	1058.9	Single isomer
704		0.031	0.4	0.036			1058.2	1058.9	Single isomer
705							940.1	941	Mixture of isomers
706		0.007	58	3.447	0.002	11.9	902.10	903.4	Mixture of isomers
707		0.017		3.414	0.001	8.3	902.10	903.4	Single isomer

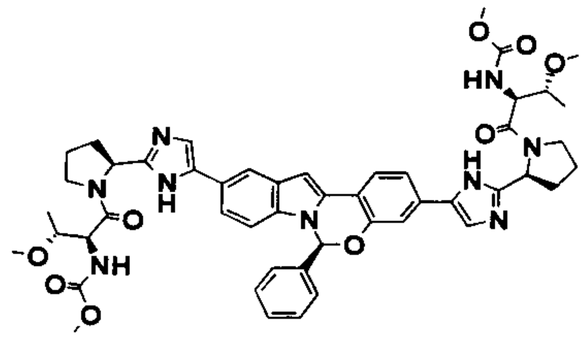
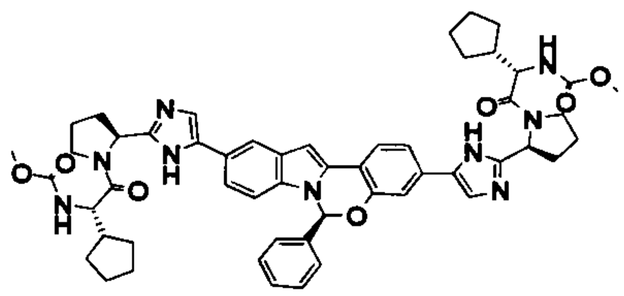
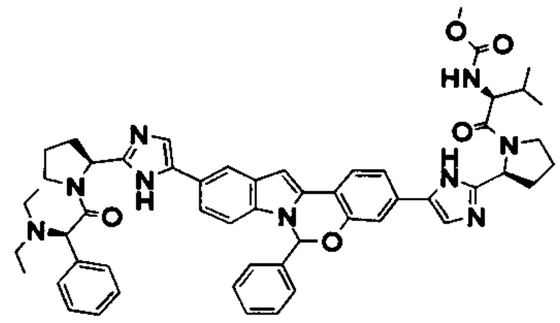
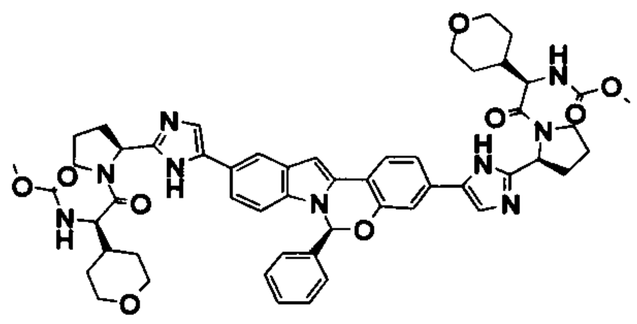
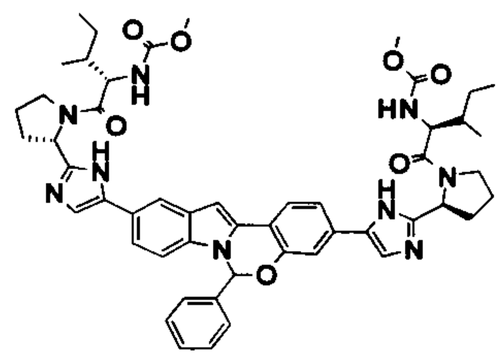
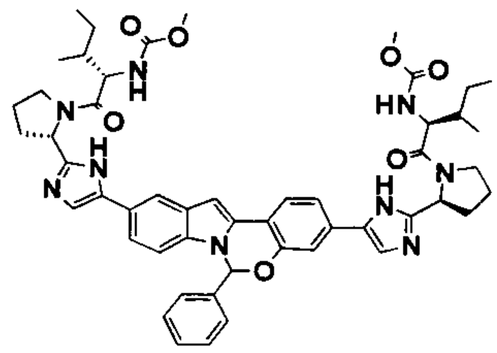
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
708							902.10	903.4	Single isomer
709		0.008	91	1	0.005	9	860.00	861.3	Mixture of isomers
710		0.050	> 1000	21.6615	0.016	890.515	977.42	978.7	Mixture of isomers
711		0.019	5.02934	1.9555	0.002	25.9449	909.45	910.7	Mixture of isomers
712		0.019	2.93552	1.9555	0.007	22.3421	909.45	651.8	Mixture of isomers

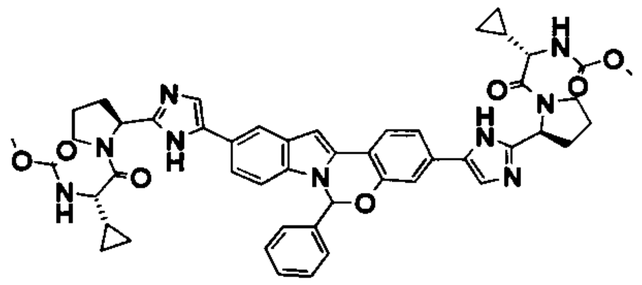
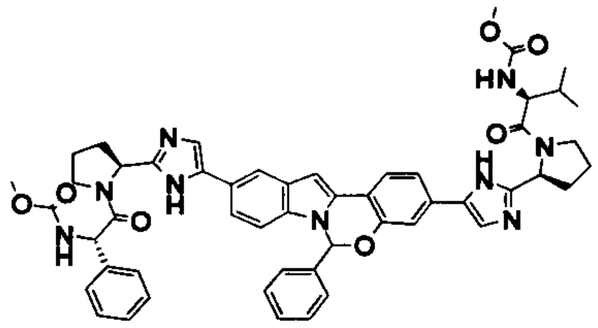
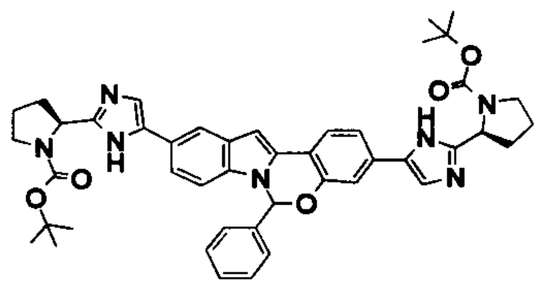
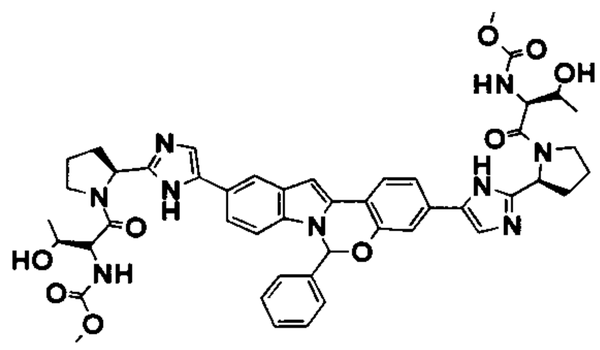
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
713		0.019	11.559	3.693	0.002	37.251	849.40	850.7	Single isomer
714							925.43	925.8	Single isomer
715		0.002	18.59	9.11	0.002	85.53	925.43	925.8	Single isomer
716		0.016	> 50	27.49	0.006	15.61	909.45	910.8	Single isomer
717		0.005	6.23	981.72	0.005	130.23	909.45	910.8	Single isomer

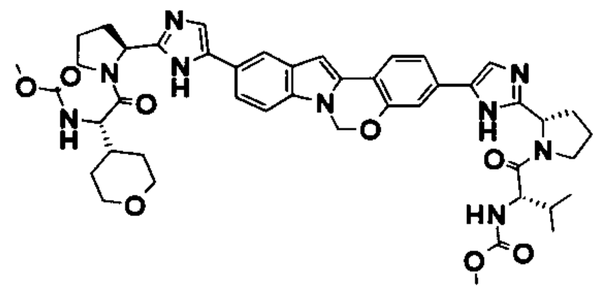
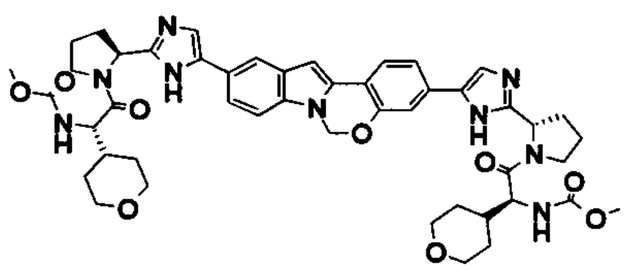
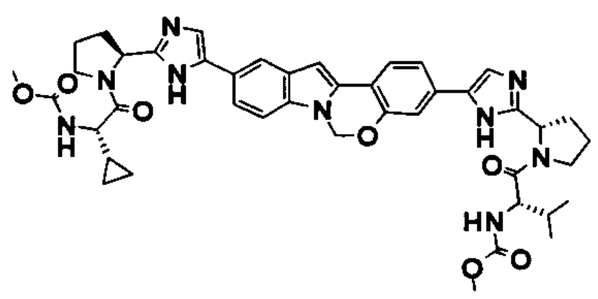
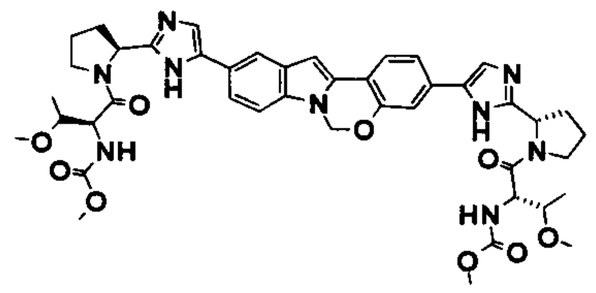
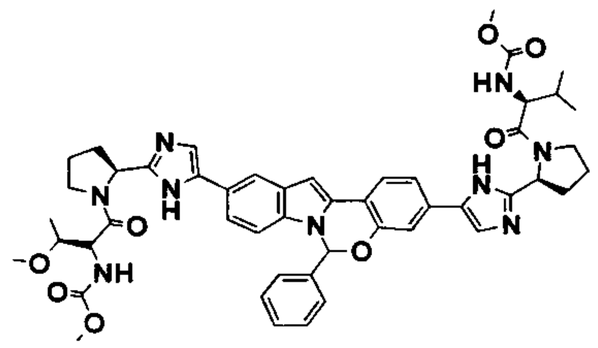
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
718		6.200	17			441	795.41	796.7	Mixture of isomers
719		574.000	996.05				811.39	812.2	Mixture of isomers
720		302.830	10000				801.36	802.2	Mixture of isomers
721		2.000	36.79				890.43	891.7	Mixture of isomers
722		1.950	188.88				989.51	990.9	Mixture of isomers
723							667.33	668.3	Mixture of isomers

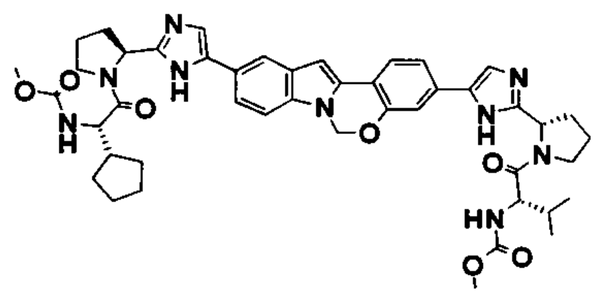
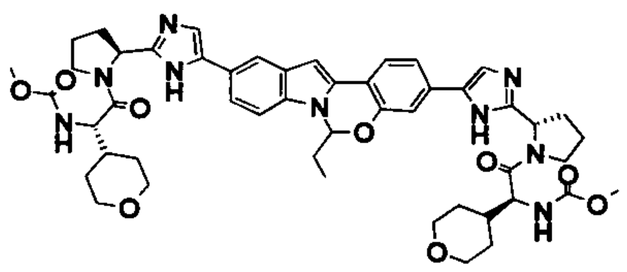
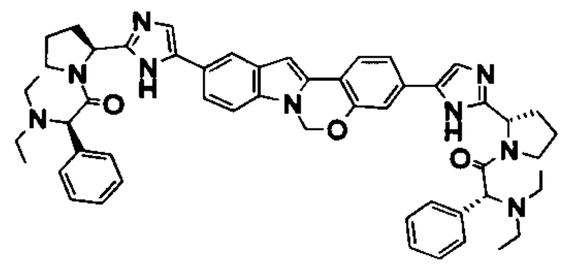
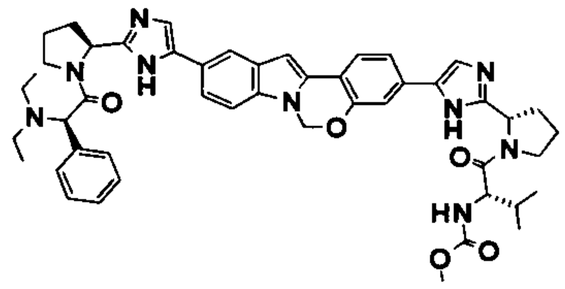
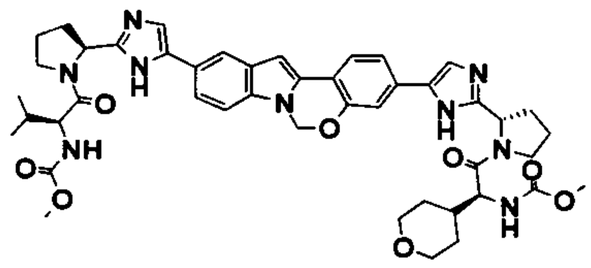
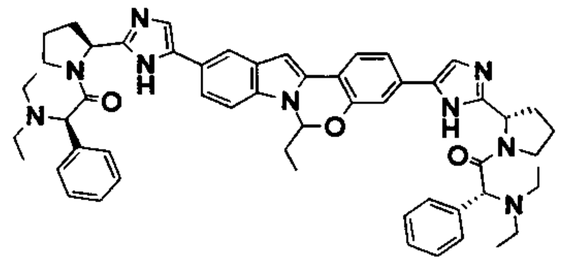
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
724							945.51	946.3	Single isomer
725							949.39	950.6	Single isomer
726							803.36	803.9	Single isomer
727							825.36	826.7	Single isomer
728							965.44	966.7	Single isomer
729		0.013	47	12.2	0.009	12	**915.41**	**916.4**	Mixture of isomers

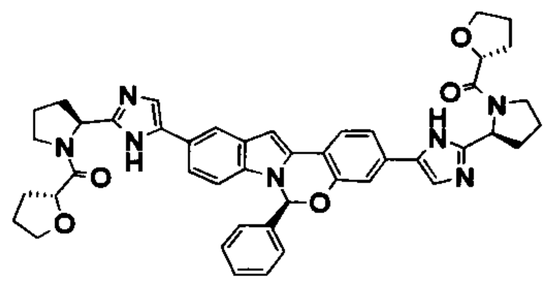
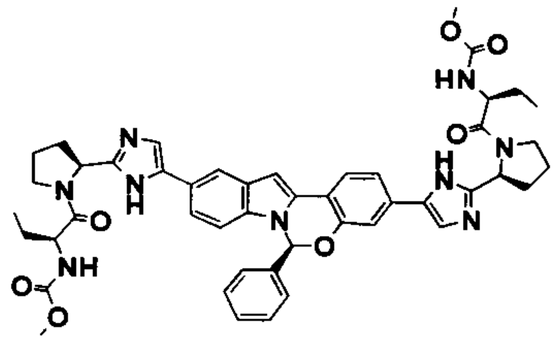
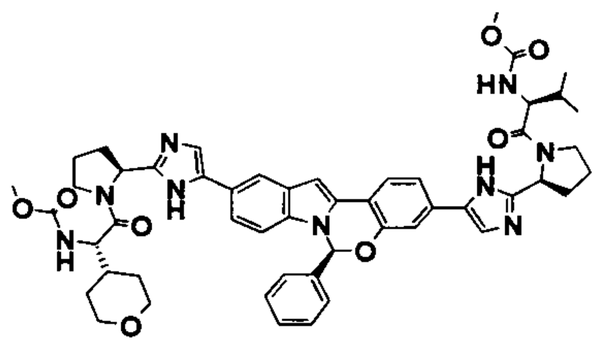
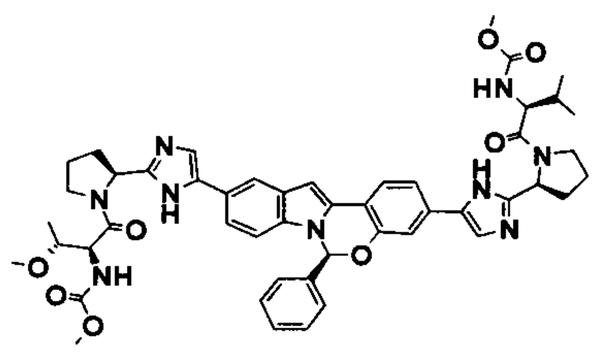
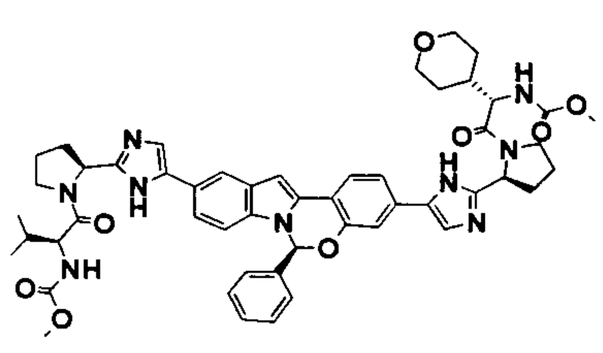
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
730		0.016	> 100	1.6	0.009	0.254	853.39	855.4	Mixture of isomers
731		0.013	4.287	0.2	0.012	1.031	923.43	924.5	Mixture of isomers
732		0.029	55.72	0.39	0.019	2.354	913.46	914.4	Mixture of isomers
733		0.371	> 100	44.8	0.035	32.027	766.36	767.3	Mixture of isomers
734		0.008	0.71	0.19	0.009	0.9	923.43	924.3	Mixture of isomers

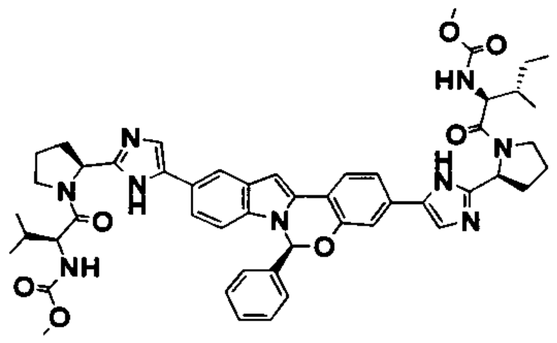
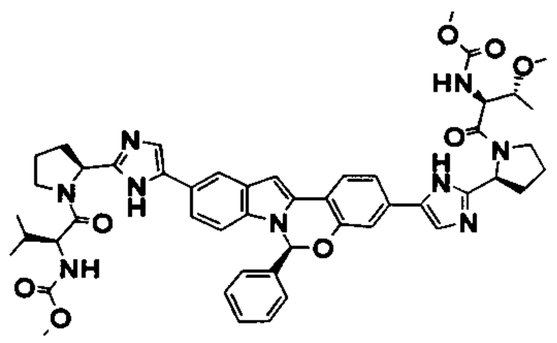
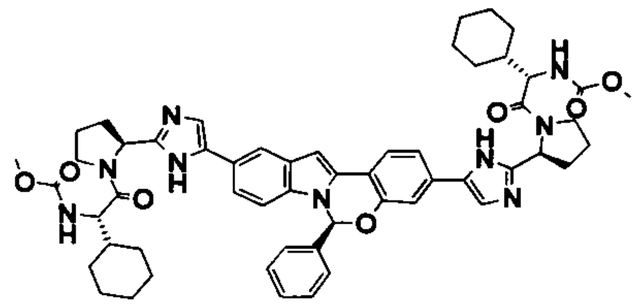
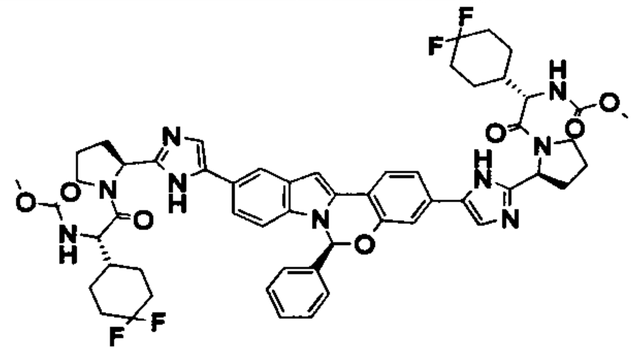
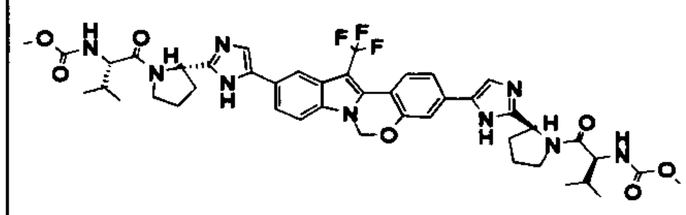
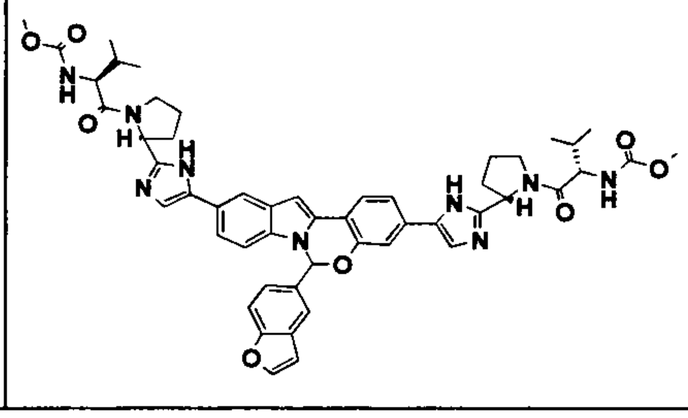
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
735		0.008	19.11		0.008	1.911	913.41	914.4	Single isomer
736		0.005	49	1.7	0.006	41.4	933.45	934.7	Single isomer
737		0.018	11	0.2	0.010		913.46	916.4	Mixture of isomers
738							965.44	967.5	Single isomer
739							909.45	911.4	Single isomer
740		0.007	32	1	0.004	16.8	909.45	911.4	Single isomer

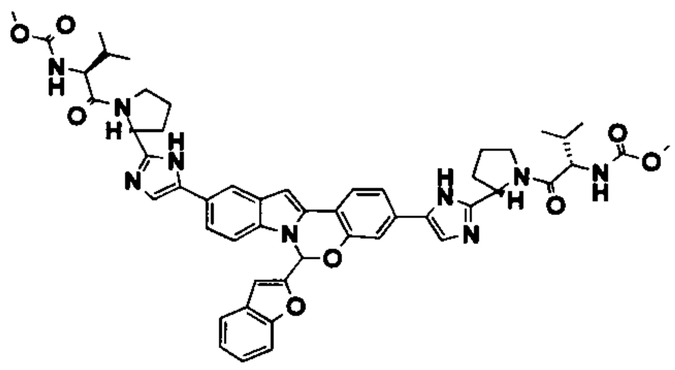
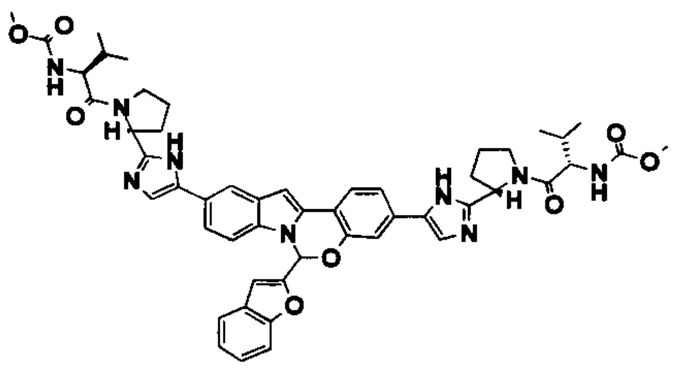
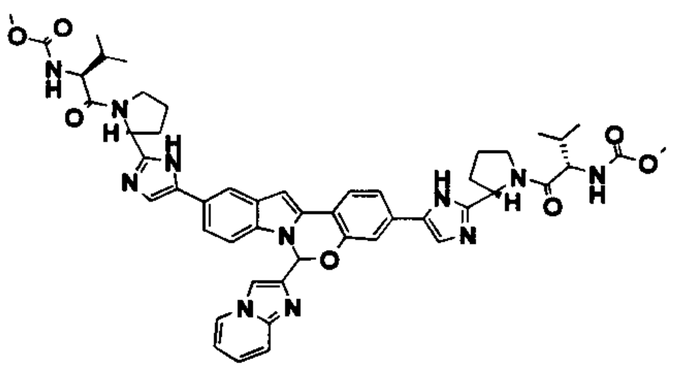
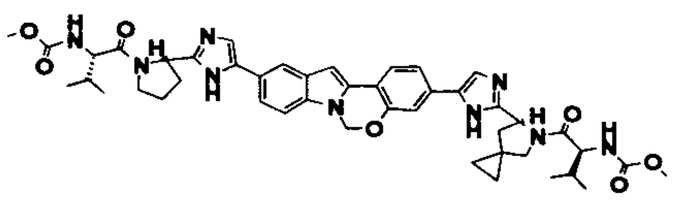
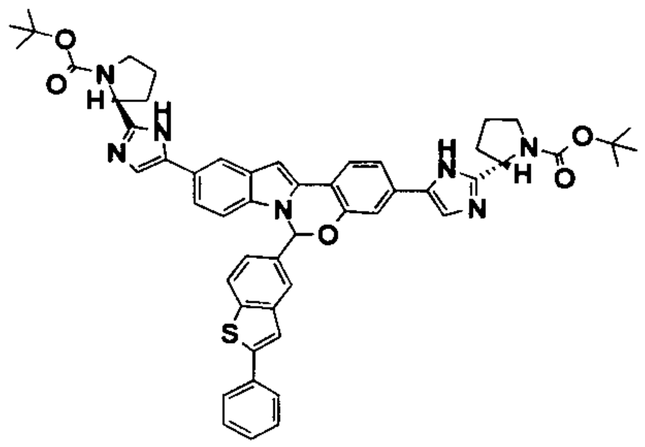
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
741		0.011	97	> 100	0.005	60	877.39	878.3	Single isomer
742		0.016	7	0	0.007	5.2	915.41	916.4	Mixture of isomers
743		128.990	678.6				767.38	768.4	Single isomer
744		> 1	> 100	85	> 1	> 100	885.38	Not observed	Single isomer

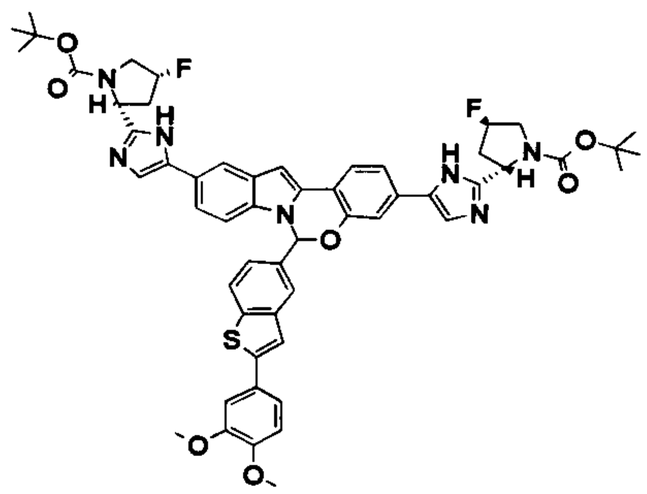
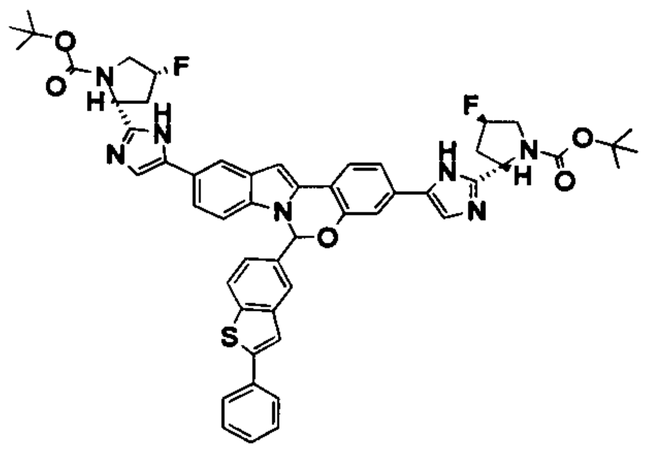
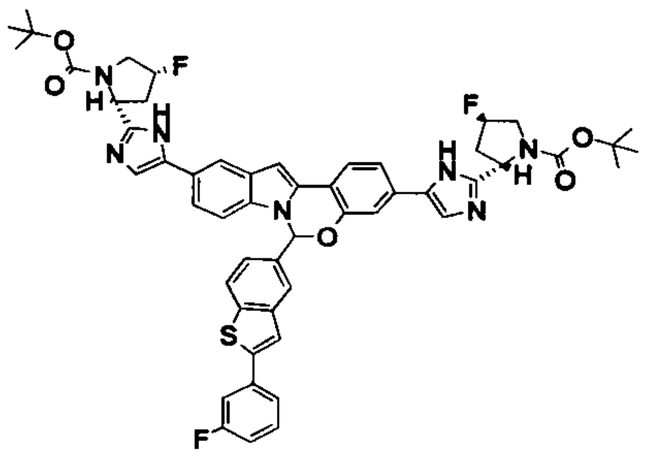
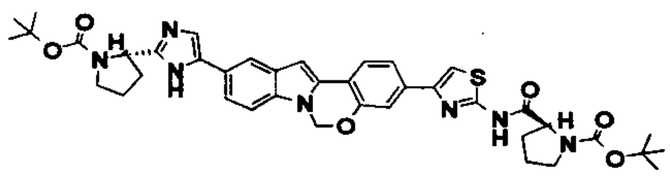
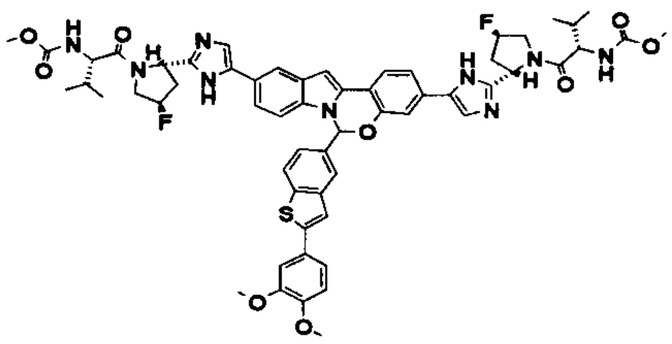
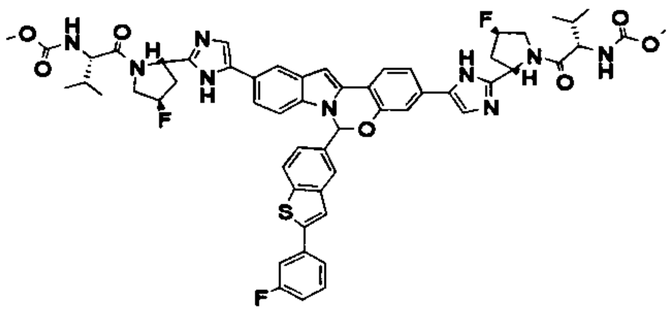
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
745		0.014	3.18	0.8	0.010	5	847.40	848.5	Single isomer
746		0.082	3.45	0.4	0.038	5.9	889.41	890.5	Single isomer
747		0.014	41.65	9	0.010	< 100	803.38	804.4	Single isomer
748		0.022	92.12	2.3	0.017	16	837.38	838.4	Single isomer
749		0.020	20.05	0.3	0.007	6.1	897.42	899.3	Mixture of isomers

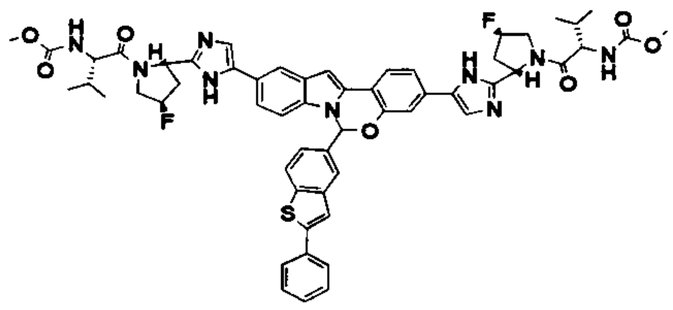
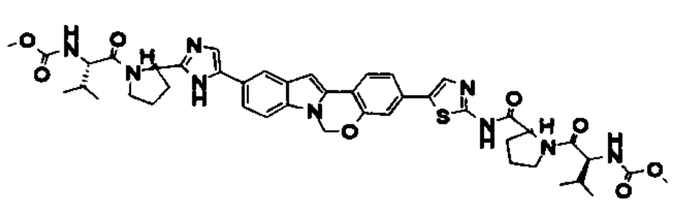
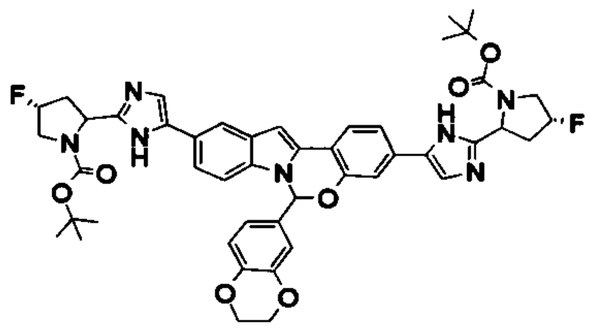
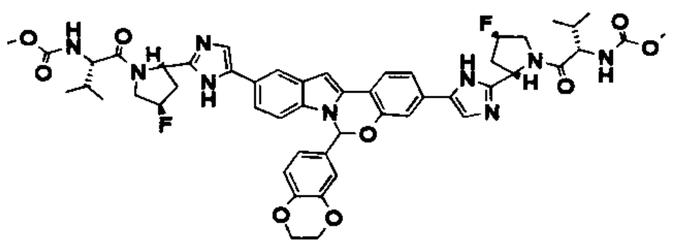
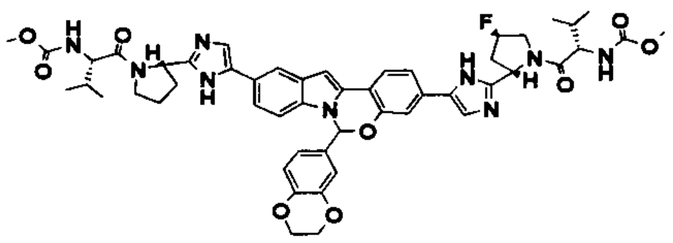
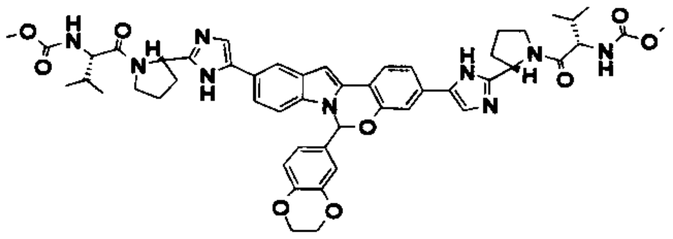
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
750		0.030		6.3	0.007	38.1	831.41	832.3	Single isomer
751		0.055	3.5	0.3	0.044	1.6	917.44	918.5	Mixture of isomers
752		0.227	> 100	1.6	0.038	0.6	869.47	870.3	Single isomer
753		0.021		1.5	0.013	4.5	837.43	839.3	Single isomer
754		0.026	5.3	1.4	0.750	15	847.40	848.3	Single isomer
755		0.200	>100	0.85	0.120	0.52	897.51	899.5	Mixture of isomers

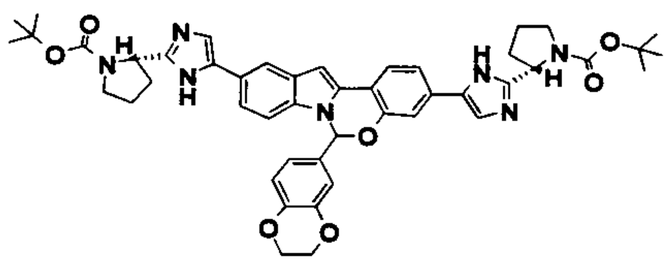
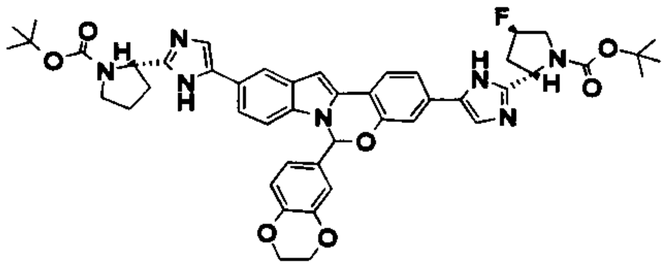
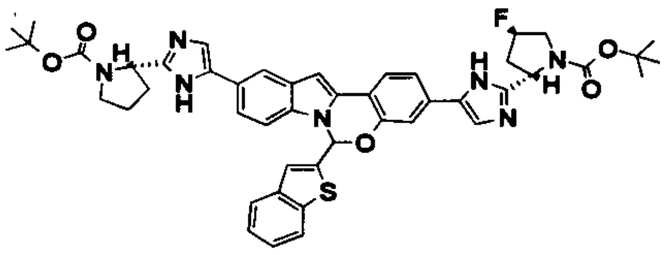
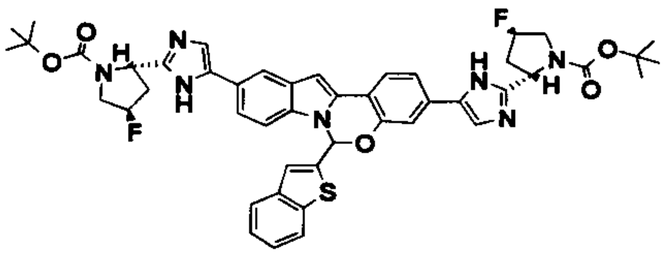
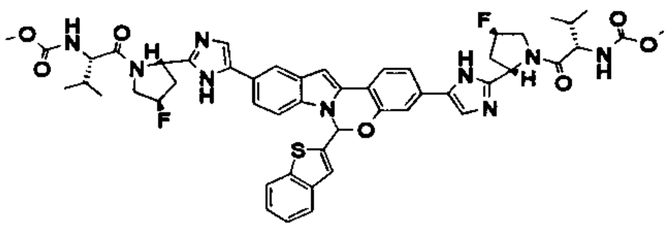
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
756		>1	>100	51.6	>1	>100	763.35	764.3	Single isomer
757		0.009	16.2	0.85	0.410	33	853.39	854.4	Single isomer
758		0.036	1.3	0.12	0.120	0.36	923.43	925.5	Single isomer
759		0.015	13.5	0.33	0.090	1.5	897.42	899.4	Single isomer
760		0.028	3.3	0.076	0.021	2	923.43	924.5	Single isomer

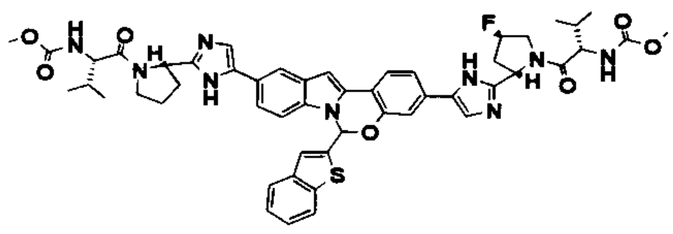
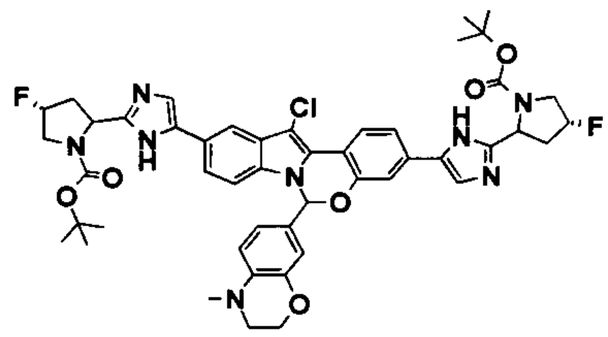
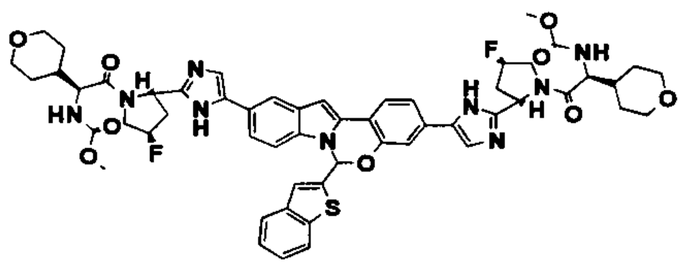
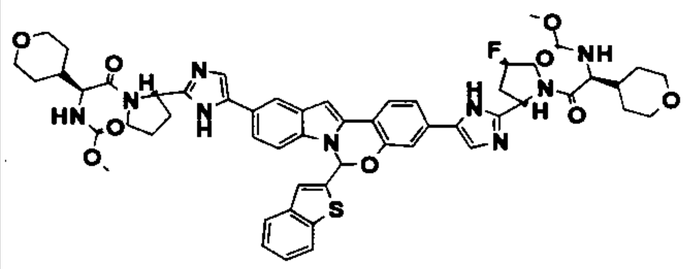
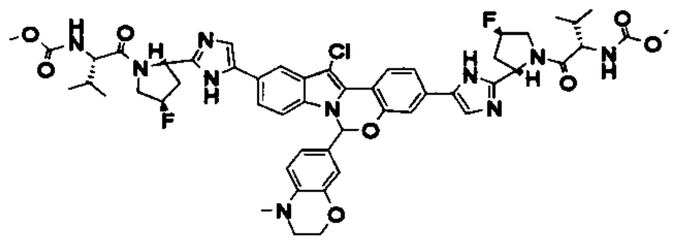
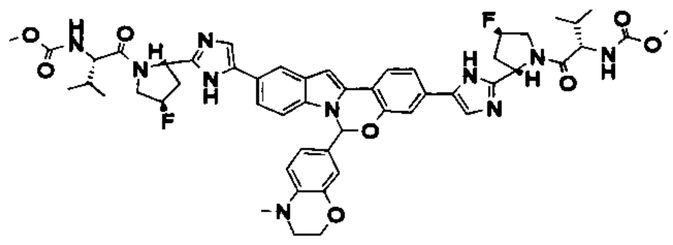
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
761		0.025	5.5	2.1	0.350	11	895.44	896.3	Single isomer
762		0.030	2.1	0.43	0.026	4.2	897.42	899.4	Single isomer
763		0.027	71.5	7.5	6.300	>100	961.49	963.3	Single isomer
764		0.010	14.3	0.21		31.2	1033.45	Not observed	Single isomer
765		0.024	> 100	11.9	0.004	15.3	873.40	874.3	Single isomer
766		1.950	12.67	1.95	0.200	3	921.40	922.5	Mixture of isomers

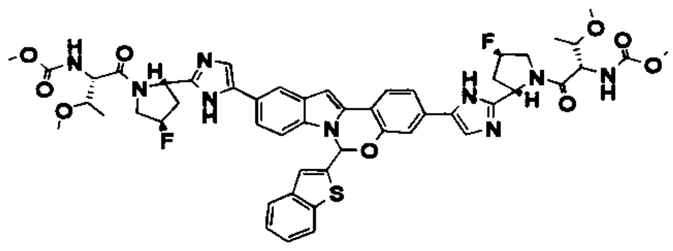
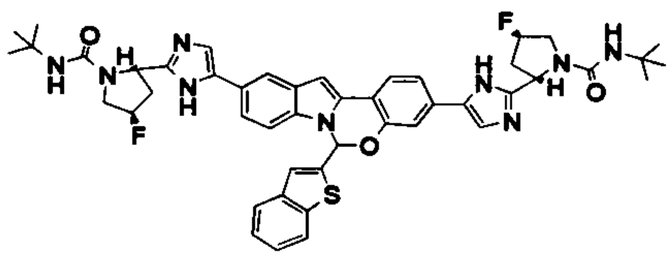
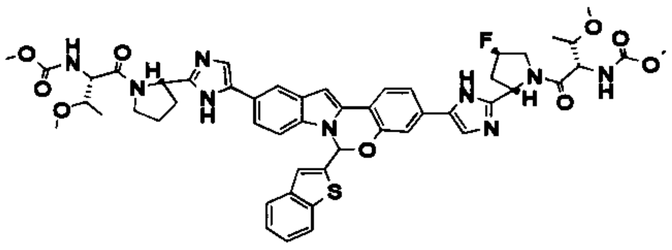
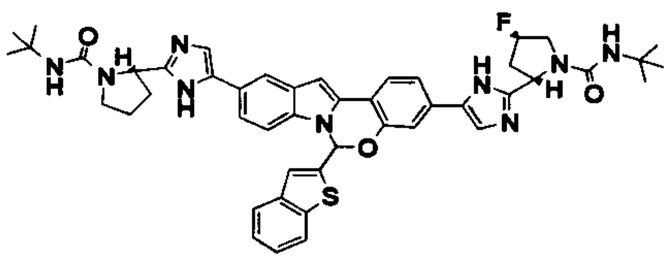
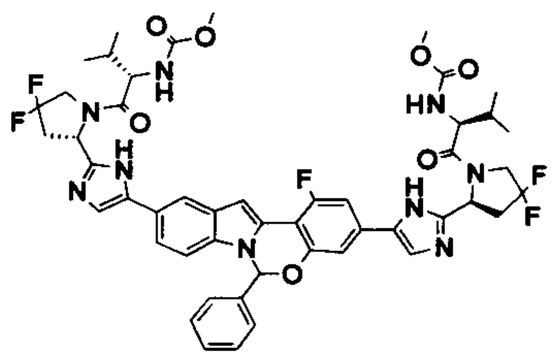
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
767		0.019	1.95	1.95	0.096	11.879	921.40	922.5	Single isomer
768		0.019	12.546	1.95	0.057	139.906	921.40	922.5	Single isomer
769		0.021	62	10		11.1	921.40	922.5	Mixture of isomers
770		1.950	17.34	1.95	0.200	178	831.40	832.5	Single isomer
771		24.000	774.73				899.40	900.3	Mixture of isomers

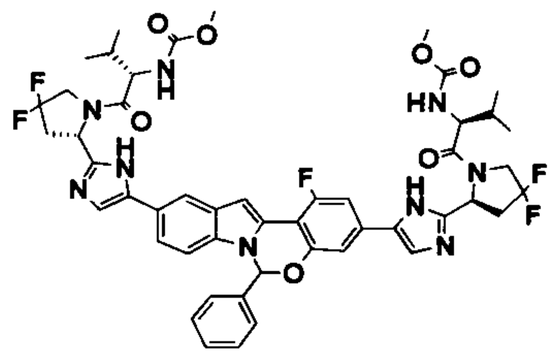
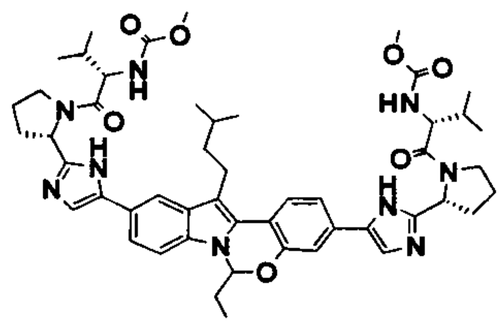
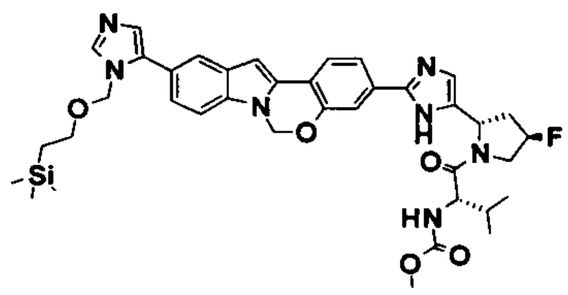
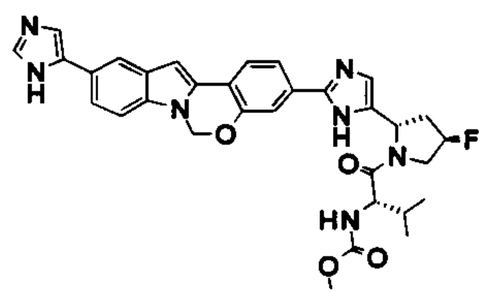
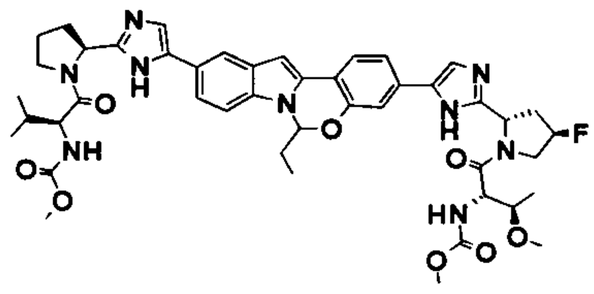
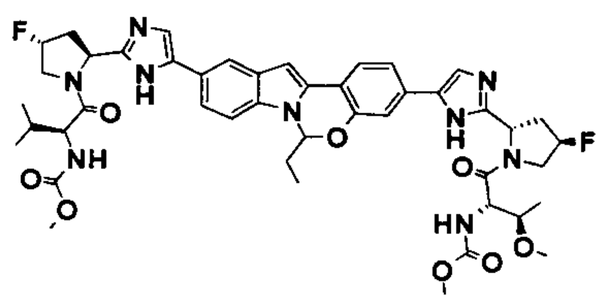
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
772		> 2000	> 20000				995.40	996.3	Mixture of isomers
773		> 2000	> 20000				935.40	936.3	Mixture of isomers
774		> 2000	> 20000				953.40	954.3	Mixture of isomers
775		165.000	> 20000				751.30	752.3	
776		0.036	1.8	3.8	0.005	46.59	1109.40	1110.3	Mixture of isomers
777		0.007	0.6	0.8	0.003	28.18	1067.40	1069.0	Mixture of isomers

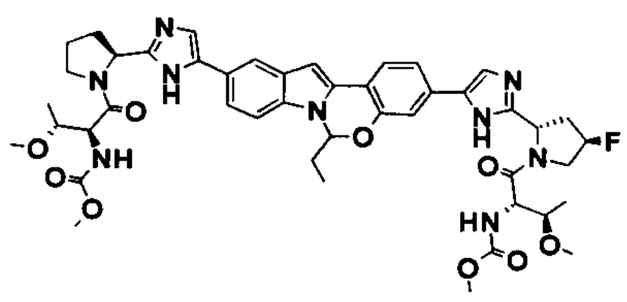
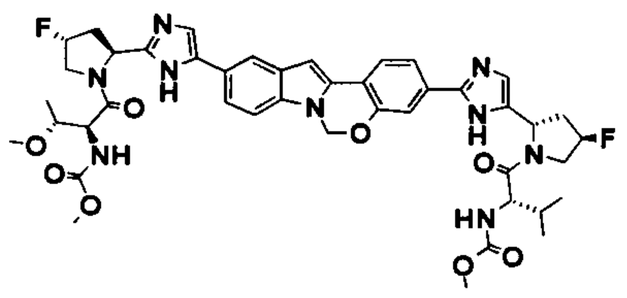
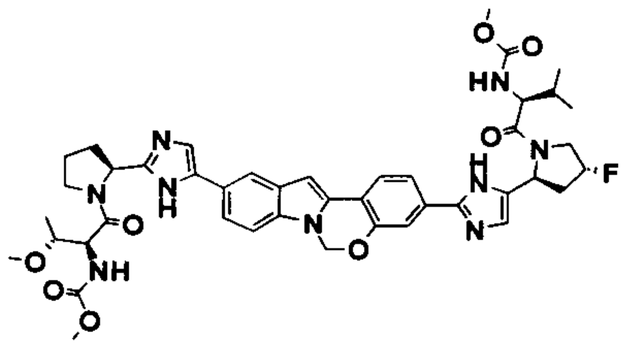
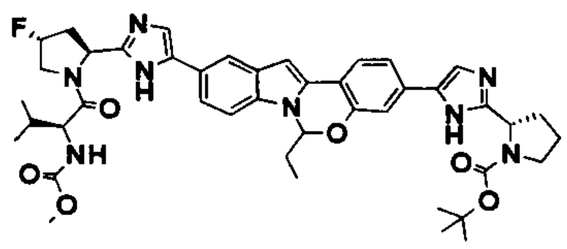
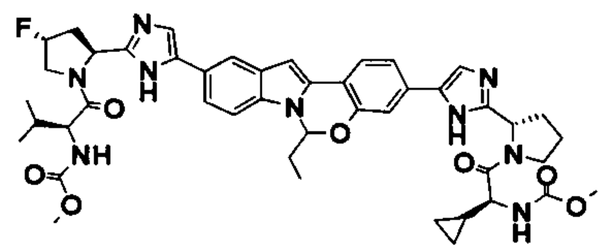
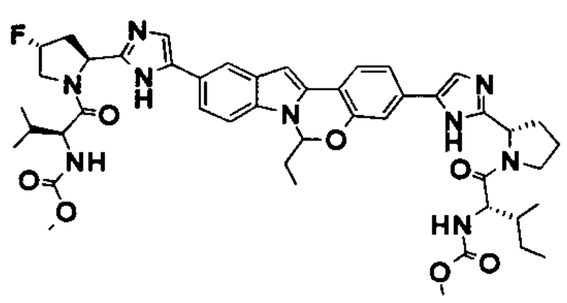
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
778		0.005	2	0.4	0.004	27.47	1049.40	1051.0	Mixture of isomers
779		1.953	454.2				865.40	867.0	
780		10.308	30.4				861.30	862.0	Mixture of isomers
781		0.060	2.2	41	0.004	> 200	975.40	976.4	Mixture of isomers
782		0.270	> 100	41	0.059	> 100	957.40	958.4	Mixture of isomers
783		0.161	> 100	31.96	0.053	38.607	939.40	940.4	Mixture of isomers

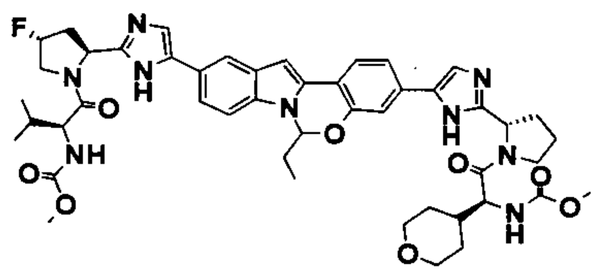
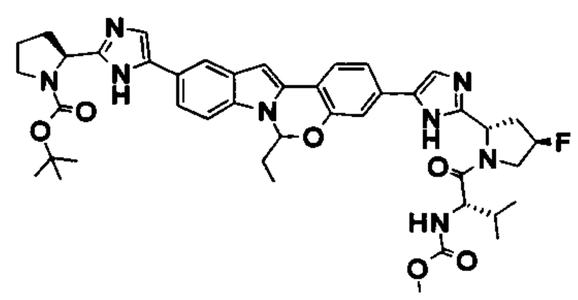
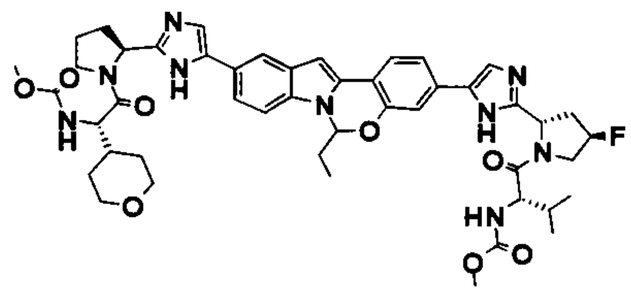
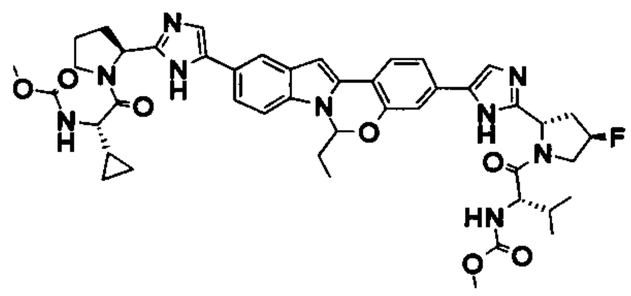
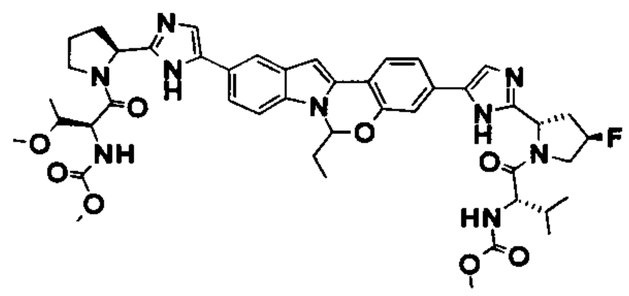
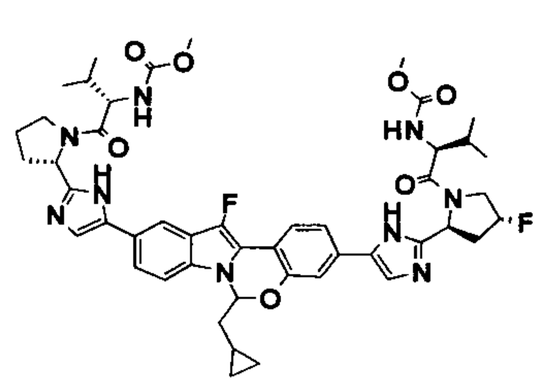
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
784		478.067	3990.18				825.40	826.4	Mixture of isomers
785		70.262	1071.01				843.40	845.4	Mixture of isomers
786		256.000	1270				841.30	842.3	Mixture of isomers
787		903.000	1251				859.30	860.3	Mixture of isomers
788		0.008	0.2	2.8	0.004	15.382	973.40	974.4	Mixture of isomers

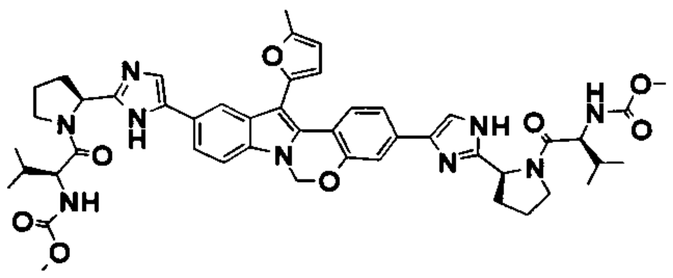
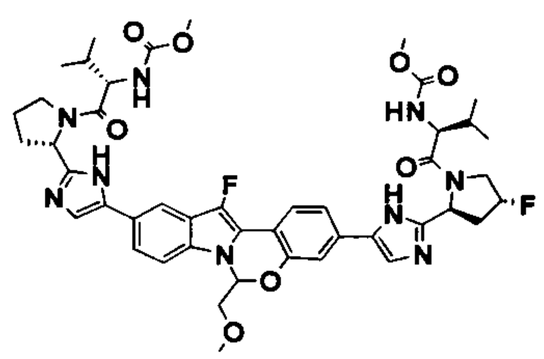
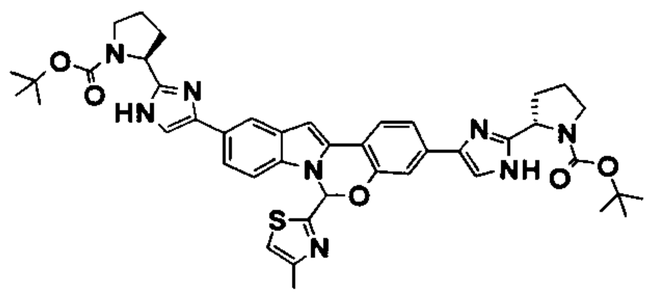
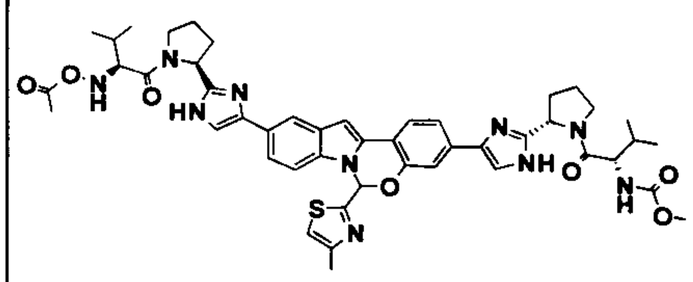
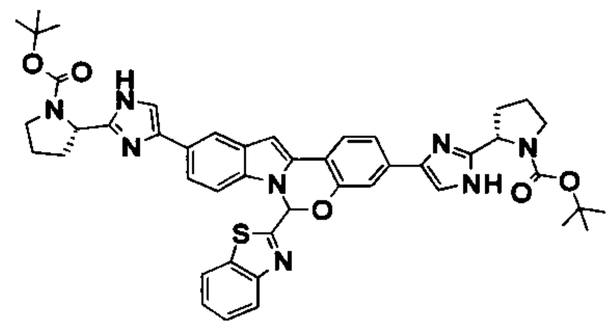
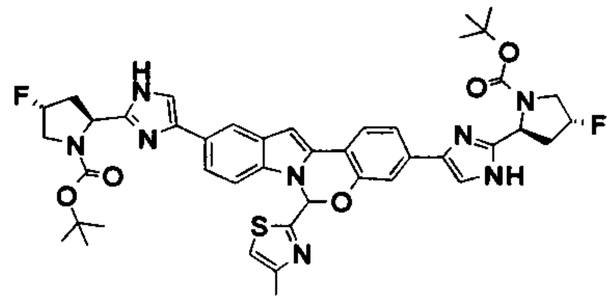
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
789		0.005		0.227	0.003	0.761	955.40	956.4	Mixture of isomers
790		619.000	1000				908.40	909.4	Mixture of isomers
791		0.015	0.2	0.195	0.006	0.353	1057.40	1058.4	Mixture of isomers
792		0.011	0.3	0.195	0.005	0.195	1039.40	1040.4	Mixture of isomers
793		0.024	0.1	> 100	0.006	18.45	1022.40	1024.4	Mixture of isomers
794		0.031	0.04	> 100	0.008	10.43	988.40	989.5	Mixture of isomers

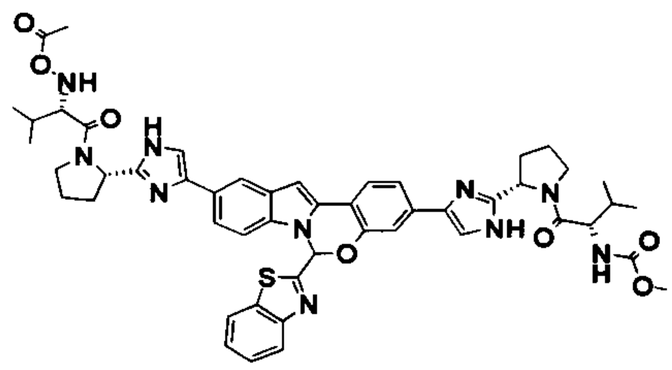
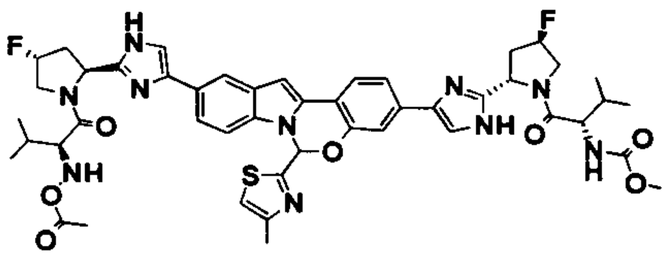
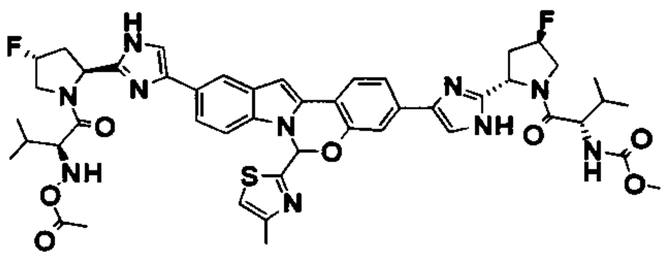
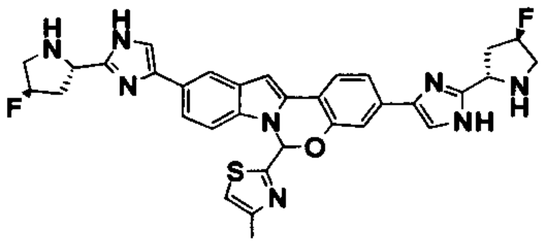
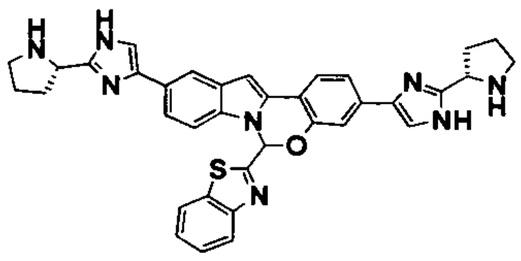
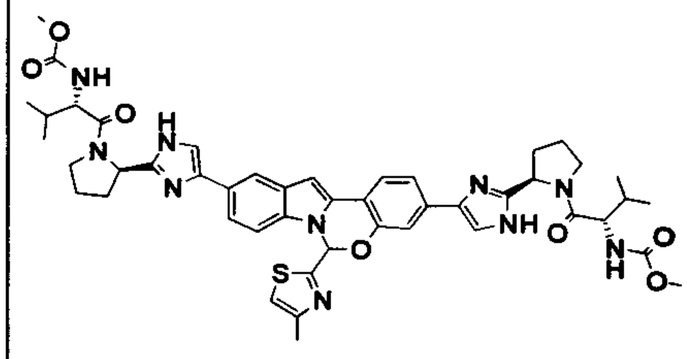
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
795				1.69			1005.40	1006.4	Mixture of isomers
796		>1	>100	>100			857.40	859.4	Mixture of isomers
797		0.023	2.234	0.26			987.40	988.4	Mixture of isomers
798		>1	>100	>100			839.40	840.4	Mixture of isomers
799		0.018	13.2	2.1	0.006	380	971.40	972.6	Mixture of isomers

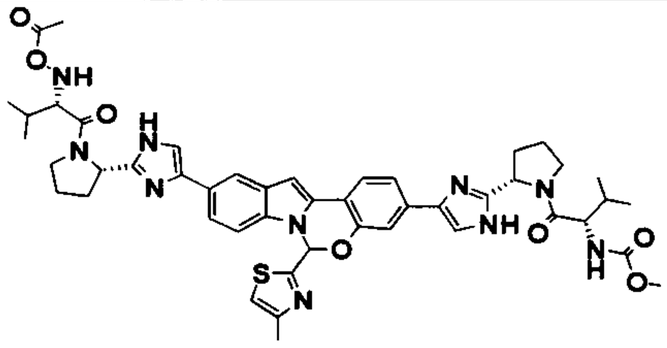
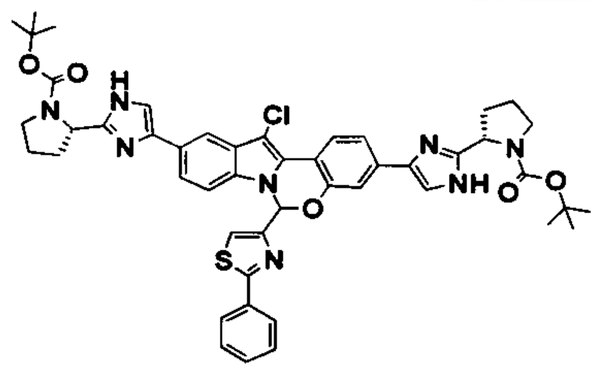
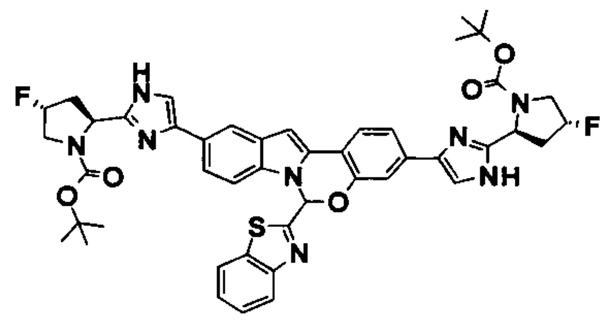
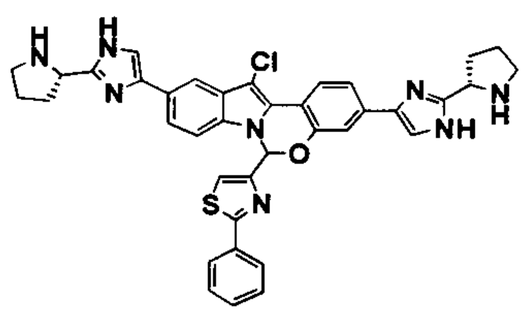
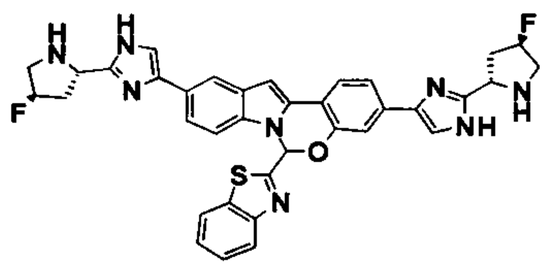
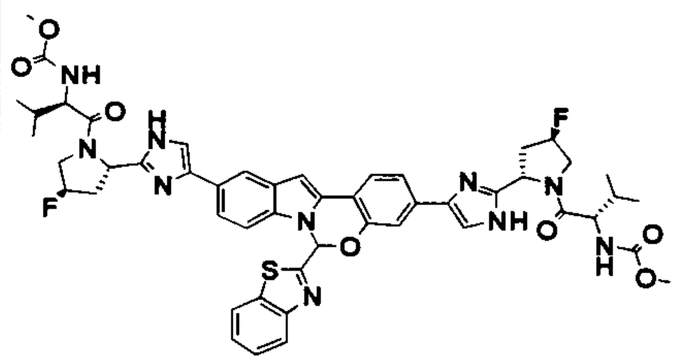
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
800		0.005	9	9	0.004	> 5000	971.40	972.6	Mixture of isomers
801		1.100	403	63.5	0.020	138.3	902.50	903.2	Mixture of isomers
802		> 2	953	1091	> 2	430	727.30	728.3	Single isomer
803		115.000	334.42				597.30	598.2	Single isomer
804		0.012	6	17.62	0.012	22	867.40	868.4	Mixture of isomers
805		0.031	0.6	32.69	0.010	85	885.40	886.4	Mixture of isomers

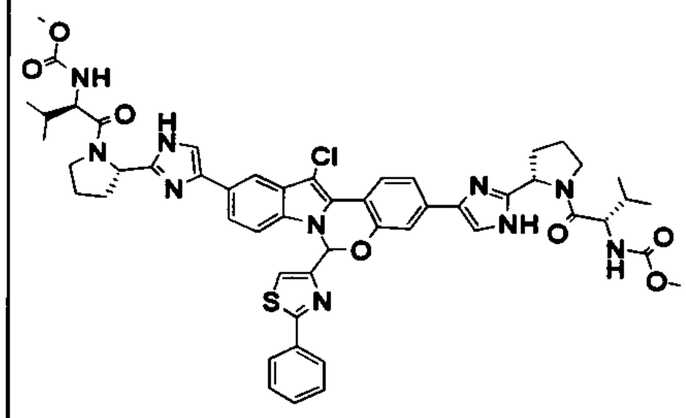
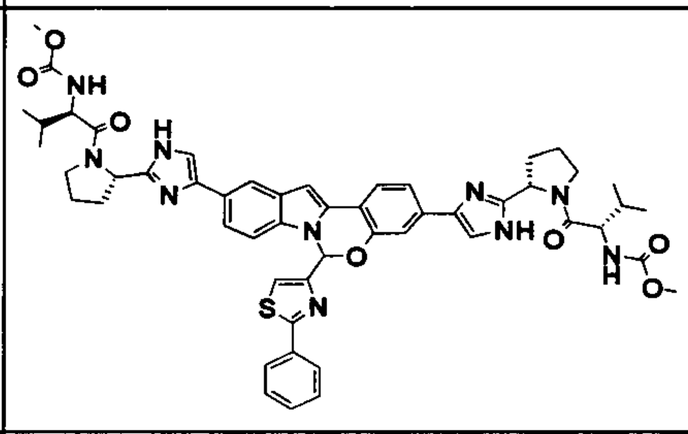
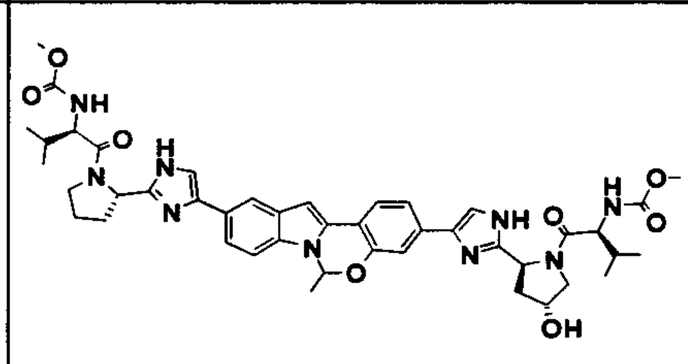
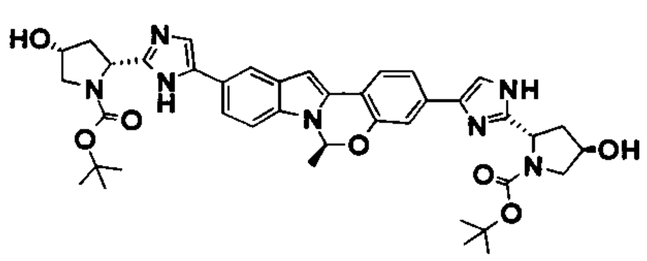
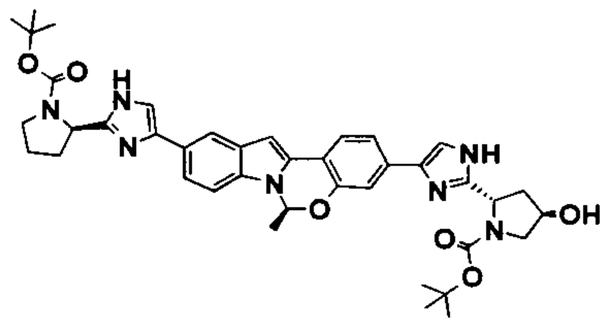
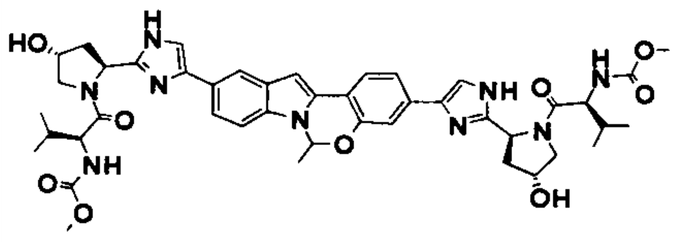
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
806		0.021	11	16.84	0.016	12	883.40	884.4	Mixture of isomers
807		0.065	2.76	39	0.012	< 100	857.40	858.4	Mixture of isomers
808		0.009	11.82	10.9	0.009	92	839.40	840.4	Mixture of isomers
809		26.800	314.1				794.40	795.4	Mixture of isomers
810		0.036	14.18	58.24		246.6	849.40	850.4	Mixture of isomers
811		0.011	17.84	35.03		169.9	865.40	866.5	Mixture of isomers

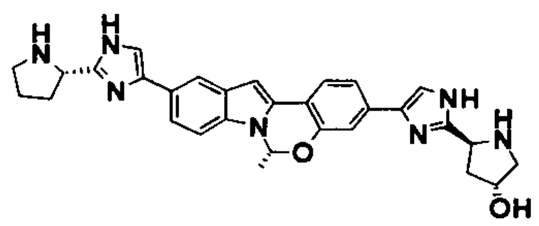
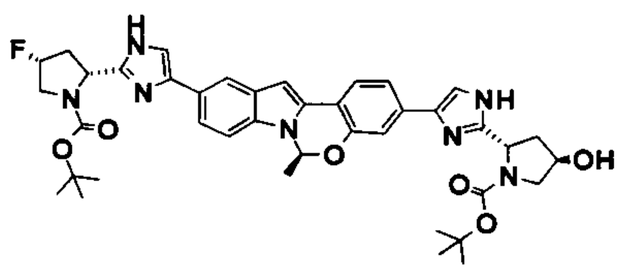
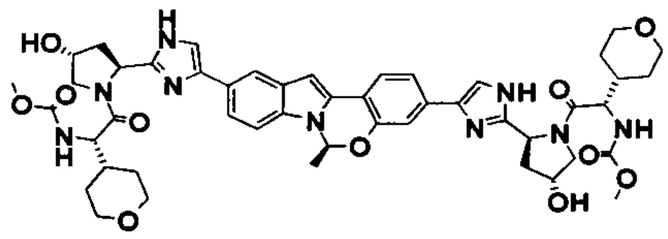
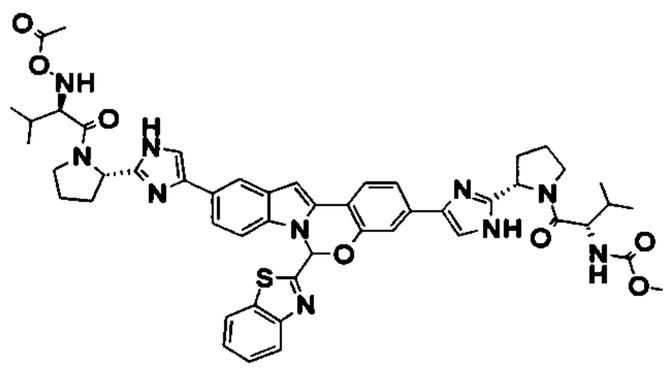
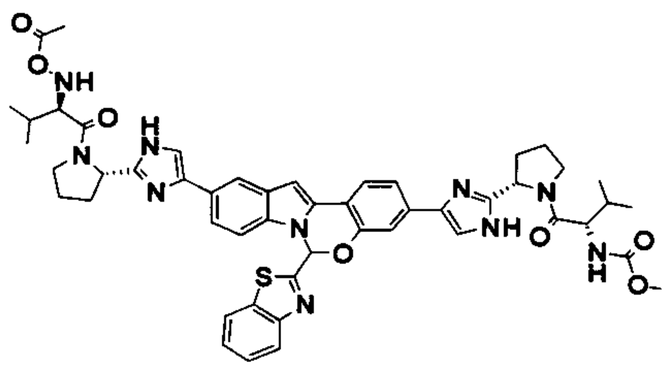
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
812		0.045	3.576	5.465		10.04	893.40	894.4	Mixture of isomers
813		1.160	11.25				794.40	795.3	Mixture of isomers
814		0.035	1.72	4.1		0.21	893.40	894.3	Mixture of isomers
815		0.020	3.76	36.2		150.3	849.40	850.3	Mixture of isomers
816		0.042	2.57	12.3		42.46	867.40	868.2	Mixture of isomers
817		0.001	0.4	2	0.001	5.7	896.02	897.0	Single isomer

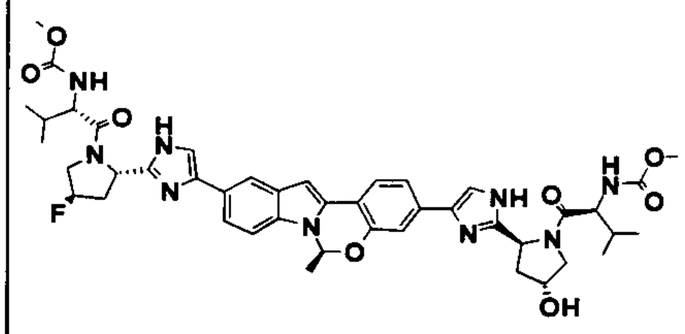
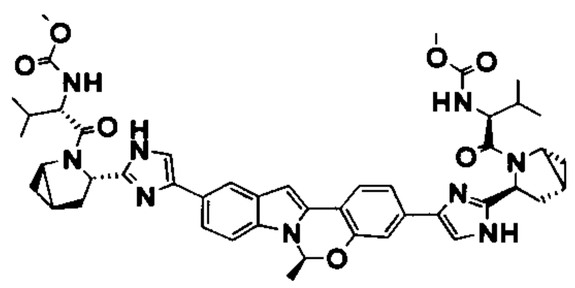
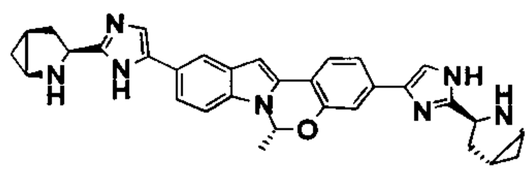
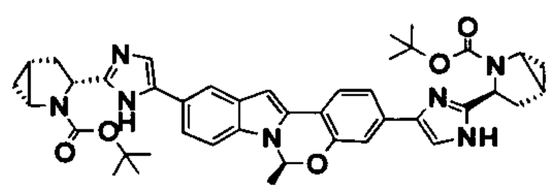
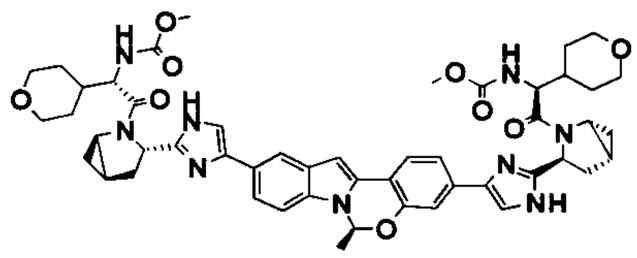
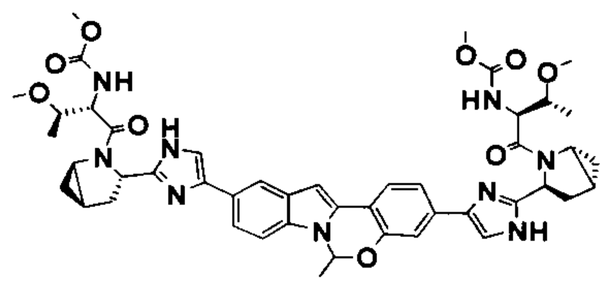
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
818		0.019		12.462	0.003	49.8	886.03	887.0	Single isomer
819		0.012	6.5	11.269	0.002	18.7	885.98	887.0	Mixture of isomers
820		101.700	581				788.35	788.7	Mixture of isomers
821		140.019	1.9555	1.9555	0.003	2.06206	902.39	902.7	Mixture of isomers
822		208.251	1170.9				824.35	824.8	Mixture of isomers
823		432.198	1102.4				824.33	824.8	Mixture of isomers

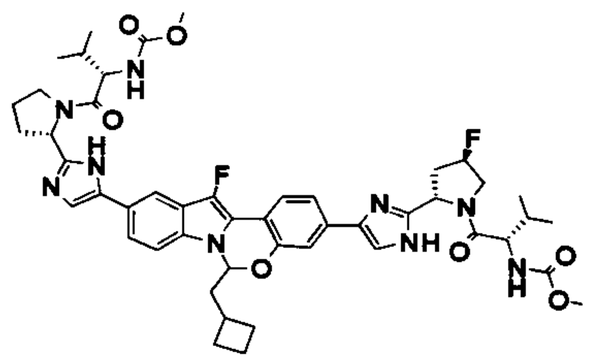
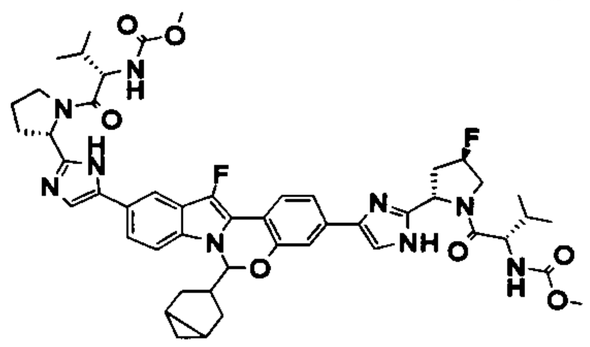
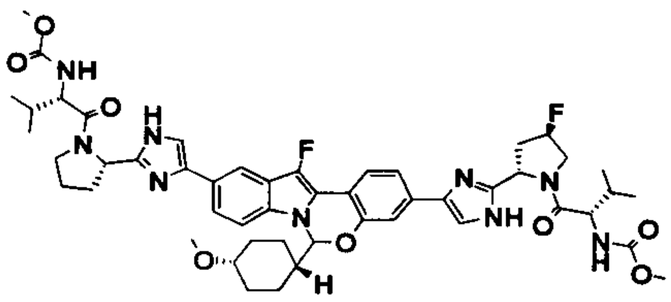
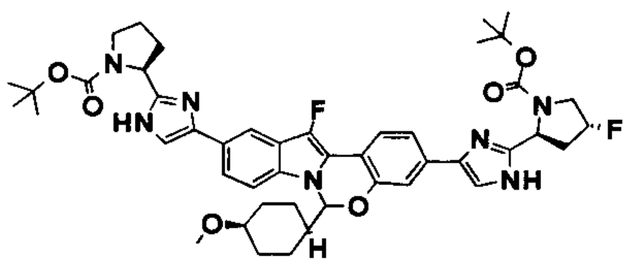
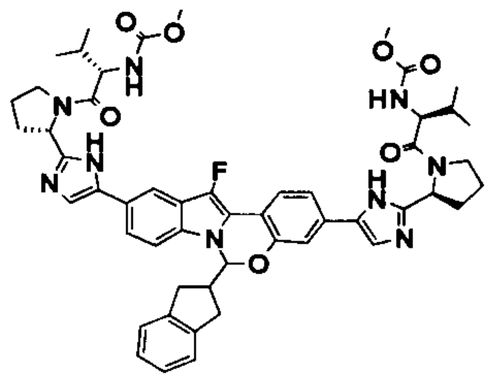
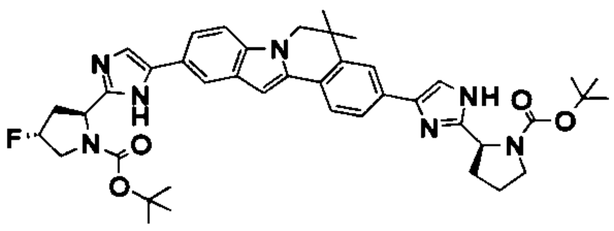
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
824		0.004	0.27	0.19	0.003	0.8	938.39	938.7	Mixture of isomers
825		0.004	19.5	3	0.005	76.8	938.37	938.7	Mixture of isomers
826		1.953	19.5				938.37	938.7	Mixture of isomers
827		4.037	19.5				624.22	624.8	Mixture of isomers
828		5.131					624.24	624.8	Mixture of isomers
829		0.013	80.1	0.674	0.011	0.74	902.39	902.7	Single isomer

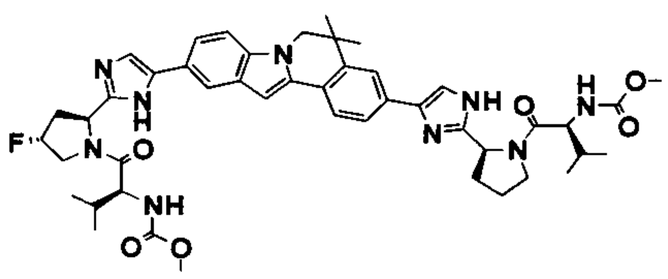
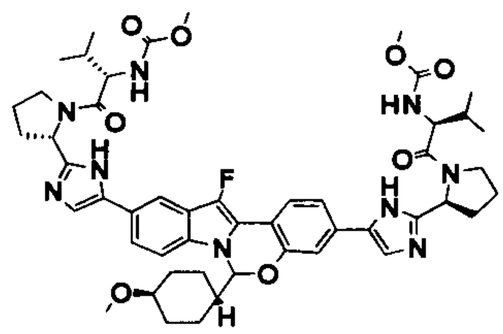
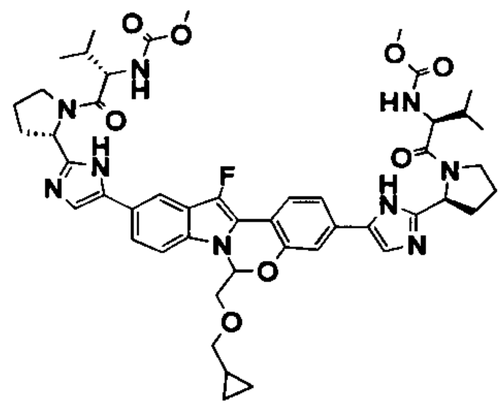
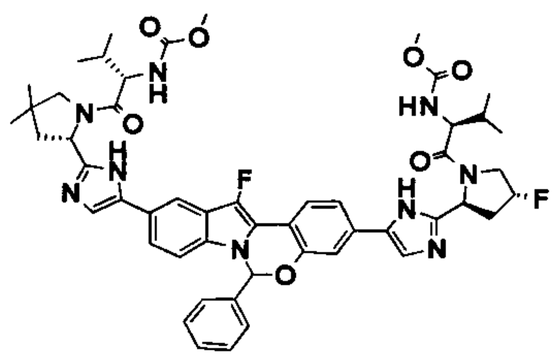
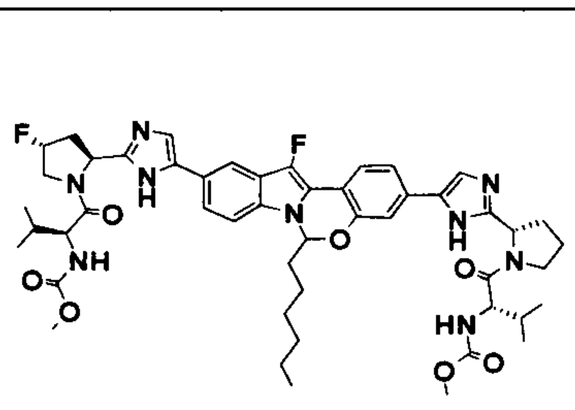
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
830		0.015	6.149	1	0.013	0.881	902.39	902.7	Single isomer
831		> 1000	1480				884.32	884.6	Mixture of isomers
832		518.300	1953				860.33	860.6	Mixture of isomers
833		> 1000	3481				684.22	684.6	Mixture of isomers
834		> 1000	7347				660.22	660.7	Mixture of isomers
835		0.008	0.15	2.7	0.007	35	974.37	975.2	Mixture of isomers

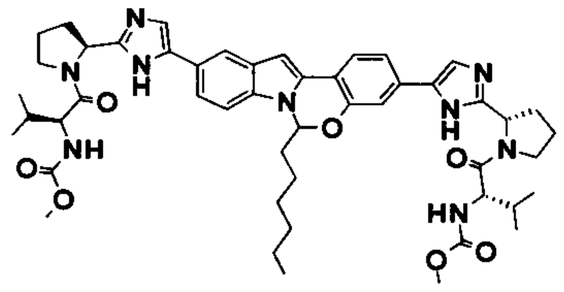
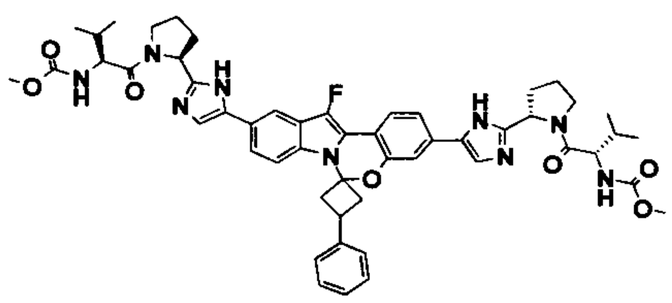
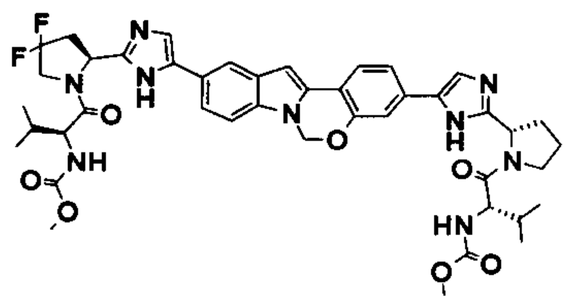
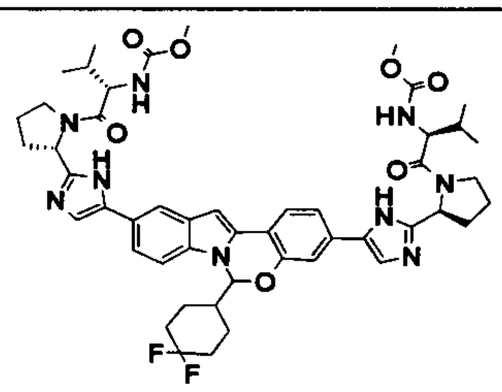
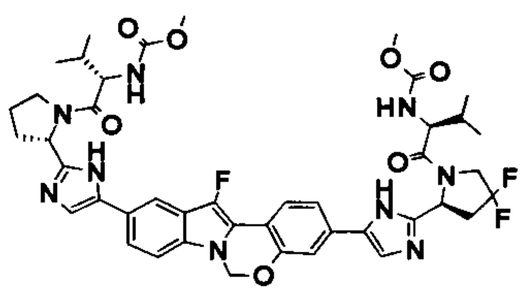
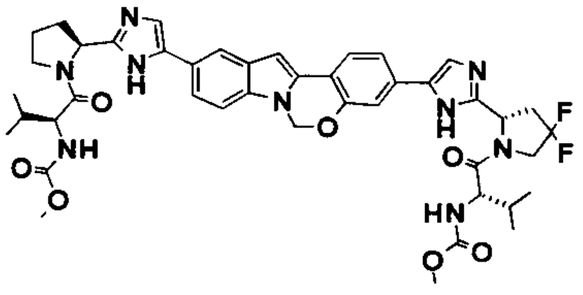
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
836		0.008	4	0.2	0.007	15	998.37	998.6	Mixture of isomers
837		0.022	6	> 100	0.009	2.549	964.41	964.7	Mixture of isomers
838		0.033	9.27	54.7	0.010	< 100	835.4	836.3	Mixture of isomers
839		5.900	212				737.35	738.2	Mixture of isomers
840		51.000	991				721.36	No M+H	Mixture of isomers
841		0.027	28.07	95.17		100	851.4	6.3[(M-16)+	Mixture of isomers

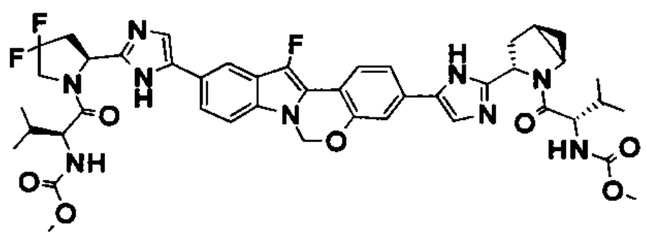
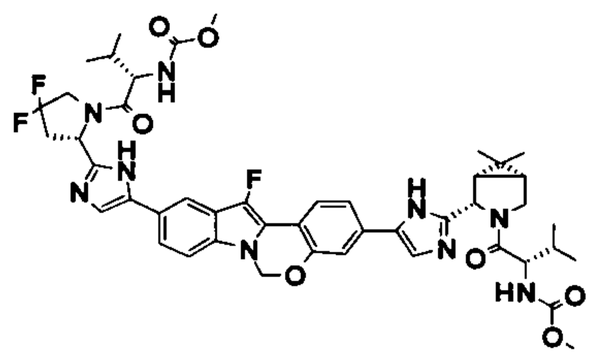
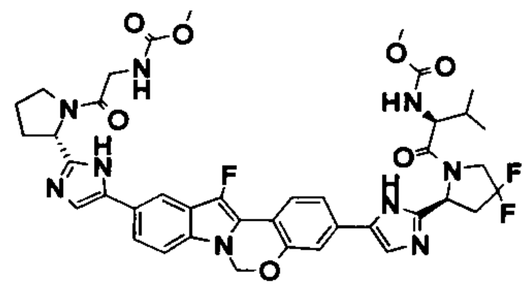
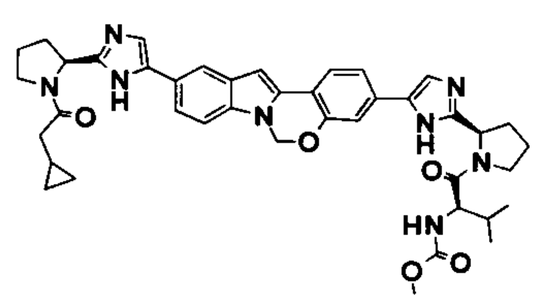
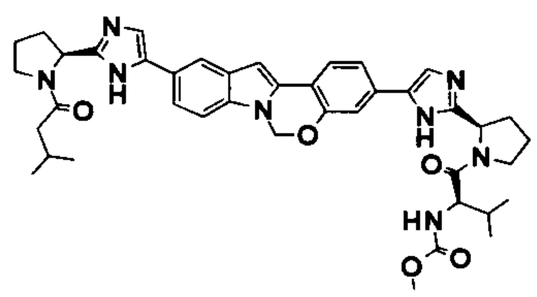
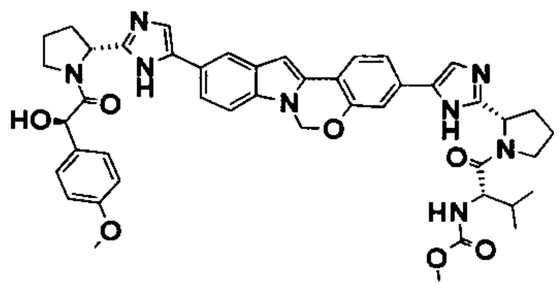
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
842		32.000	1000				521.25	522.2	Mixture of isomers
843		895.000	1000				739.35	740.2	Mixture of isomers
844		0.990	5.99	17.58		99.99	935.42	0.3[(M-16)+	Mixture of isomers
845		0.032	10	2		2	939.09	939.3	Single isomer
846		0.020	5	0.09		0	939.09	939.6	Single isomer

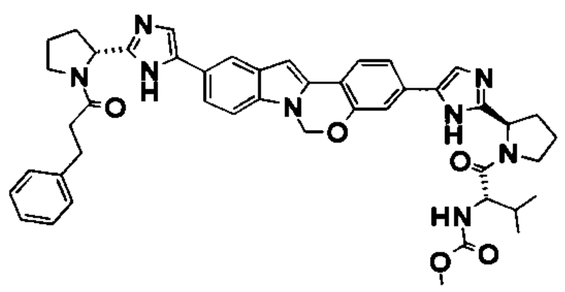
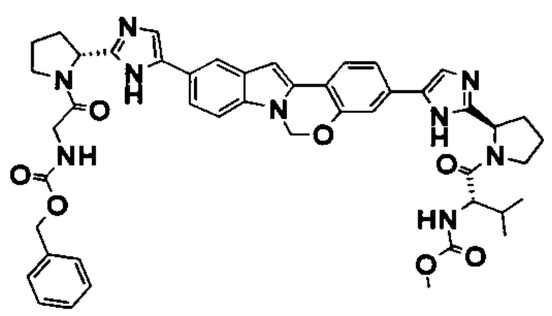
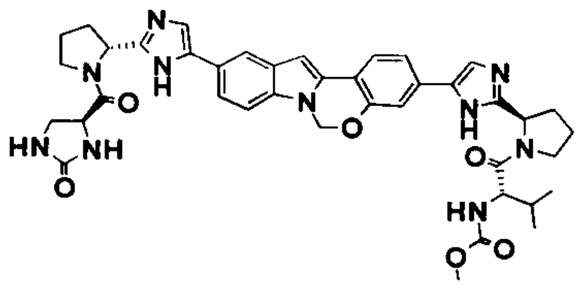
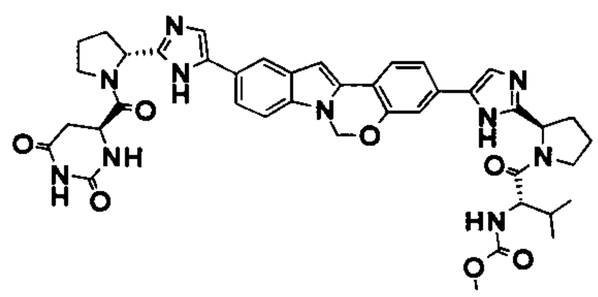
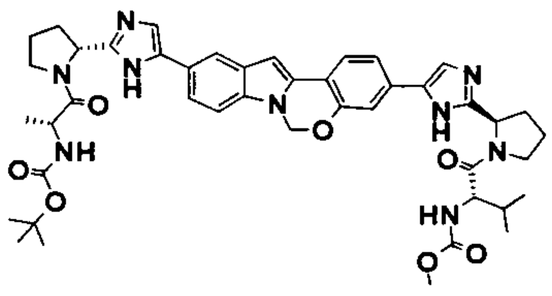
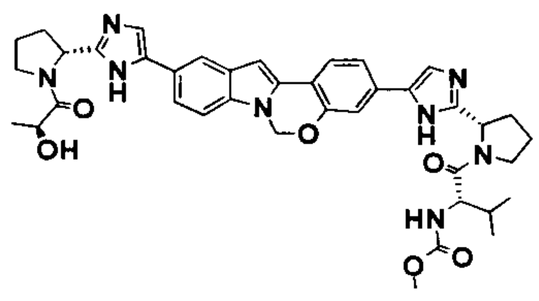
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
847		0.530	5	415		999	853.39	854.3	Mixture of isomers
848		0.010	1	1		31	843.97	844.3	Mixture of isomers
849		278.000	1000				529.26	Not Obs	Mixture of isomers
850		212.020	601				729.36	730.3	Mixture of isomers
851		0.040	0.21	0.11		0.56	927.43	928.3	Mixture of isomers
852		0.010	8.14	0.64		2.62	875.4	876.3	Mixture of isomers

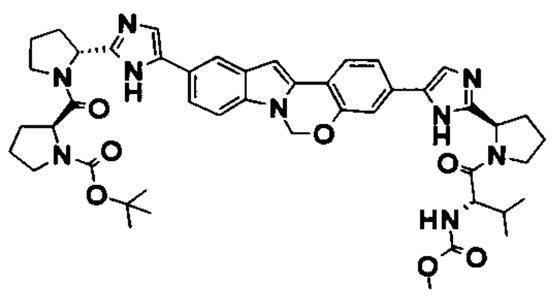
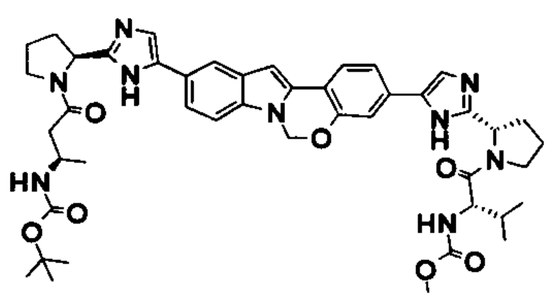
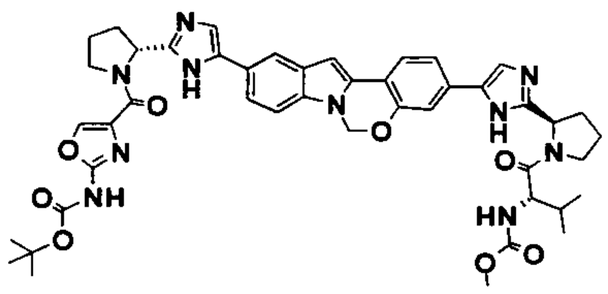
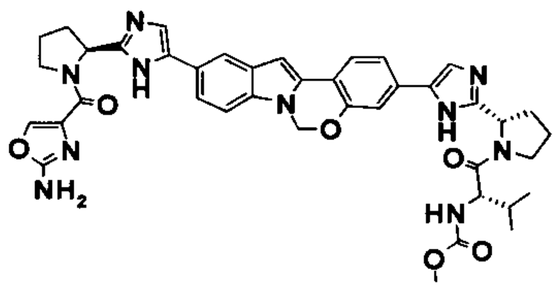
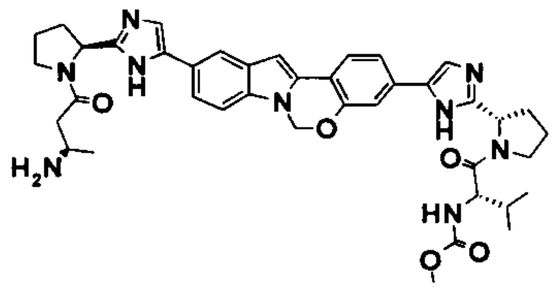
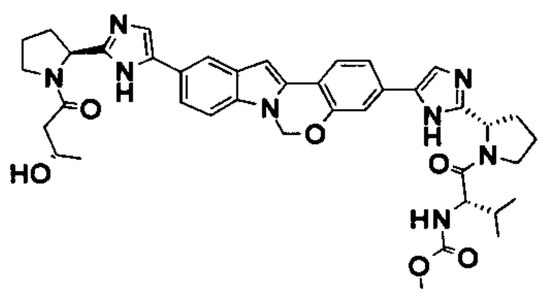
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
853		0.005	1.4	3.7	0.001	18	910.04	**911.0**	Mixture of isomers
854		0.010	1	2.6	0.020	7.7	922.05	**923.1**	Mixture of isomers
855		0.010	0.5	1.2	0.020	8.3	954.10	**955.1**	Mixture of isomers
856		> 0.2	> 100	63	> 0.2	369	839.99	**841.0**	Mixture of isomers
857		0.002	619.1	0.79	0.002	9.4	940.10	**941.1**	Mixture of isomers
858		> 2	< 100	> 102	> 0.2	> 2000	735.91	**736.9**	Single isomer

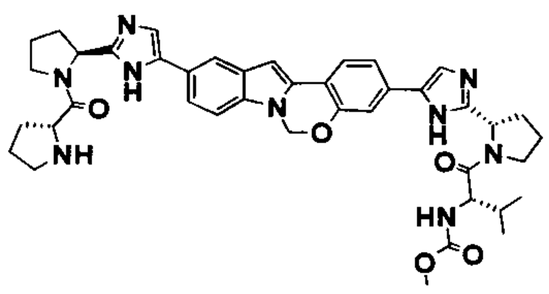
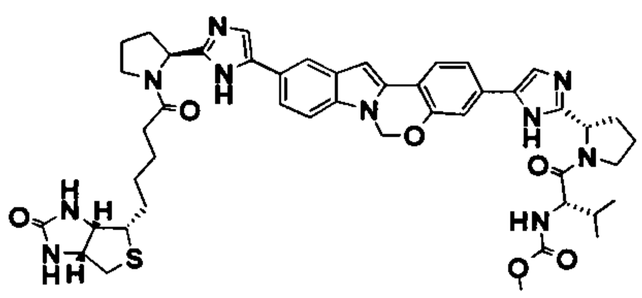
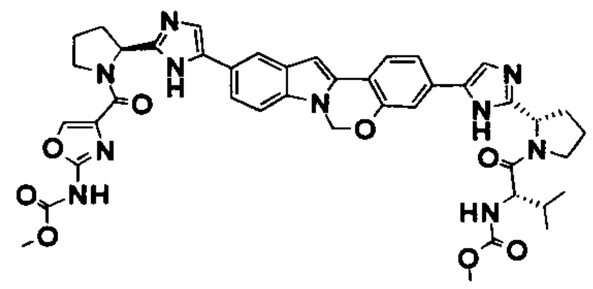
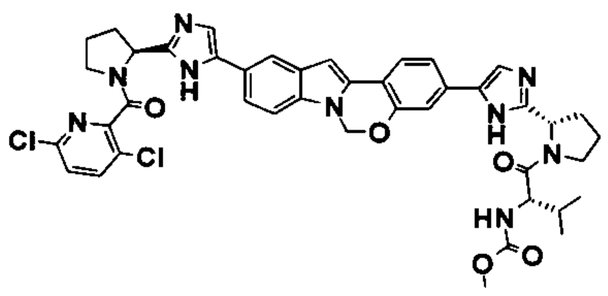
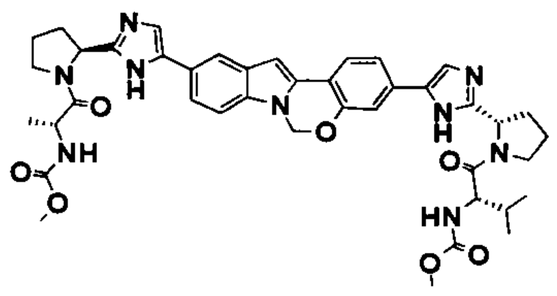
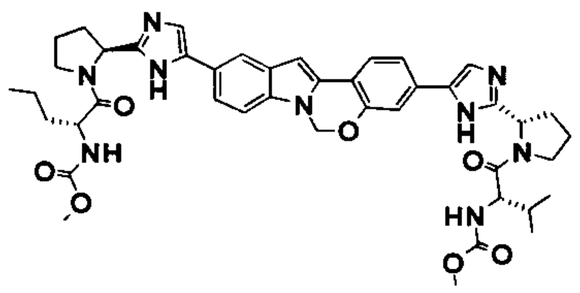
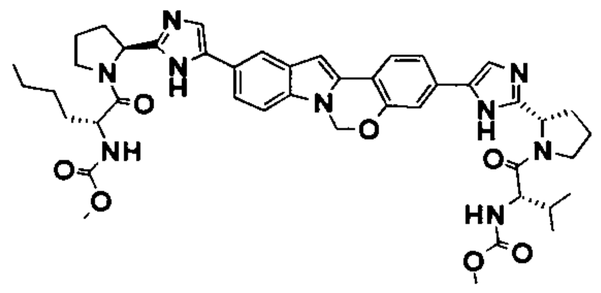
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
859		0.026	> 2000	36.47	0.001	696.3	850.01	851.0	Single isomer
860		0.003	360	0.76	0.002	3.4	936.11	937.1	Mixture of isomers
861		0.002	210.3	1.73	0.001	8.4	908.05	909.1	Single isomer
862		0.002		1.8	0.001	156.8	946.08	947.1	Single isomer
863		0.005	4.1	1	0.001	14	926.09	927.1	Mixture of isomers

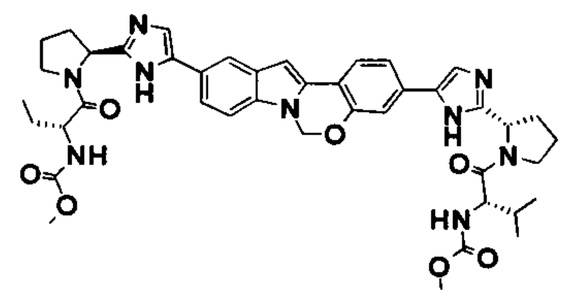
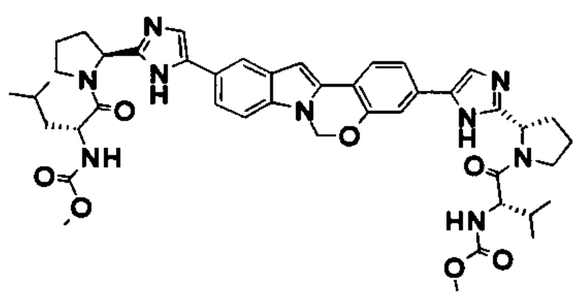
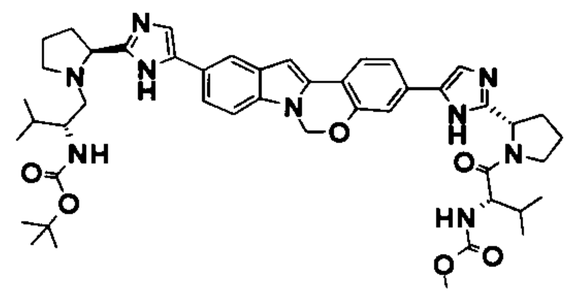
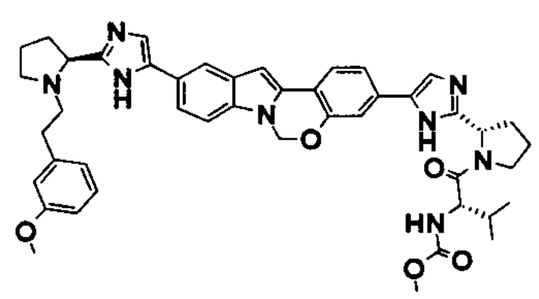
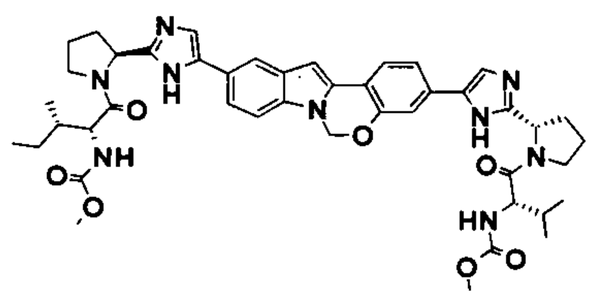
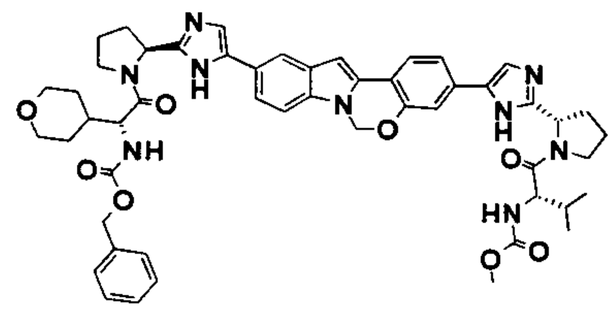
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
864		0.002	5.6	1	0.002	2.2	890.11	891.1	Mixture of isomers
865		0.005	31	4.2	0.001	13	940.10	941.1	Single isomer
866		0.003	4	1	0.001	42	841.92	842.9	Single isomer
867		0.002	19.4	1.6	0.001	4	924.07	925.1	Mixture of isomers
868		0.002	6.3	1.4	0.000	79	859.91	860.9	Single isomer
869		0.002	3.3	2	0.002	68	841.92	842.9	Single isomer

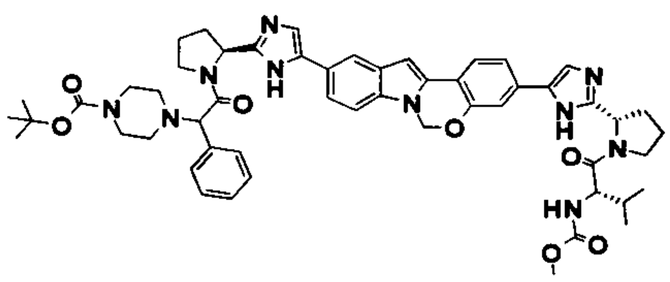
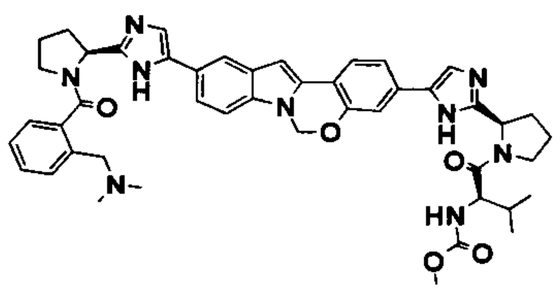
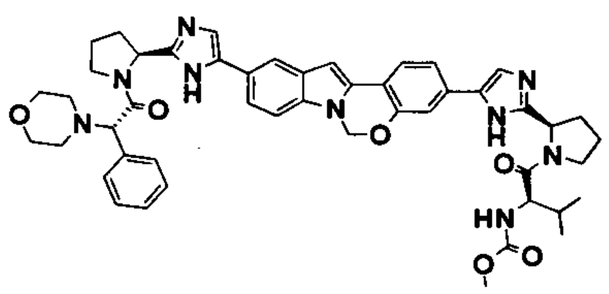
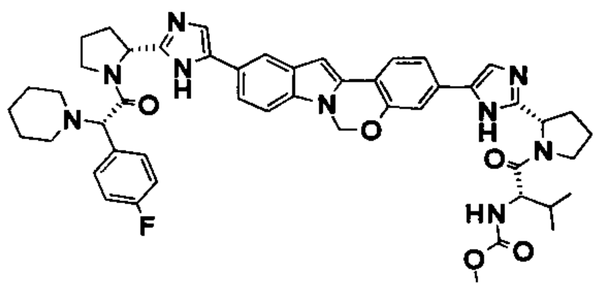
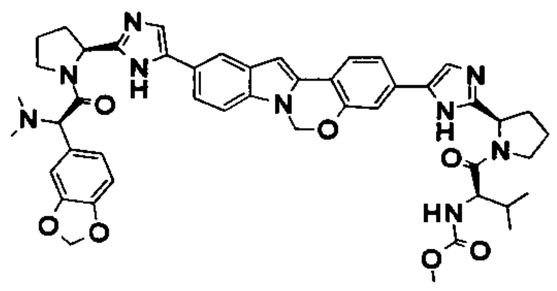
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
870		0.003	0.6	1	0.001	106	871.92	872.9	Single isomer
871		0.027	7.64	31	0.002	2	899.98	901.0	Single isomer
872		0.034	> 200	91.9	0.008	200	817.83	818.8	Single isomer
873		> 2	> 200	200	0.045	200	730.87	731.9	Single isomer
874		> 2	> 200	200	0.034	92.8	732.89	733.9	Single isomer
875		0.115	> 200	200	0.031	200	812.93	813.9	Mixture of isomers

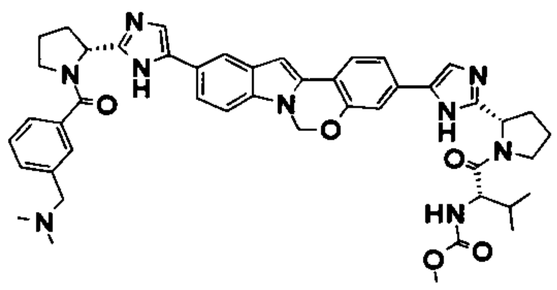
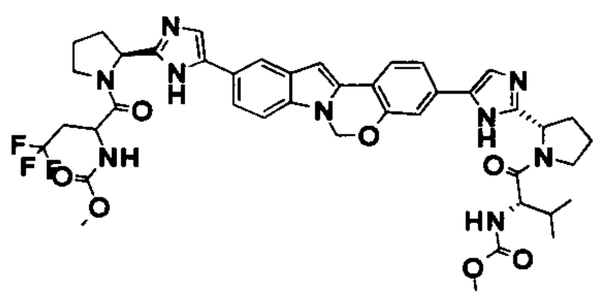
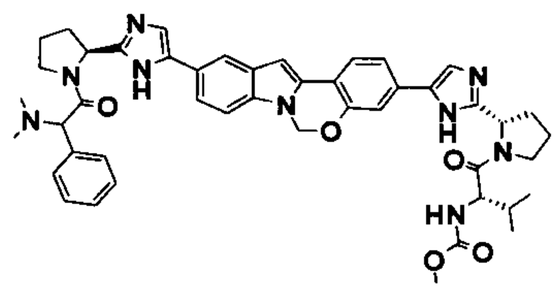
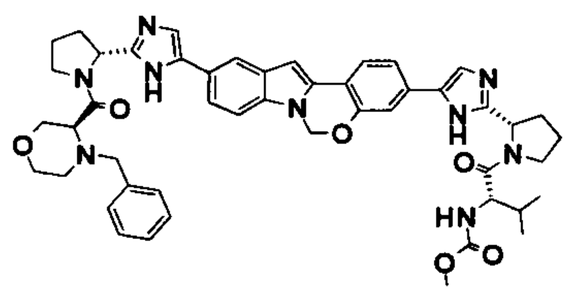
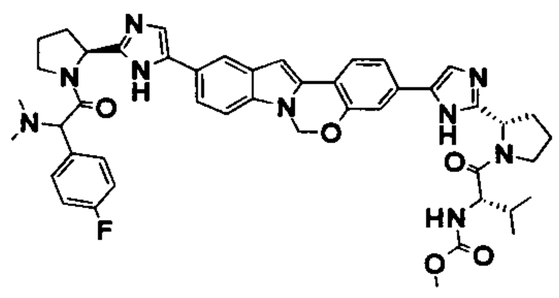
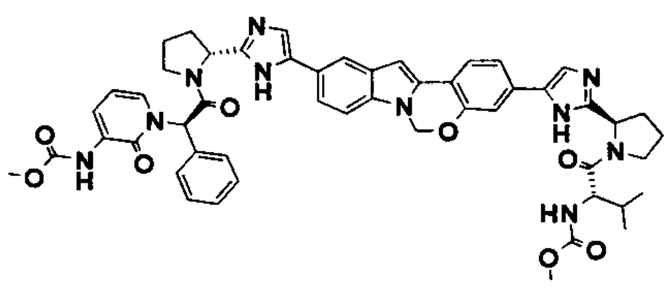
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
876		> 2	> 200	200	0.033	200	780.94	781.9	Single isomer
877		0.354	> 200	200	0.123	200	839.96	841.0	Single isomer
878		> 2	> 200	200	0.070	200	760.86	761.9	Single isomer
879		> 2	> 200	200	0.037	200	788.87	789.9	Single isomer
880		0.316	> 200	200	0.028	200	819.97	821.0	Single isomer
881		0.777	> 200	200	0.030	200	720.84	721.8	Single isomer

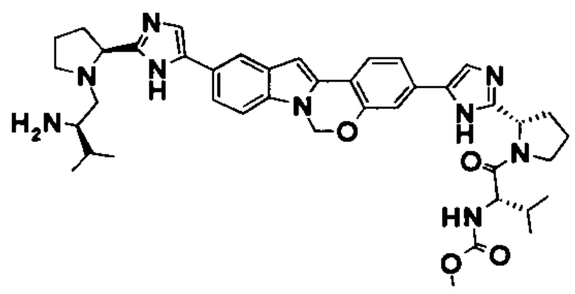
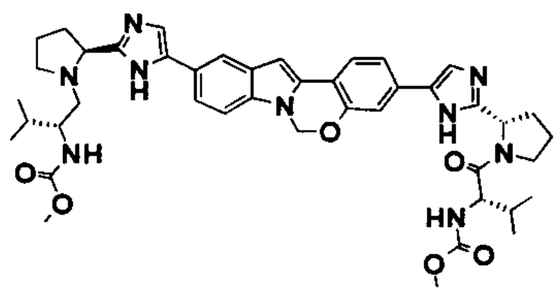
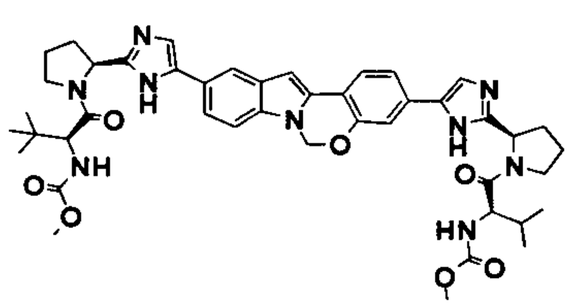
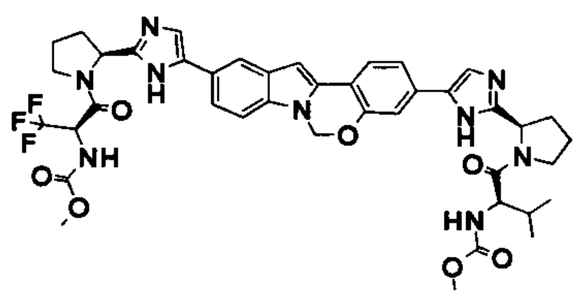
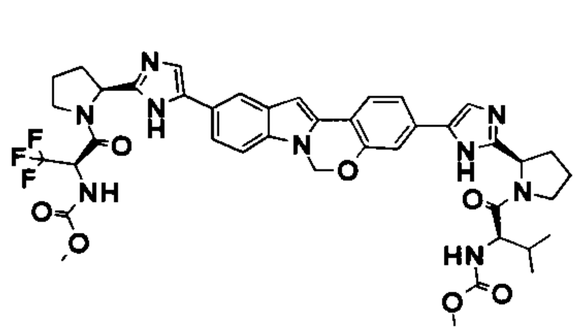
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
882		> 2	> 200	> 200	0.463	> 200	846.01	847.0	Single isomer
883		> 2	> 200	> 200	0.098	> 200	834.00	835.0	Single isomer
884		> 2	> 200	> 200	0.022	> 200	858.96	860.0	Single isomer
885		> 2	> 200	200	0.036	> 200	758.84	759.8	Single isomer
886		> 2	> 200	> 200	0.056	> 200	733.88	734.9	Single isomer
887		> 2	> 200	> 200	0.020	> 200	734.86	735.9	Single isomer

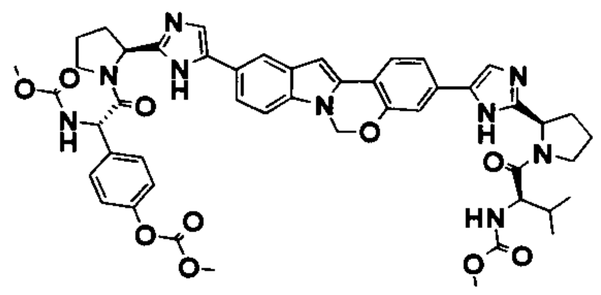
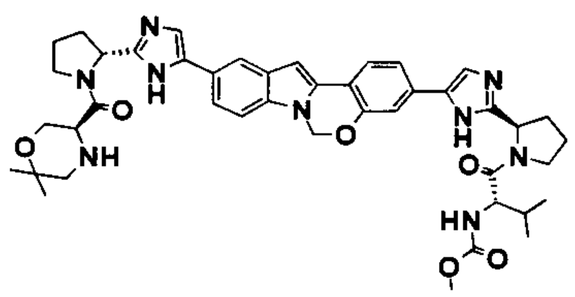
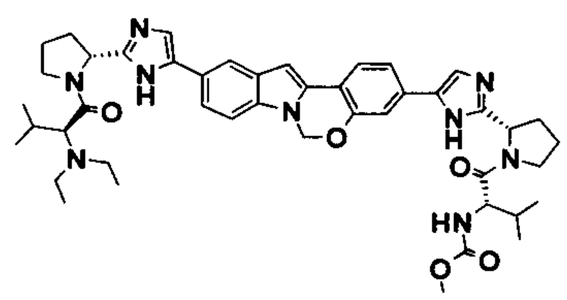
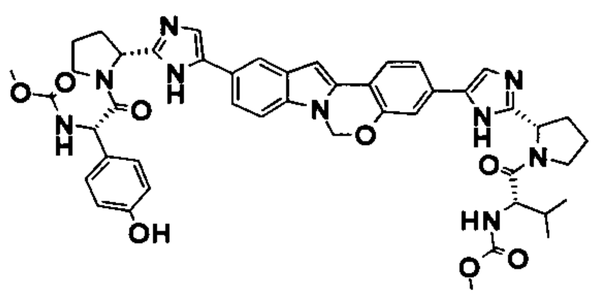
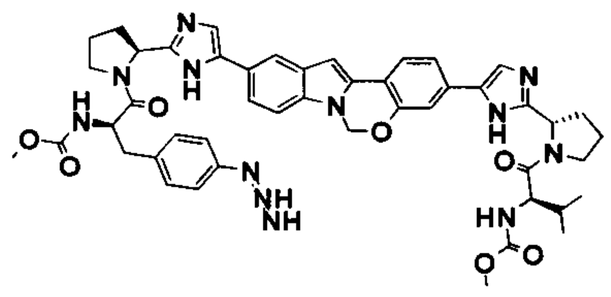
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
888		0.500	> 200	> 200	0.116	> 200	745.89	746.9	Single isomer
889		2.037					875.07	876.1	Single isomer
890							816.88	817.9	Single isomer
891							822.76	823.8	Single isomer
892							777.89	778.9	Single isomer
893							805.94	806.9	Single isomer
894		0.018	42	16.1	0.010	112	819.97	821.0	Single isomer

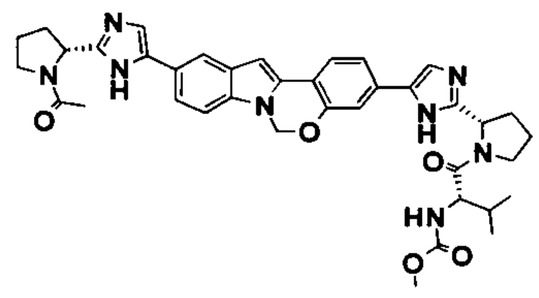
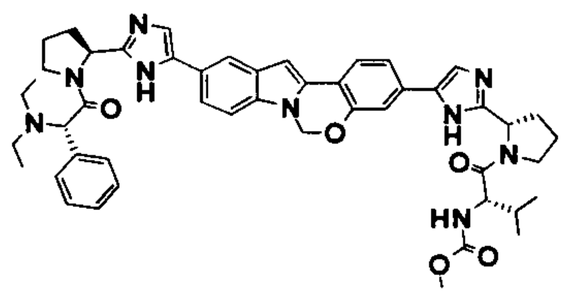
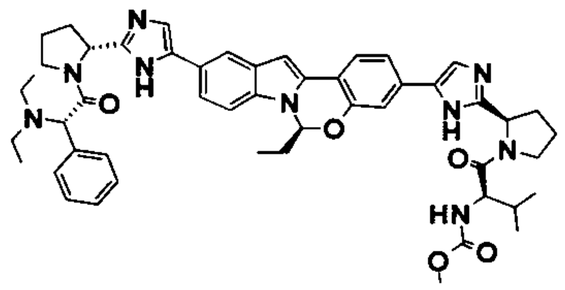
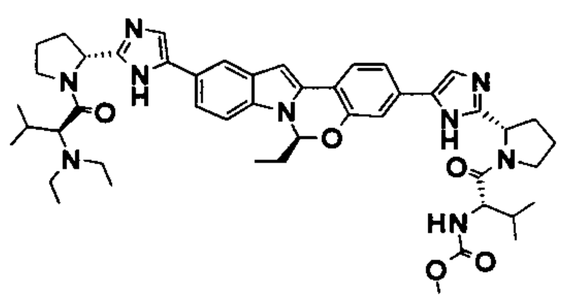
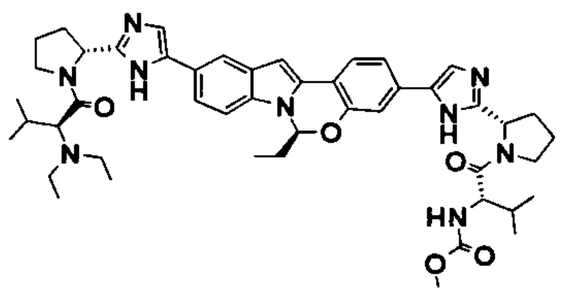
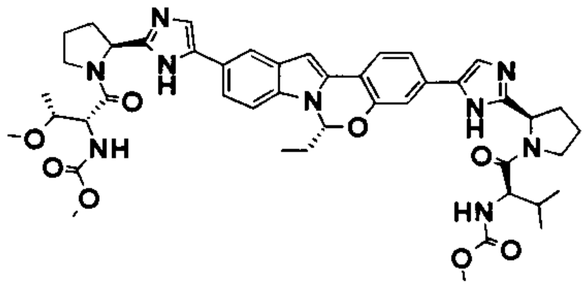
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
895		0.014	7	6.5	0.013	96	791.92	792.9	Single isomer
896		0.013	32.89	10.1	0.007	1.166	819.97	821.0	Single isomer
897		218.024	2408.33				834.04	835.0	Single isomer
898		32.000	401				782.95	784.0	Single isomer
899		0.004	43	3	0.002	51.1	819.97	821.0	Single isomer
900		0.233	> 100	93	0.070	> 100	924.08	925.1	Single isomer

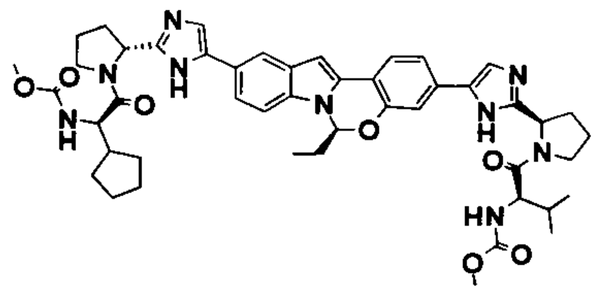
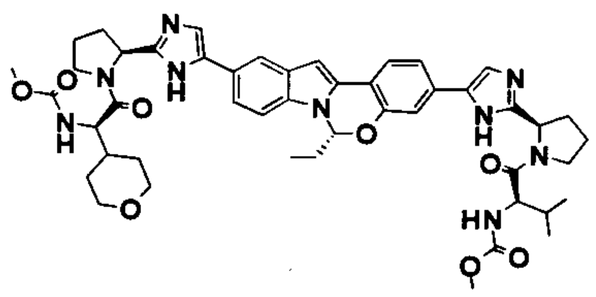
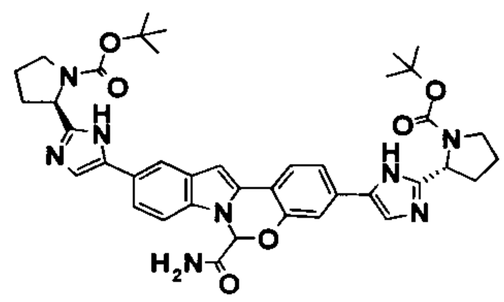
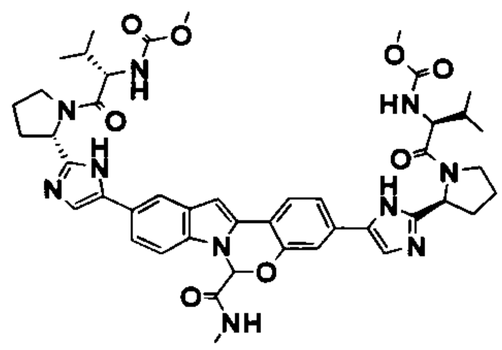
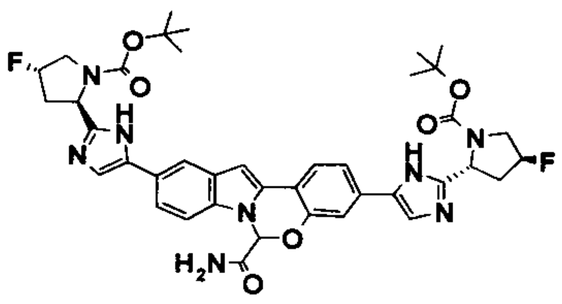
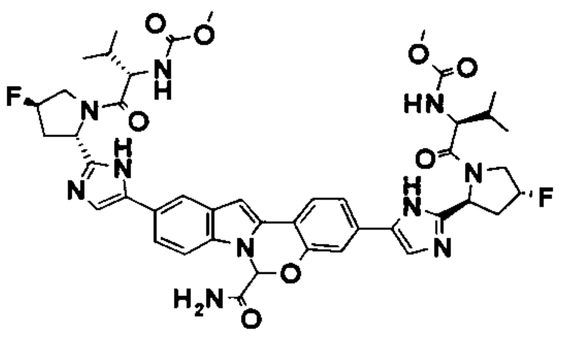
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
901		1.910	591				951.15	952.1	Single isomer
902		53.000	1891				809.98	811.0	Single isomer
903		1.910	285				761.89	762.9	Single isomer
904		2.000	532				852.01	853.0	Single isomer
905		2.000	258				868.03	869.0	Single isomer
906		2.000	586				853.99	855.0	Single isomer

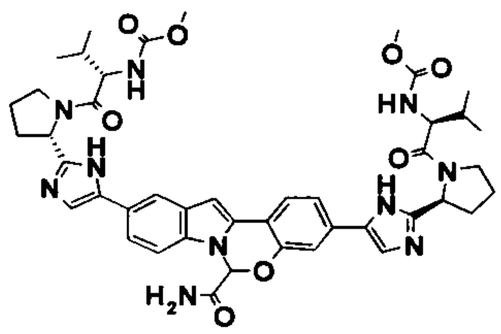
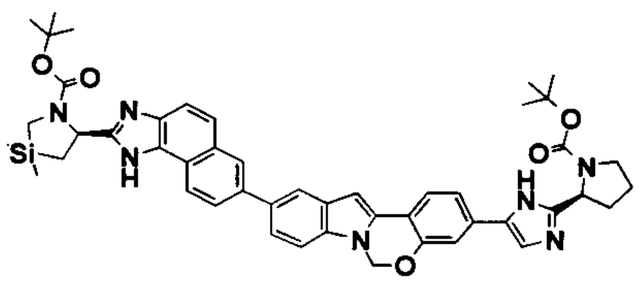
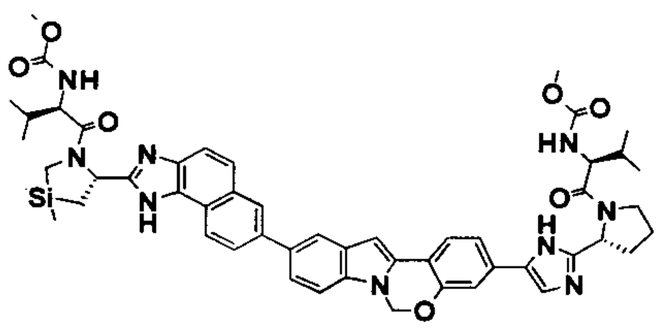
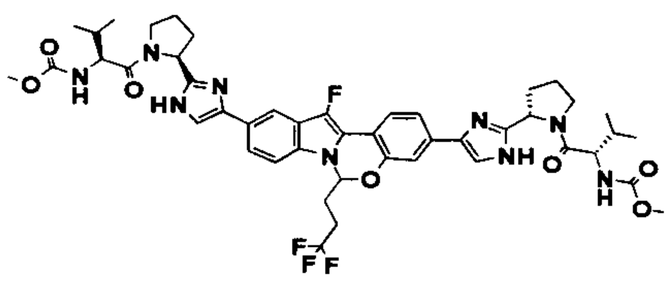
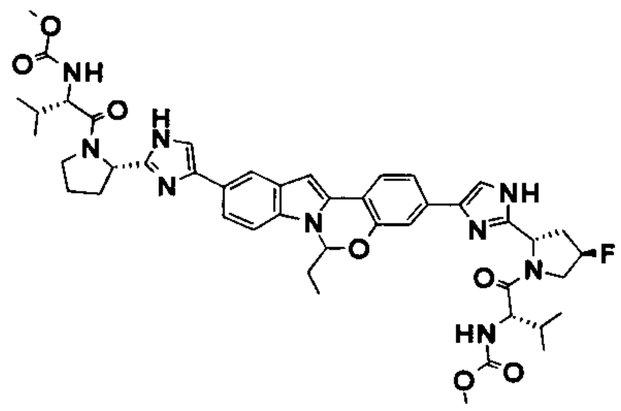
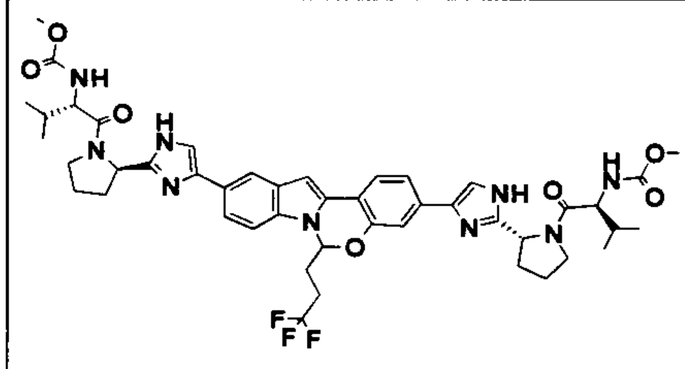
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
907		7.000	2977				809.98	811.0	Single isomer
908		0.032	96.78	29.62	0.020	> 100	845.89	846.9	Single isomer
909		2.000	493				809.98	811.0	Mixture of isomers
910		24.000	1061				852.01	853.0	Mixture of isomers
911		2.000	183				827.97	829.0	Mixture of isomers
912		5.700	1854				933.05	934.0	Single isomer

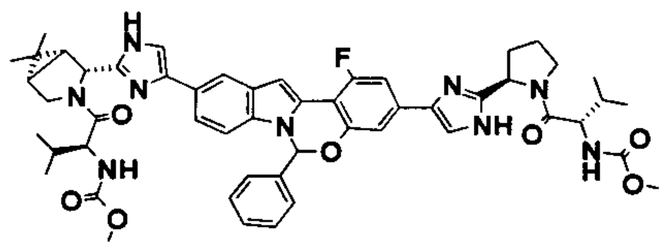
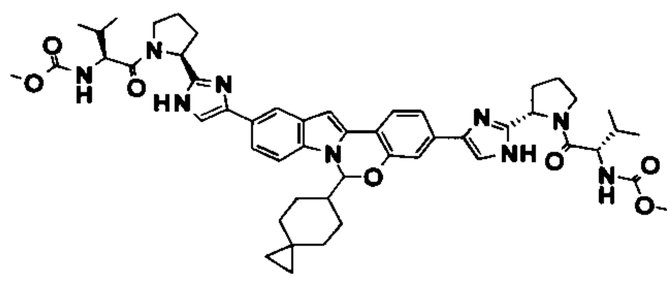
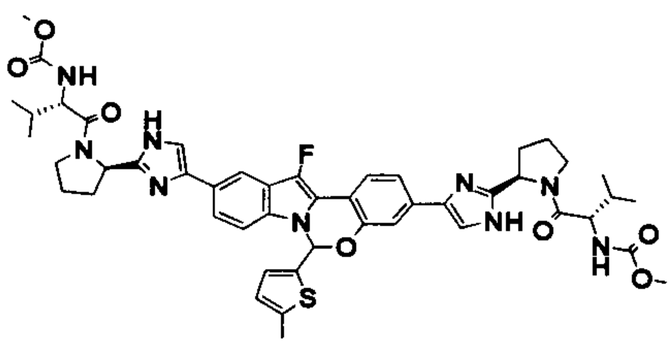
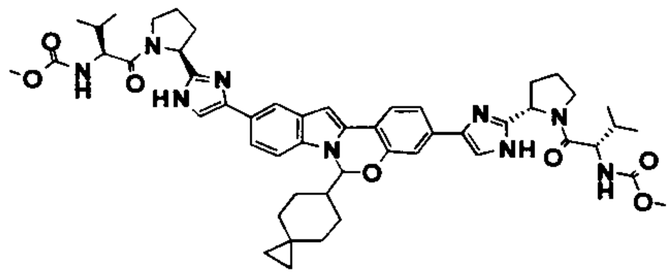
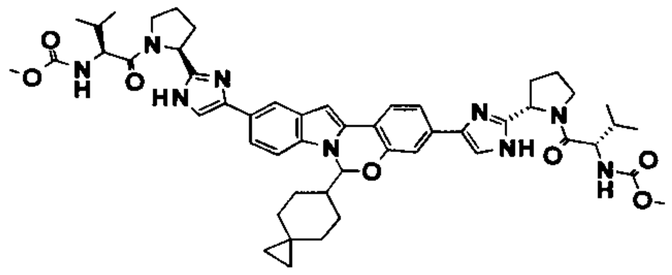
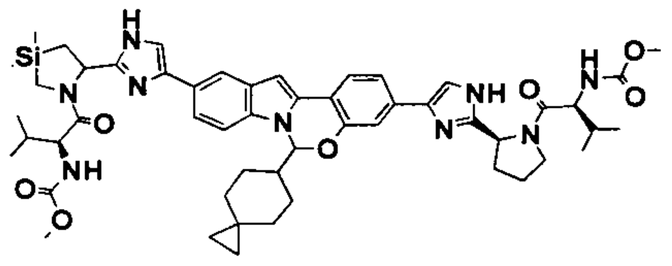
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
913		533.300	2192				733.92	734.9	Single isomer
914		43.100	1355				791.96	793.0	Mixture of isomers
915		0.020	> 100	12	0.010	89.2	819.97	821.0	Single isomer
916		0.010	81	> 100	0.009		831.86	832.9	Mixture of isomers
917		0.020	> 100	26	0.009		831.86	832.9	Mixture of isomers

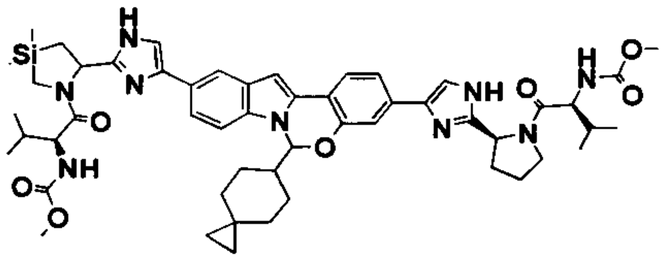
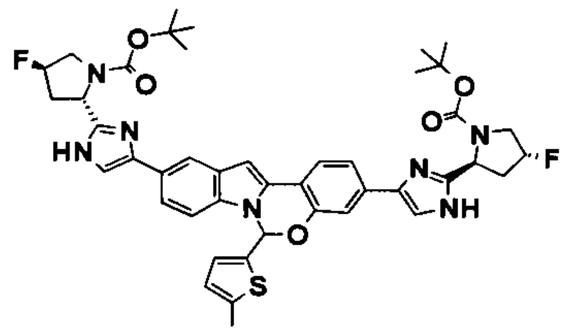
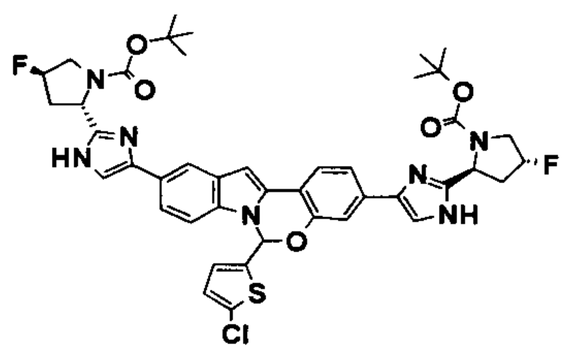
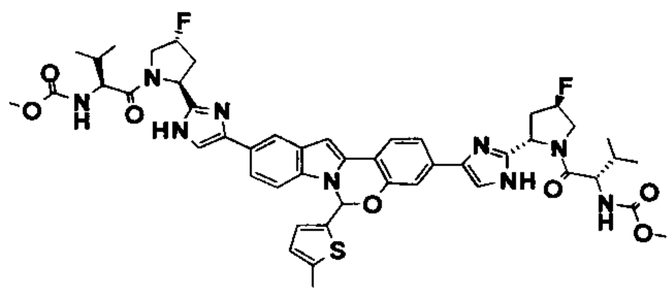
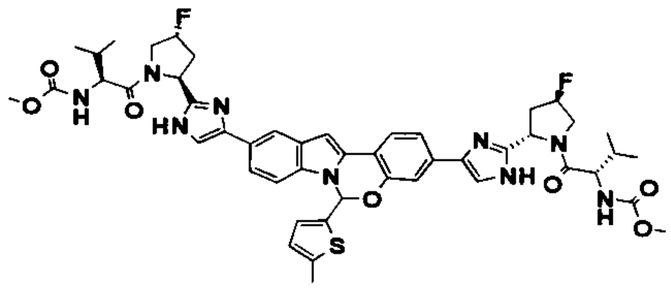
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
918		0.131	109.9	109.9	0.019	110	914.00	915.0	Single isomer
919		0.300	> 100	> 100	0.088		789.94	790.9	Single isomer
920		> 2	109.9	109.9	0.368	110	804.01	805.0	Single isomer
921		0.136	109.9	109.9	0.016	110	855.96	857.0	Single isomer
922		0.154	109.9	65.72	0.034	110	895.00	896.0	Single isomer

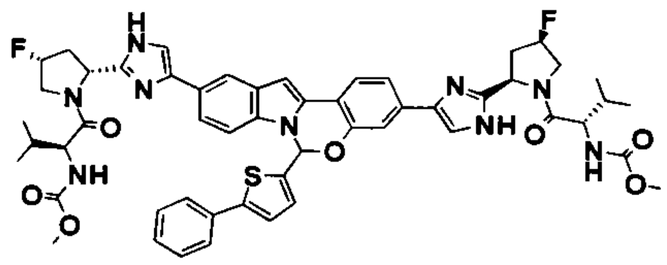
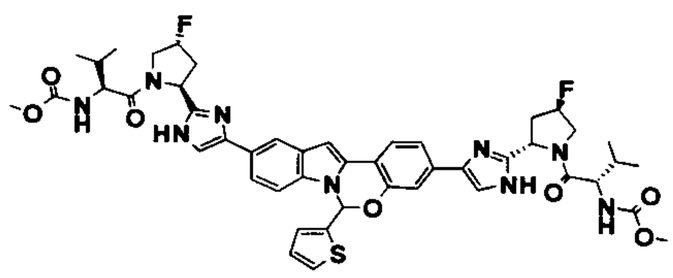
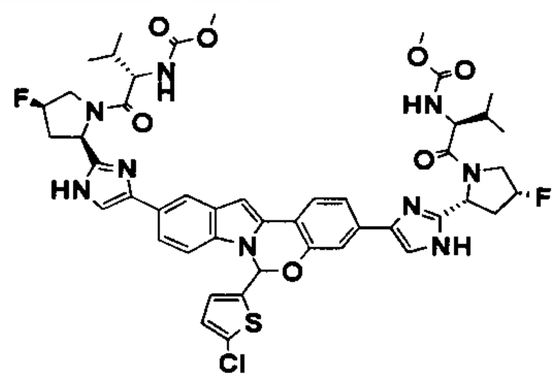
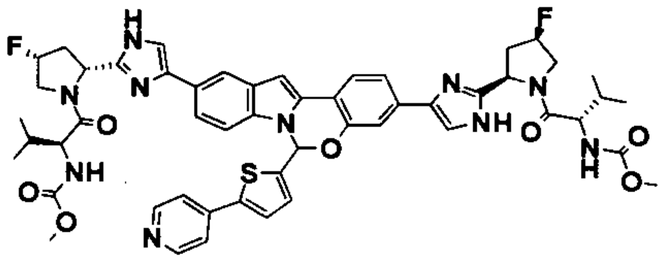
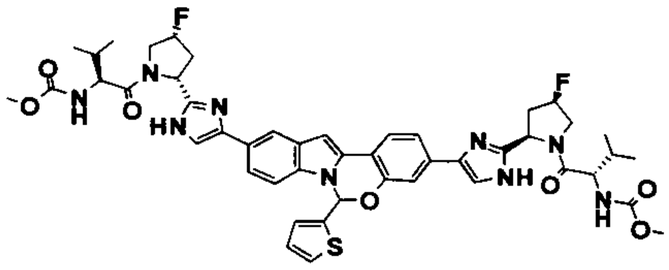
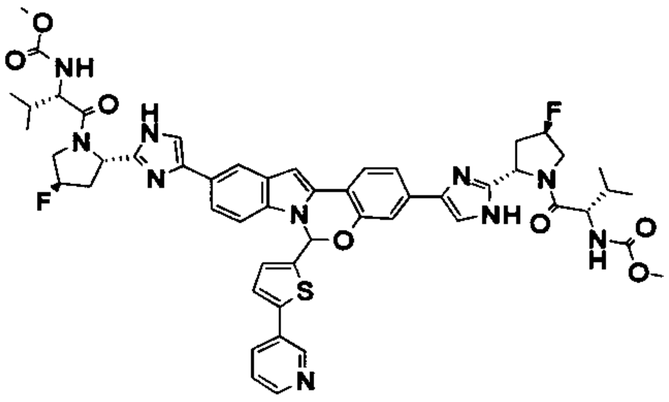
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
923							690.81	691.8	Single isomer
924							838.03	839.0	Single isomer
925							866.09	867.1	Single isomer
926							832.07	833.1	Mixture of isomers
927							832.07	833.1	Mixture of isomers
928							850.00	851.0	Mixture of isomers

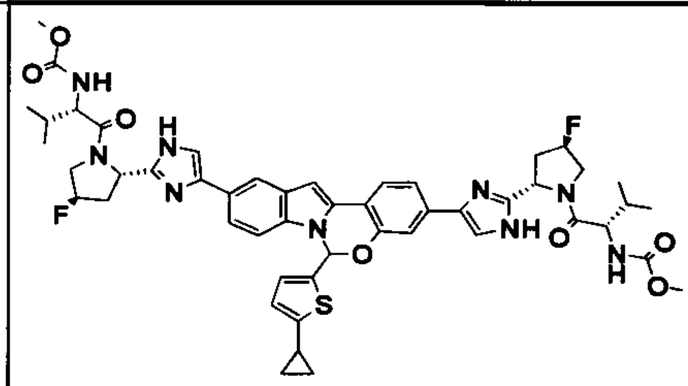
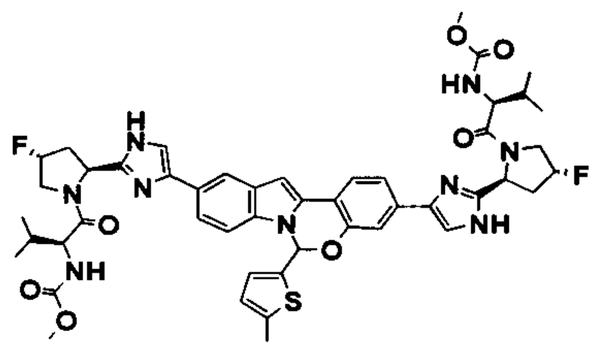
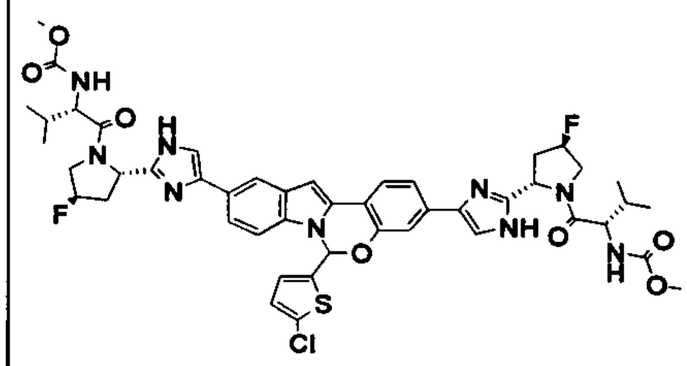
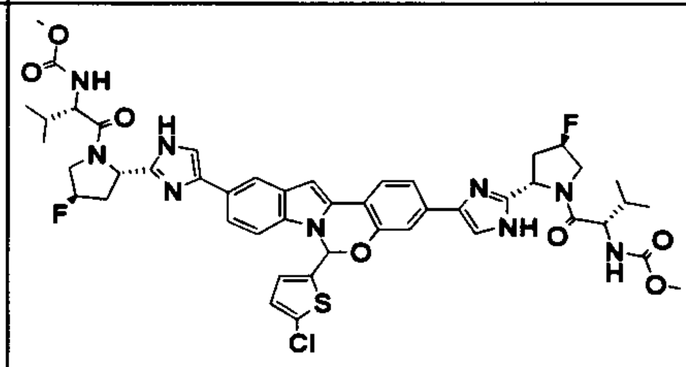
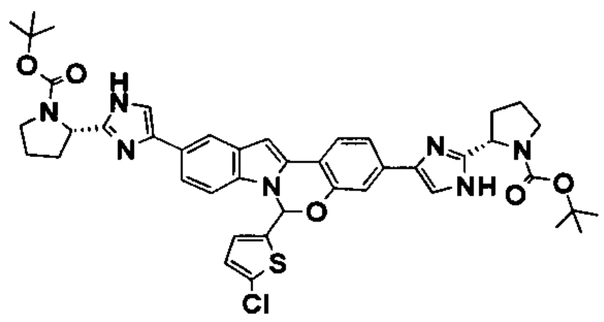
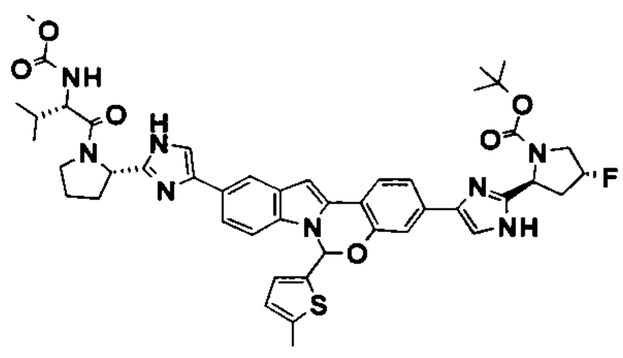
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
929							860.03	861.0	Mixture of isomers
930							876.03	877.0	Mixture of isomers
931		> 10	> 1000	> 1000	> 2	> 1000	734.86	735.9	Mixture of isomers
932		0.362	> 1000	524	0.205	> 1000	862.99	863.8	Mixture of isomers
933		> 10	> 1000	> 1000	> 2	> 1000	770.84	771.7	Mixture of isomers
934		> 10	465.092	> 1000	0.100	> 1000	884.95	885.9	Mixture of isomers

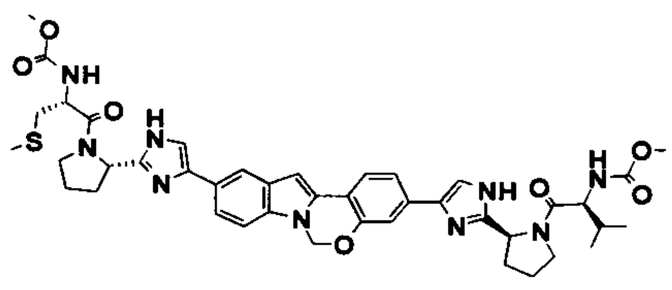
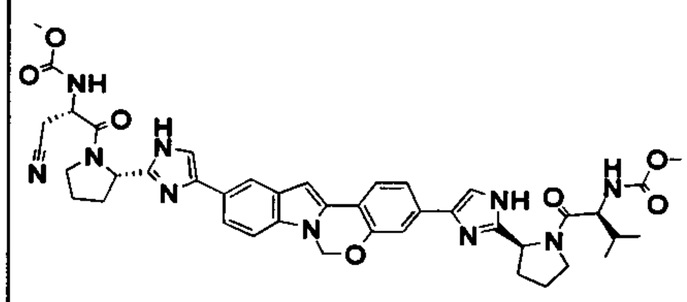
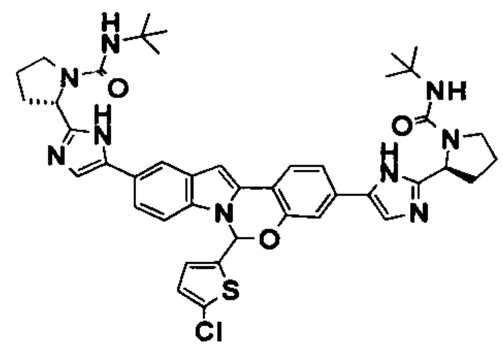
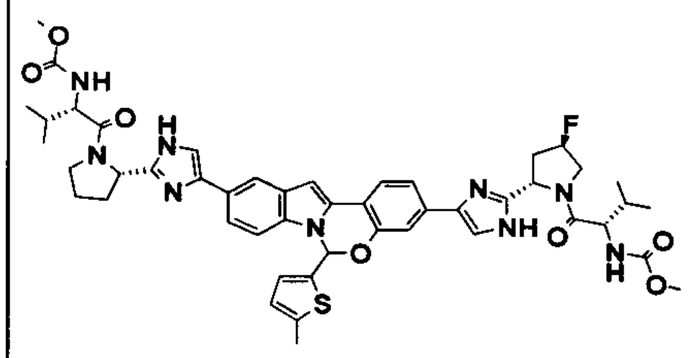
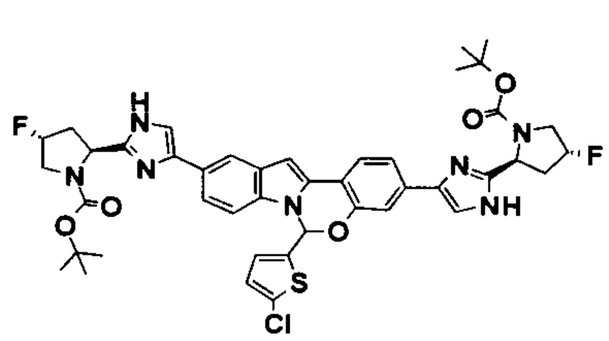
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
935		1.950	1000	457.51	0.200	1000	848.97	850.0	Mixture of isomers
936							836.09	836.7	Single isomer
937		> 1	> 100	92	0.407	> 100	950.19	950.5	Single isomer
938		0.004	23.48	1	0.001	5.504	919.40	920.4	Mixture of isomers
939		0.002	5.61	7	0.001	25.107	851.40	852.3	Mixture of isomers
940		0.006	8.63	1.83	0.002	5	901.40	902.4	Mixture of isomers

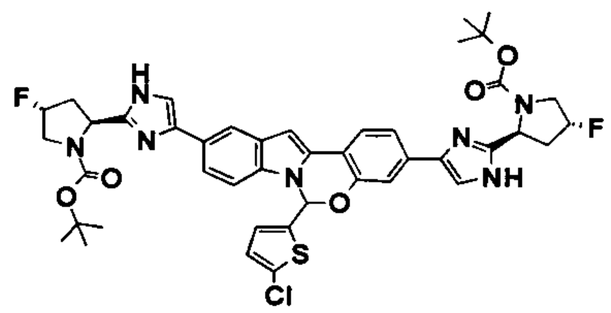
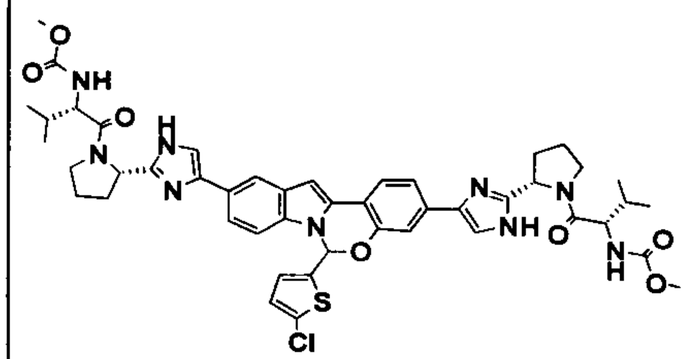
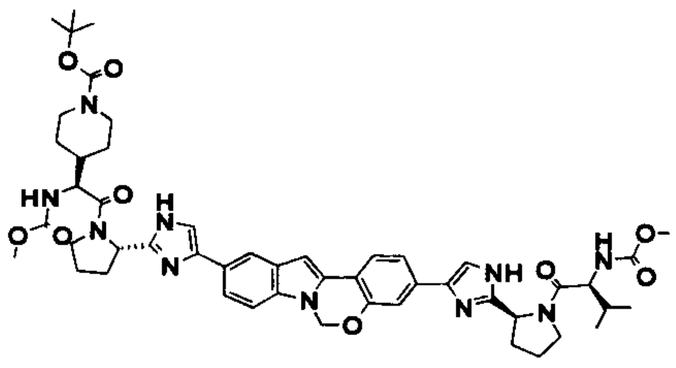
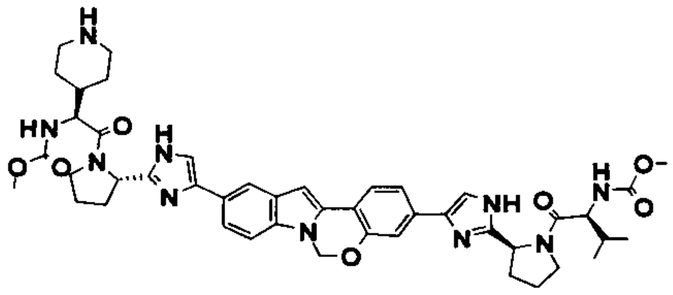
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
941		0.008	79.27	12.87	0.002	162	939.40	940.0	Mixture of isomers
942		0.008	6	2	0.003	4	913.50	914.5	Mixture of isomers
943		0.003	0.4		0.001	2	919.40	920.5	Mixture of isomers
944		0.010	48	2.1	0.020	11	913.40	914.5	Single isomer
945		0.010	4	1.1	0.010	2.1	913.40	914.5	Single isomer
946		0.010	> 100	6.4	0.020	111.9	957.50	959.4	Single isomer

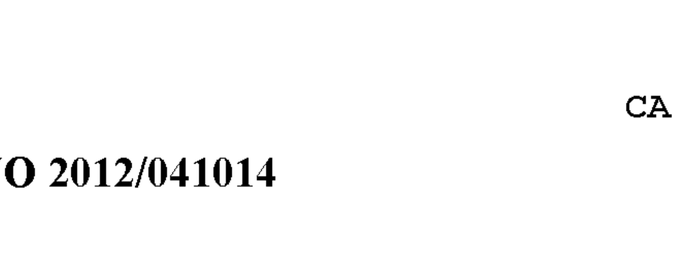
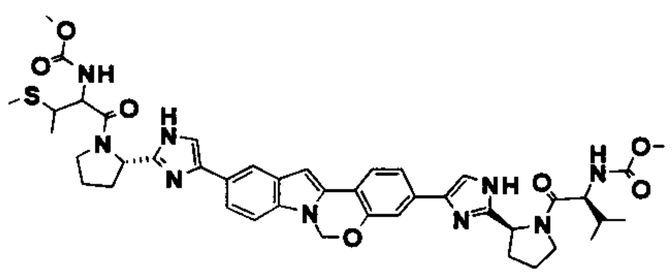
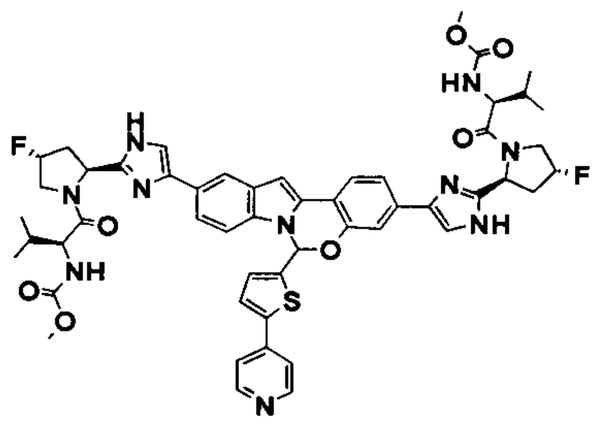
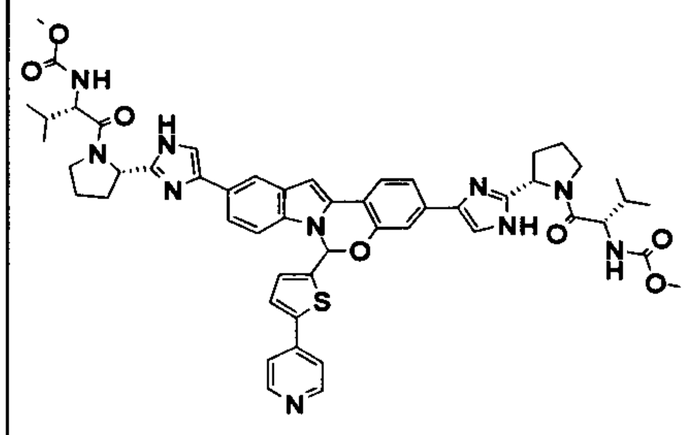
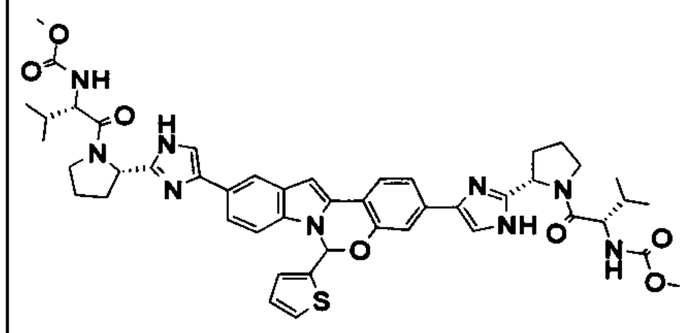
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
947		0.010	39	4	0.020	35.9	957.50	959.4	Single isomer
948		332.501	5099				823.30	8234.3	Mixture of isomers
949		12.500	57				843.30	844.2	Mixture of isomers
950		0.011	0.4	5.3	0.007	17	937.40	938.4	Single isomer
951		0.020	9	4.6	0.049	23	937.40	938.3	Single isomer

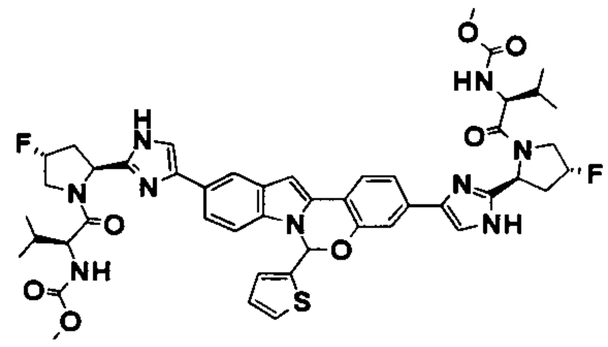
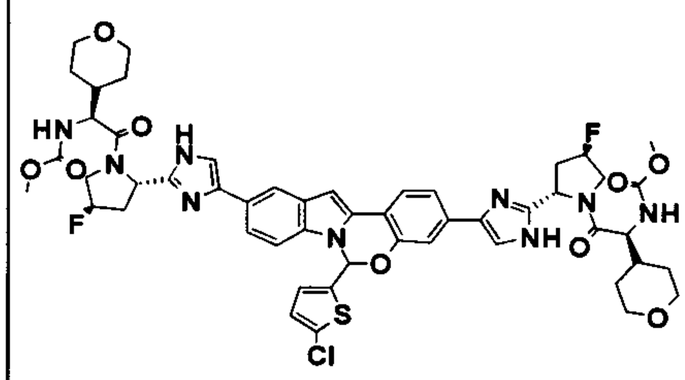
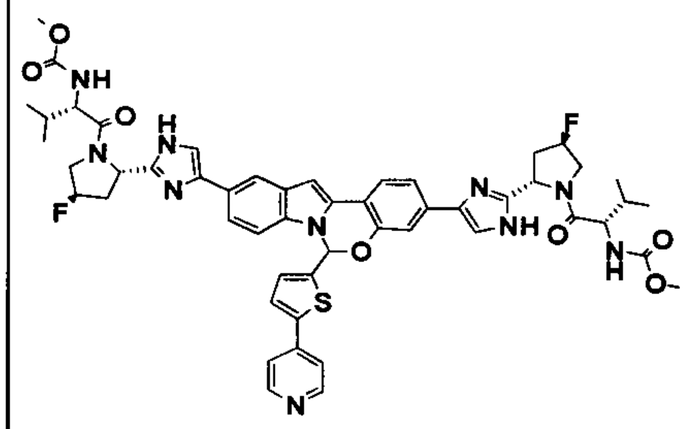
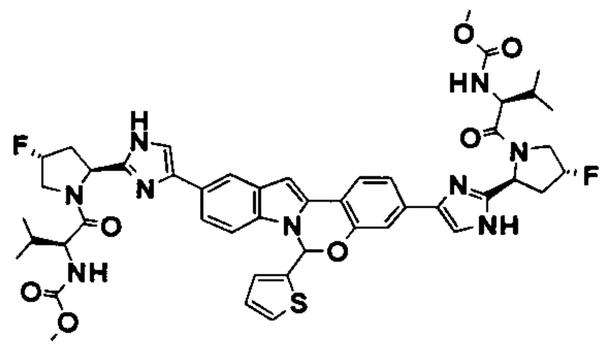
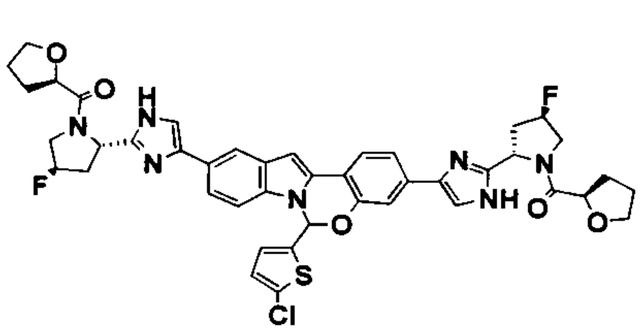
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
952		0.005	0.09	0.6	0.007	9.11	999.40	1002.3	Mixture of isomers
953		0.512	15	589	0.047	275	923.40	924.3	Mixture of isomers
954		0.008	0.2	4.492	0.004	6	957.30	959.2	Mixture of isomers
955		0.012	0.09	2.9	0.011	49.1	1000.40	1001.3	Mixture of isomers
956		0.015	0.26	11.4	0.011	93.988	923.40	924.3	Mixture of isomers
957		0.007		1.6	0.006	19.7	1000.40	1001.0	Mixture of isomers

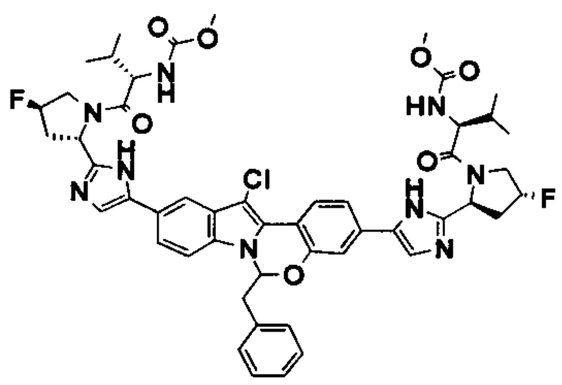
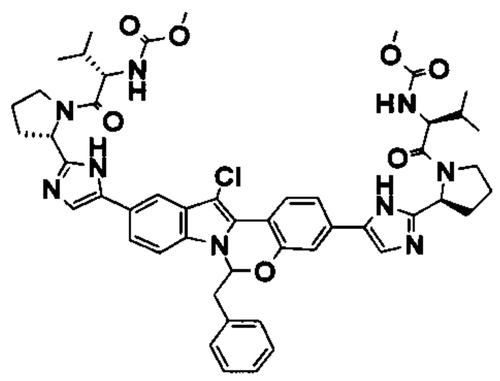
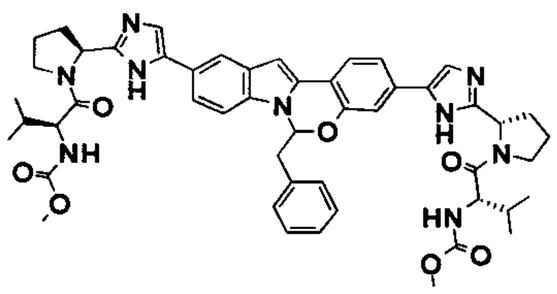
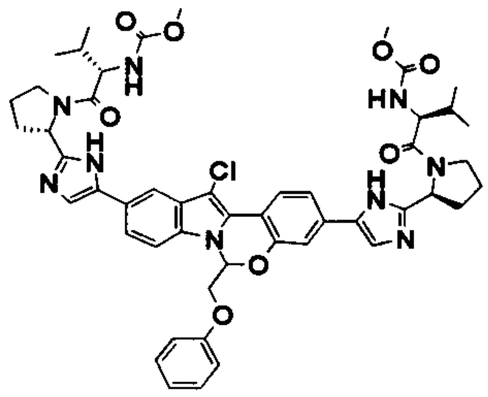
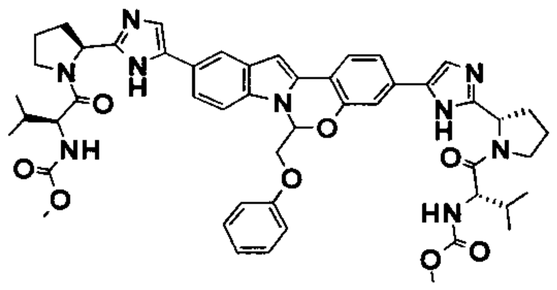
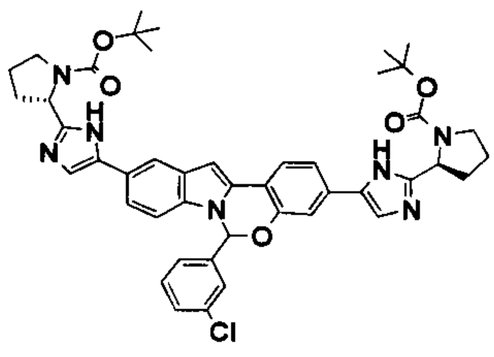
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
958		0.008		1	0.003	8.4	963.40	964.4	Mixture of isomers
959		0.005	> 100	1	0.004	7.8	937.40	938.4	Mixture of isomers
960		0.010	12.19	22.82	0.007	> 100	957.30	958.3	Single isomer
961		0.003	4.03	0.492	0.004	43.878	957.30	958.3	Single isomer
962		114.400	322				807.30	NA	Mixture of isomers
963		0.492	54.5		0.158	110	862.40	NA	Mixture of isomers

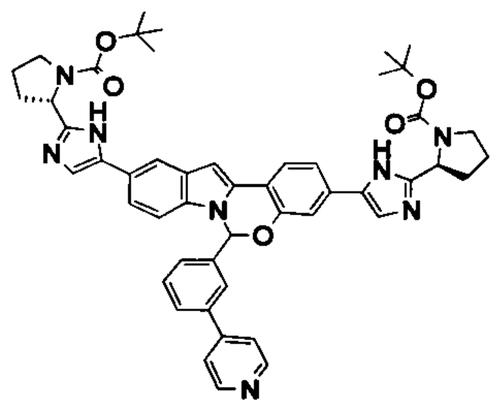
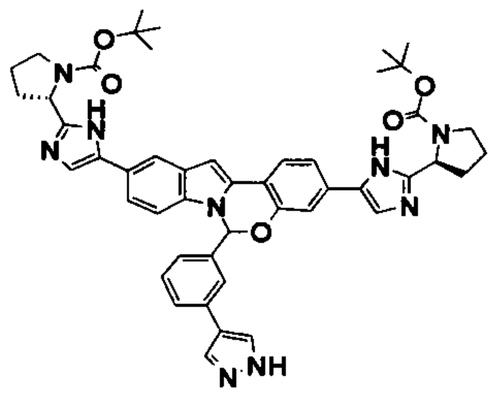
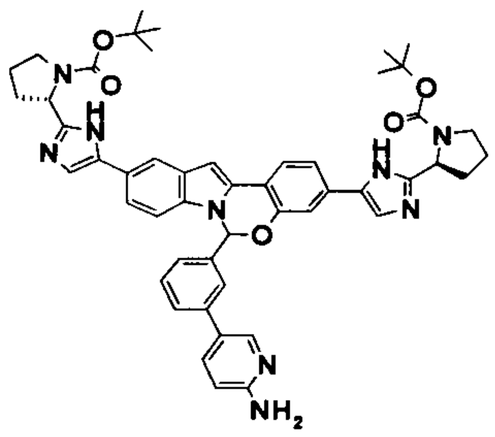
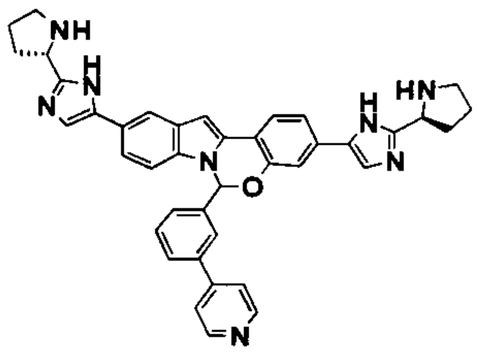
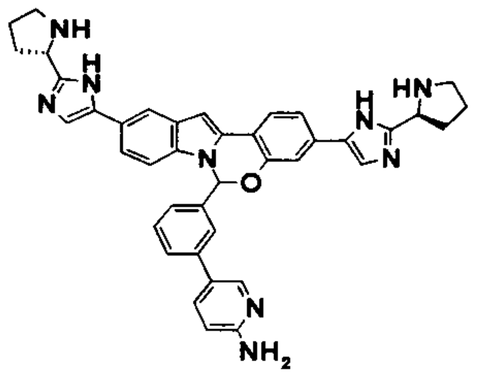
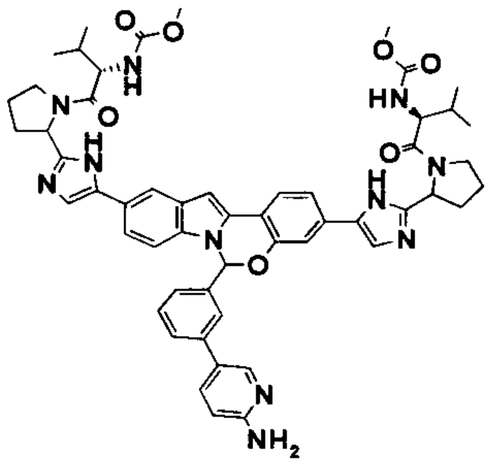
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
964		1.100	36				823.40	824.3	Single isomer
965		1.100	40				802.40	803.4	Single isomer
966		1.000	89	52.7	0.760	84.7	805.30	807.3	Mixture of isomers
967		0.010	0.13	0.2	0.006	0.9	919.40	920.3	Mixture of isomers
968		> 1	> 100	> 100	> 1	> 100	843.30	NA	Single isomer

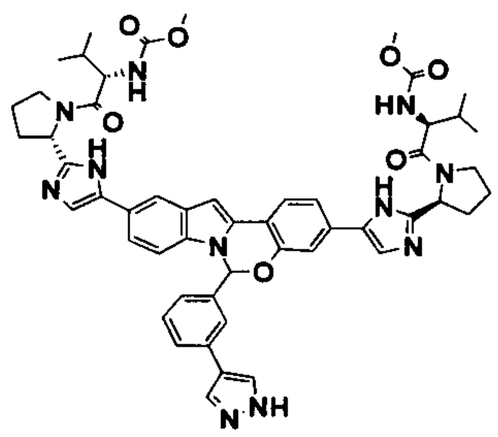
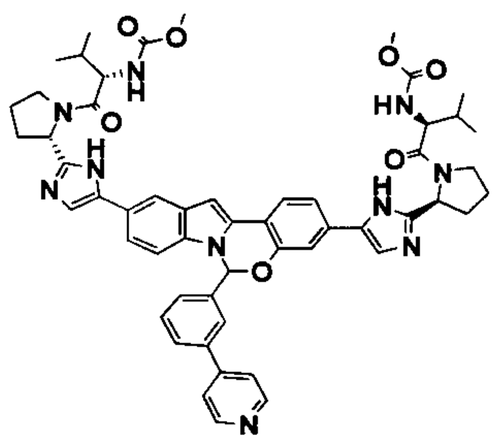
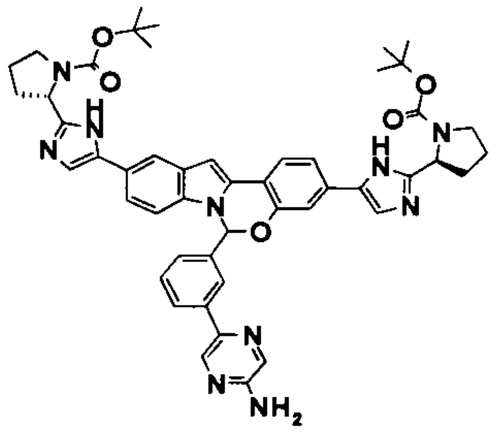
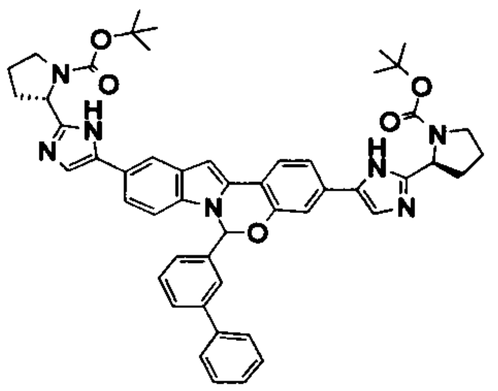
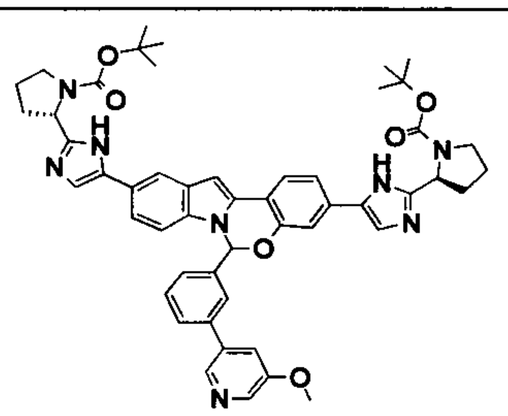
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
969		> 1	> 100	> 100	> 1	> 100	843.30	NA	Single isomer
970		0.016	0.3	> 100	0.009	0.315	921.30	921.2	Mixture of isomers
971		0.010	8	37	0.015	76.656	946.50	947.5	Single isomer
972		0.467	> 100	< 100	0.146	< 100	846.40	847.4	Single isomer

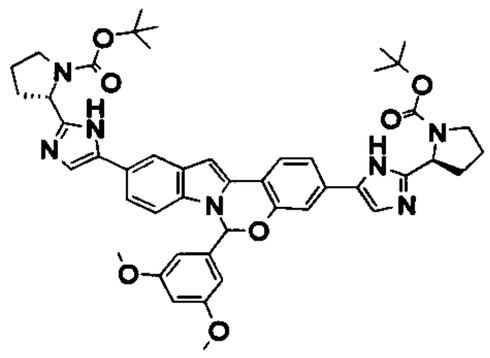
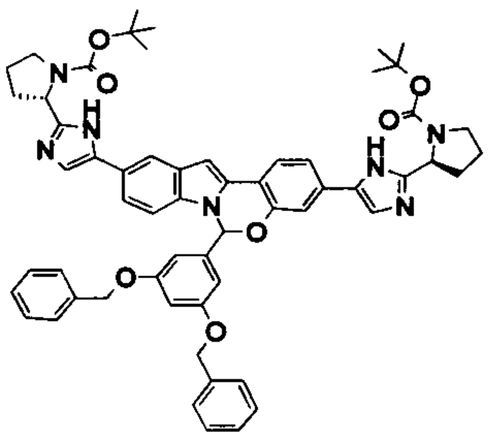
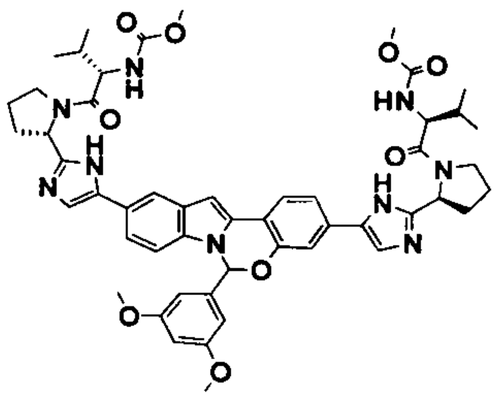
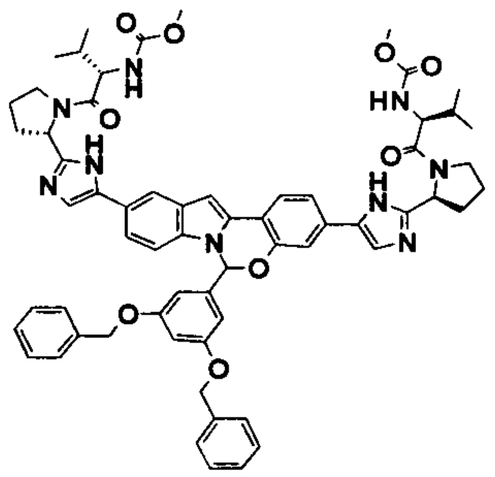
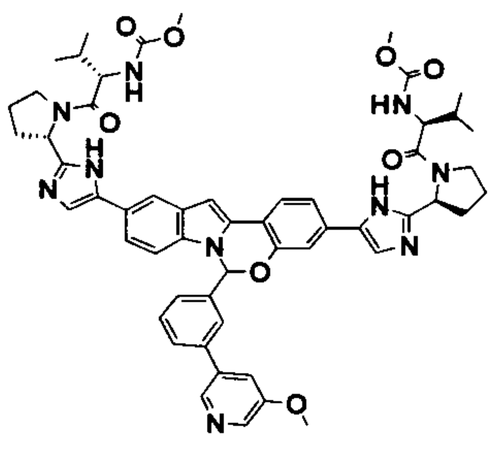
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
973		0.009	43.48	4.3	0.007	21.9	837.40	838.4	Single isomer
974		0.057	109.9	20.563	0.013	110	837.40	838.4	Single isomer
975		0.020		3	0.008	50.2	1000.40	1001.4	Single isomer
976		0.007	2.7	0.2	0.005	2.3	964.40	965.4	Mixture of isomers
977		0.018		1	0.009	2.1	887.40	888.4	Mixture of isomers

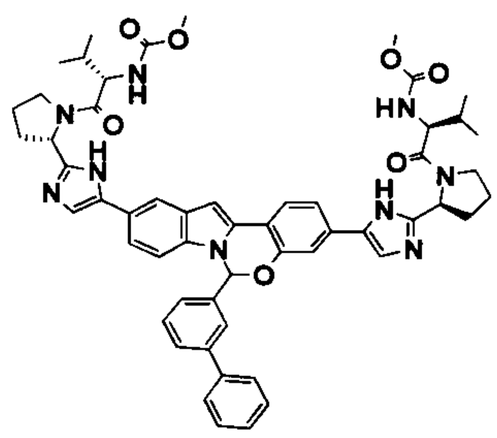
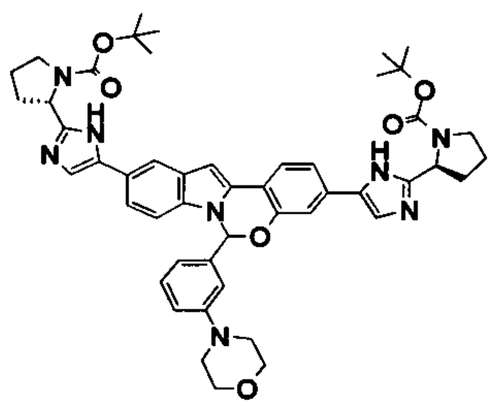
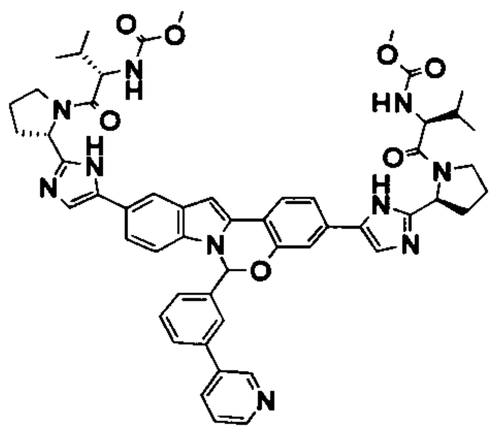
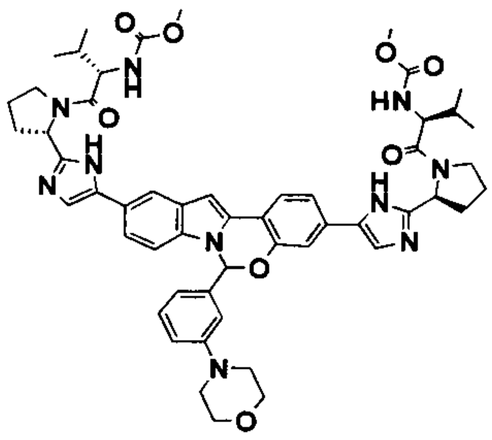
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
978							923.40	NA	Single isomer
979		0.029	0.383	0.294		3.2	1041.30	1045.1	Single isomer
980							1000.40	1002.1	Single isomer
981							923.40	924.2	Single isomer
982		81.700	167.19	161.6		297.56	839.30	842.1	Single isomer

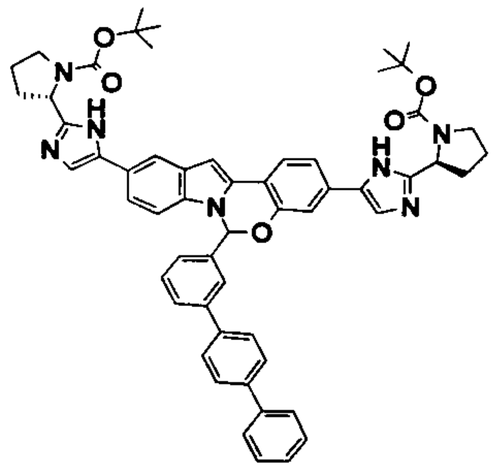
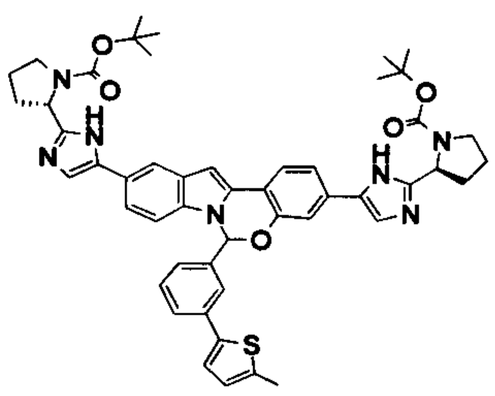
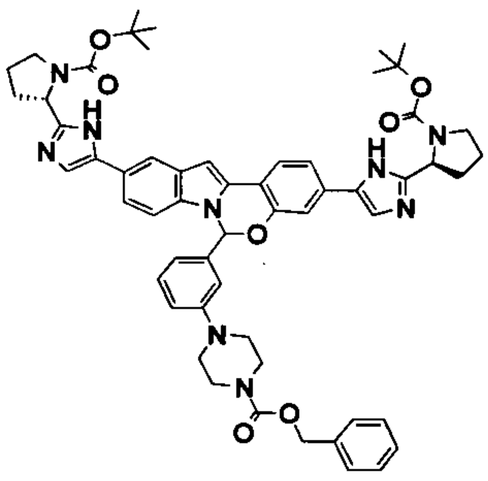
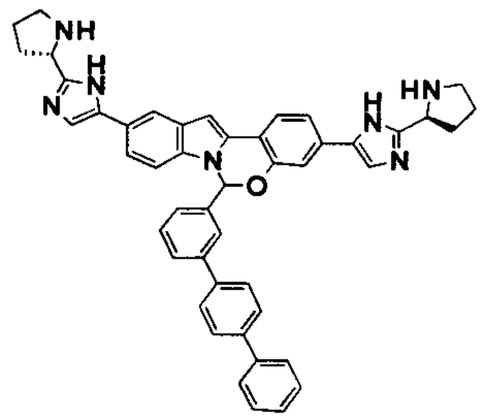
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
983		0.026	0.49	8.1	0.001	67	966.40	966.0	Mixture of isomers
984		0.006	29.88	0.7	0.002	57	930.40	930.0	Mixture of isomers
985		0.003	8	1	0.002	15	896.40	896.5	Mixture of isomers
986		0.003	20.8	0.27	0.001	6.2	946.40	946.2	Mixture of isomers
987		0.004	8.8	0.8	0.004	1.9	912.40	912.4	Mixture of isomers
988		> 10	275.009	35.1221	> 2	156.107	802.40	802.4	Mixture of isomers

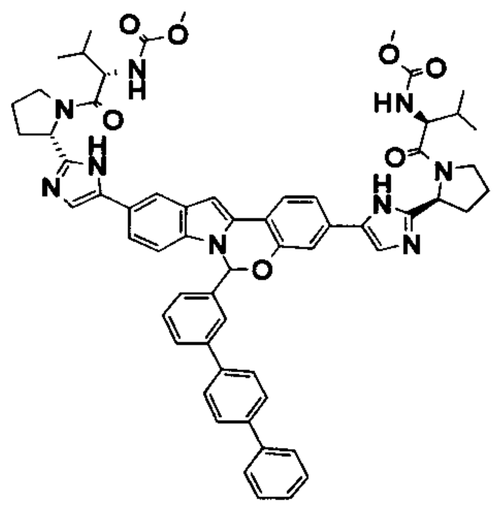
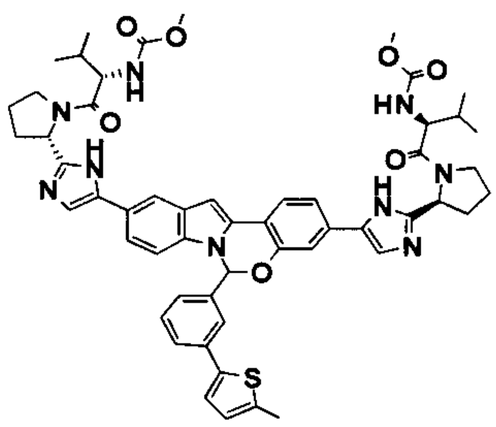
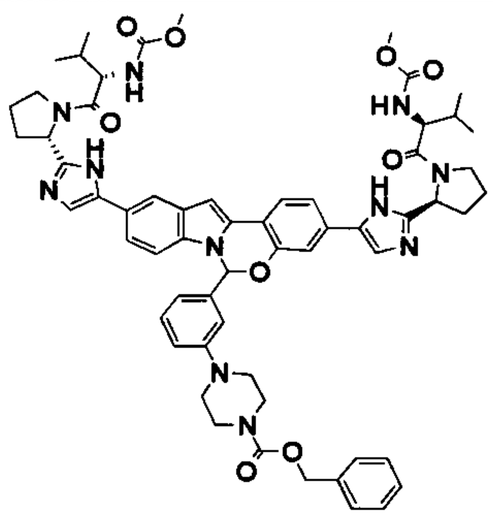
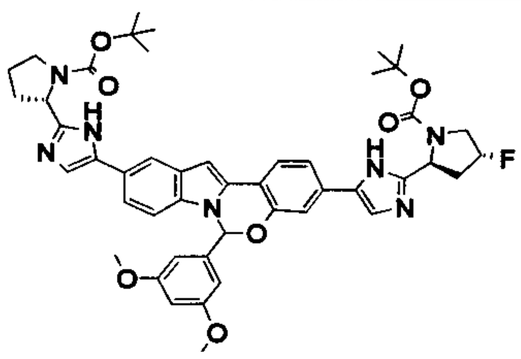
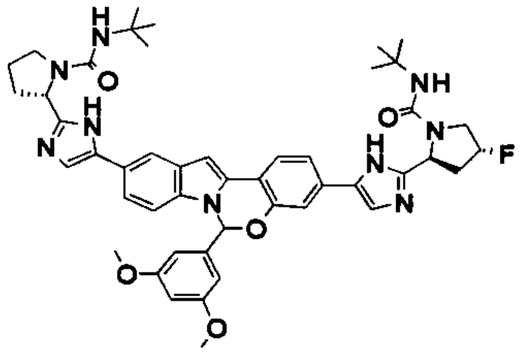
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
989		16.000	95.7794	77.0776	> 2		845.40	845.4	Mixture of isomers
990		143.510	1000	544.35	23.770	456	834.40	834.4	Mixture of isomers
991		98.590	1000	412.46	21.370	374	860.40	860.4	Mixture of isomers
992		349.000	> 5000				645.30	645.3	Mixture of isomers
993		3.000	> 5000				660.30	660.3	Mixture of isomers
994		1.950	10.44	1.95	0.200	2	974.50	974.7	Mixture of isomers

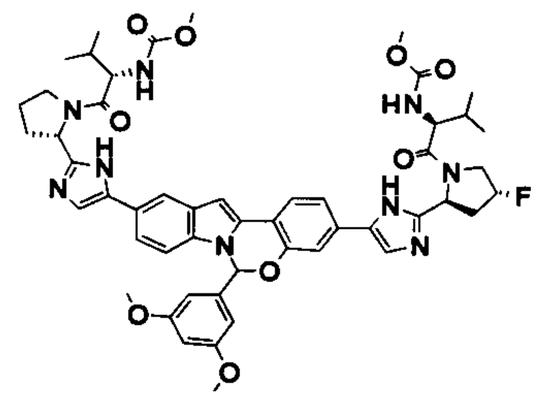
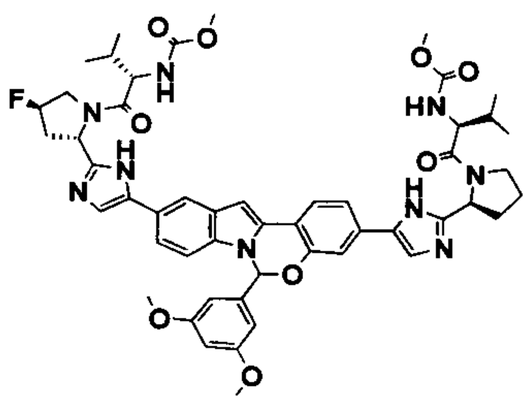
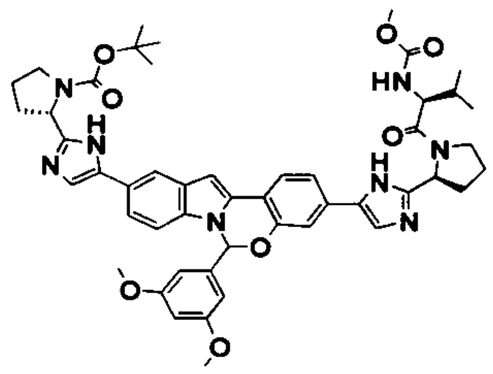
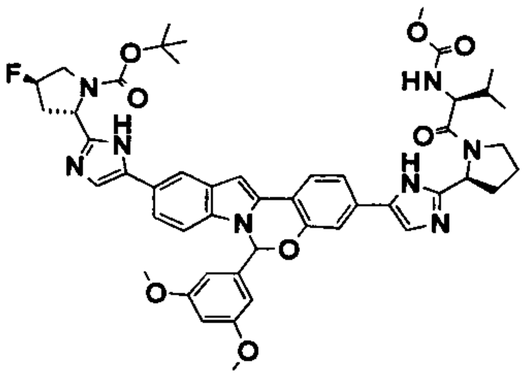
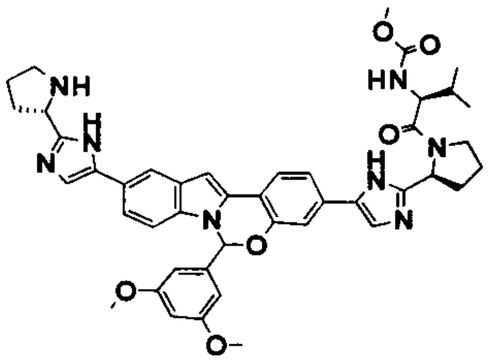
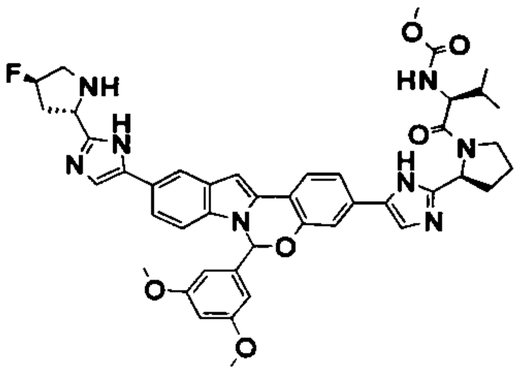
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
995		0.010	>100	10		24.8	948.40	948.3	Mixture of isomers
996		0.007	40	10		9.8	959.50	959.4	Mixture of isomers
997		139.157	3562.44				861.40	861.3	Mixture of isomers
998		3.900	52.94	27	0.218	> 100	844.40	844.4	Mixture of isomers
999		325.000	> 5000				875.40	875.4	Mixture of isomers

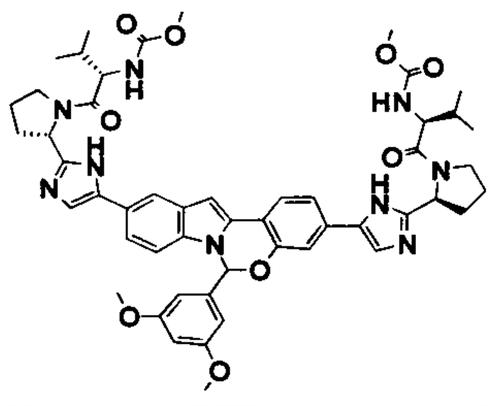
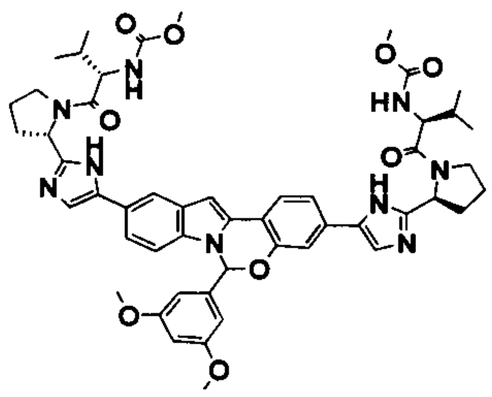
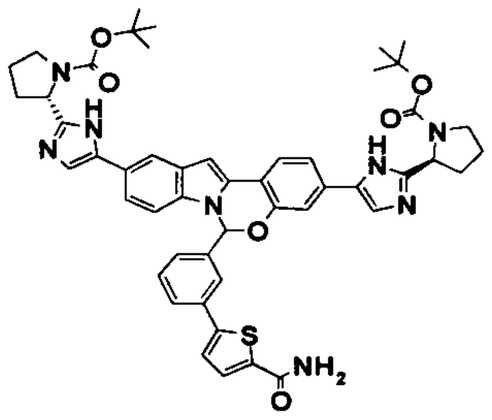
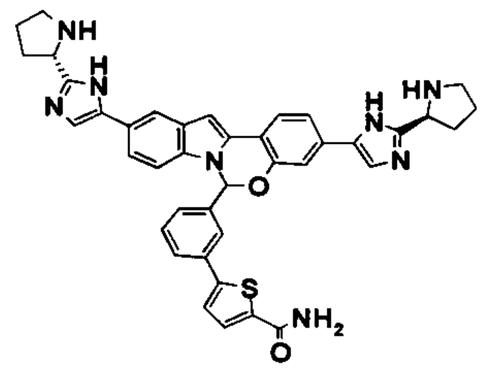
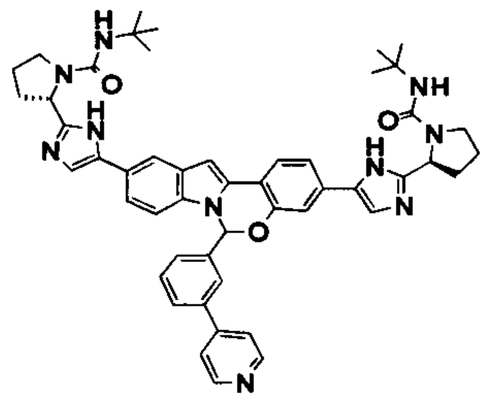
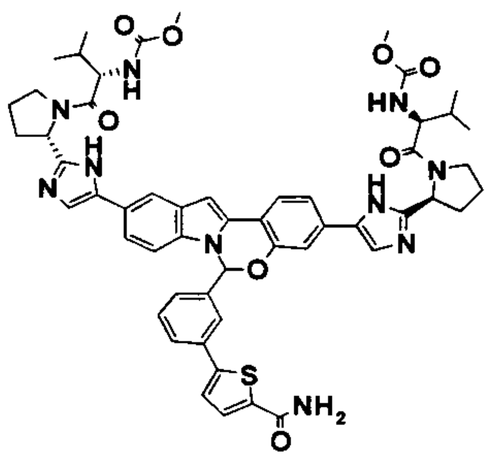
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1000		189.210	1230.32				828.40	828.3	Mixture of isomers
1001		592.717	> 20000				981.50	981.4	Mixture of isomers
1002		0.004	1.48		0.005	0.3	942.40	942.4	Mixture of isomers
1003		0.007	2.76	0.5	0.005	11.9	1094.50	1094.5	Mixture of isomers
1004		0.003	0.19	2	0.003	12.9	989.50	989.4	Mixture of isomers

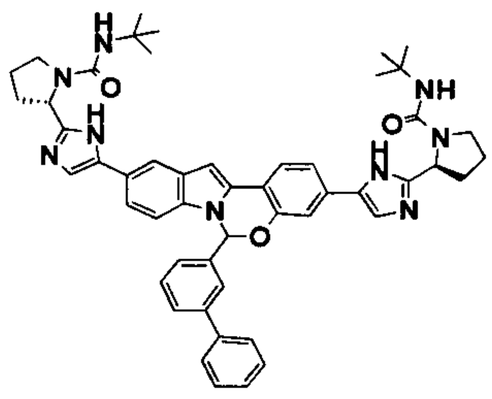
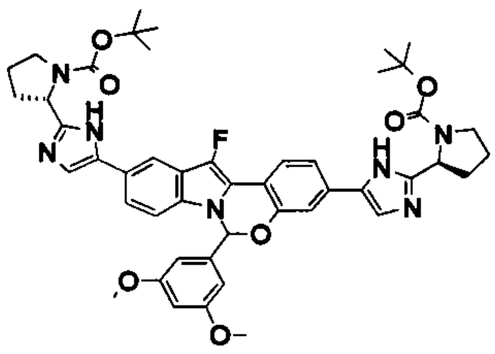
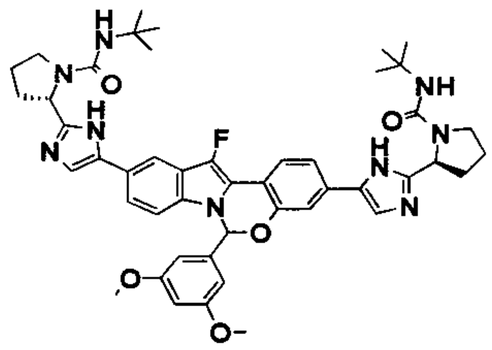
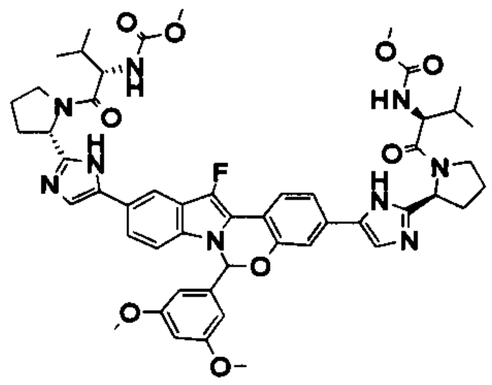
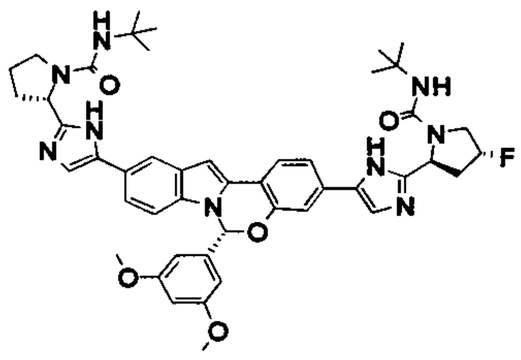
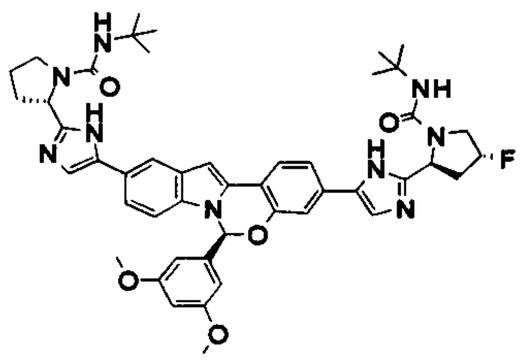
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1005		0.003	7.89	0.3	0.004	1	958.50	958.5	Mixture of isomers
1006		230.000	> 20000				853.40	853.3	Mixture of isomers
1007		0.006	25.94	0.2	0.008	7.6	959.50	959.5	Mixture of isomers
1008		0.004	52.2	0.3	0.006	16.869	967.50	967.5	Mixture of isomers

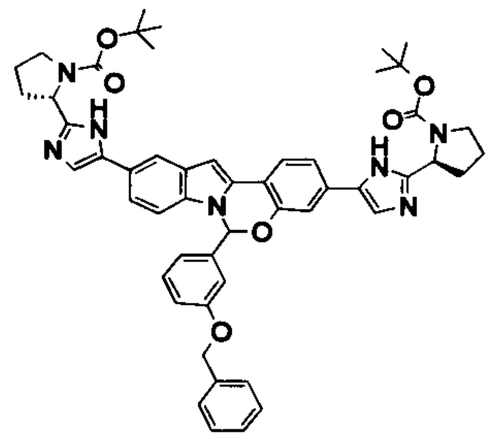
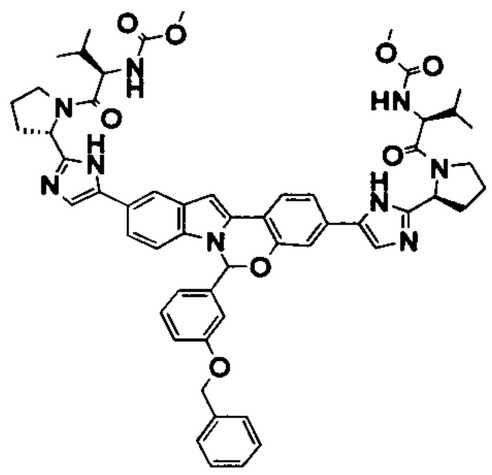
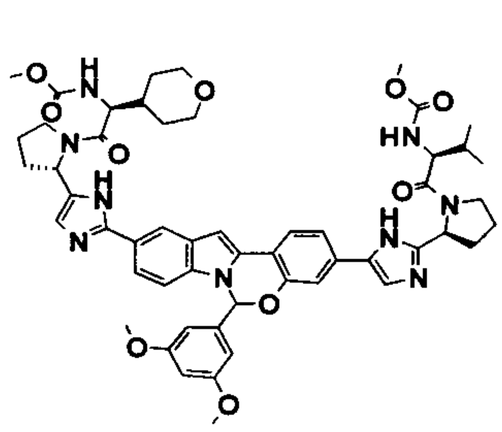
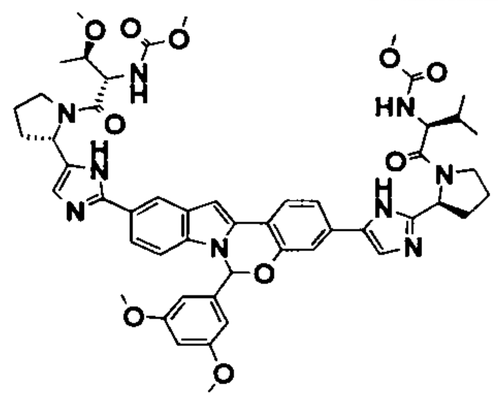
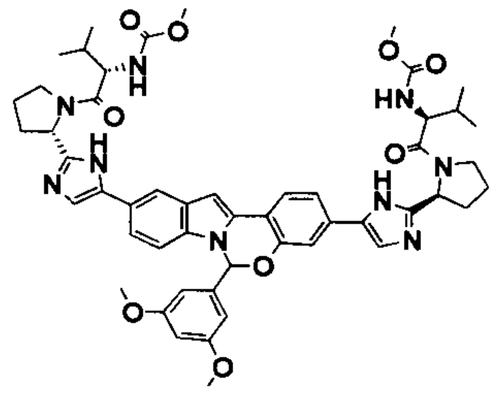
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1009							920.40	920.4	Mixture of isomers
1010							864.40	864.1	Mixture of isomers
1011							986.50	986.1	Mixture of isomers
1012							720.30	720.1	Mixture of isomers

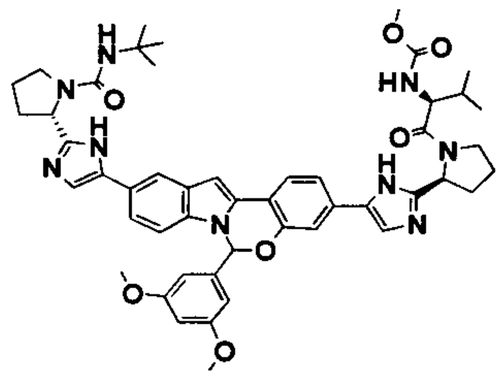
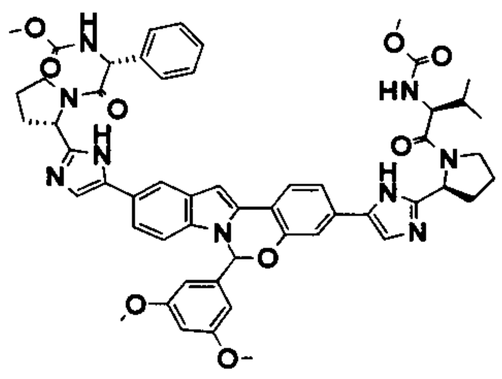
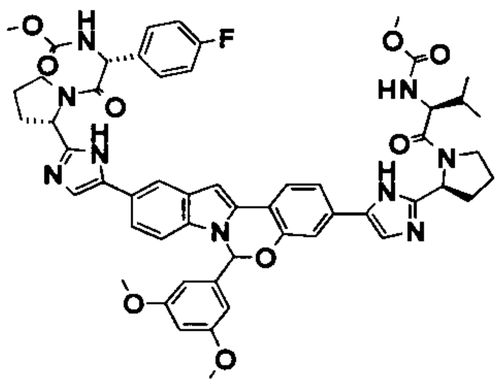
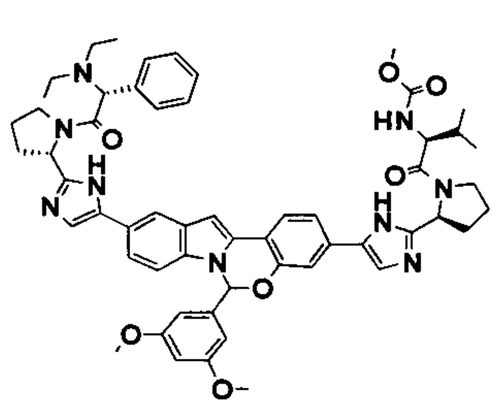
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1013		0.006	2.1	0.256	0.003	3.3	1034.50	1034.5	Mixture of isomers
1014		0.003	2.3	0.2	0.002	2.2	978.40	978.4	Mixture of isomers
1015		0.004	32.2	0.21	0.005	6.8	1100.50	1100.5	Mixture of isomers
1016		225.000	1390				846.40	846.4	Mixture of isomers
1017		0.274	1.63	1	0.129	21.3	844.40	844.5	Mixture of isomers

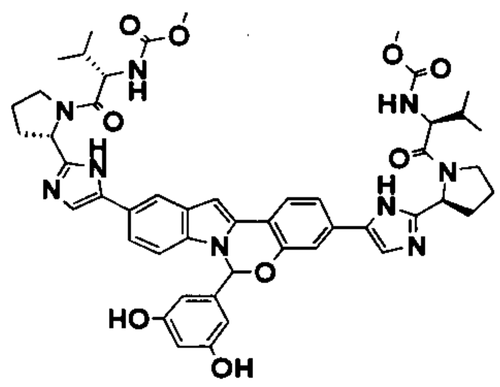
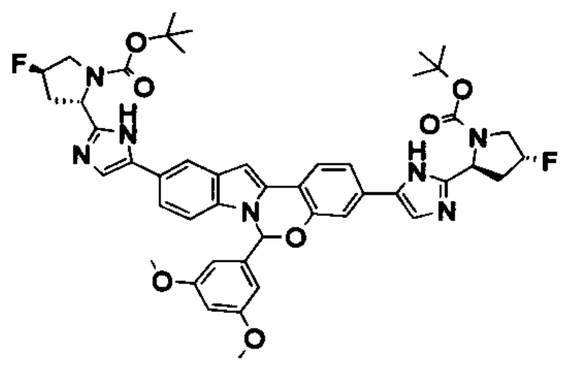
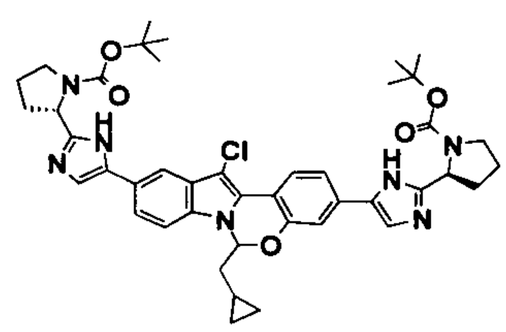
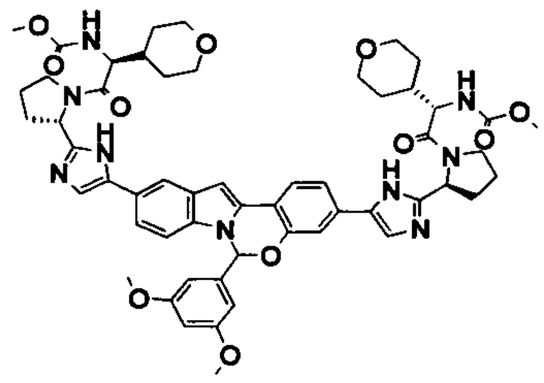
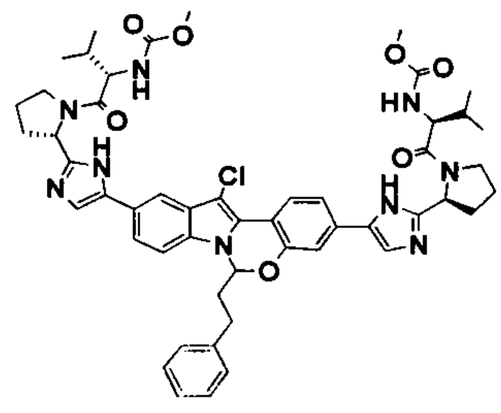
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1018		0.007	0.69		0.004	7	960.40	960.5	Mixture of isomers
1019		0.006	1.17	0.497	0.006	0.512	960.40	960.5	Mixture of isomers
1020		1.111	403.99				885.40	885.4	Mixture of isomers
1021		2.045	520.8				903.40	903.5	Mixture of isomers
1022		7.490	1228.75				785.40	785.4	Mixture of isomers
1023		2.836	700.87				803.40	803.4	Mixture of isomers

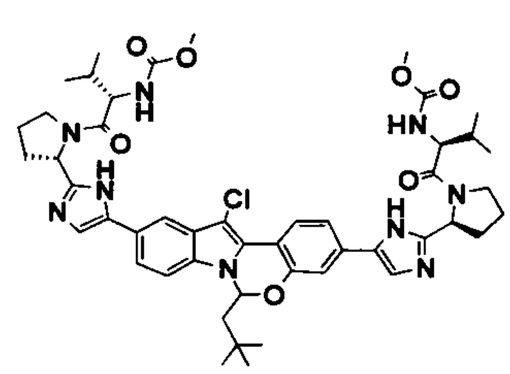
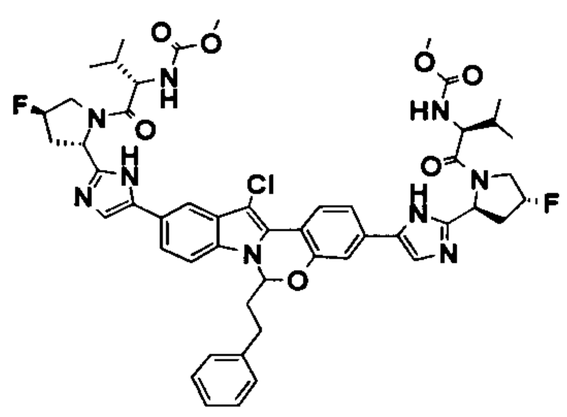
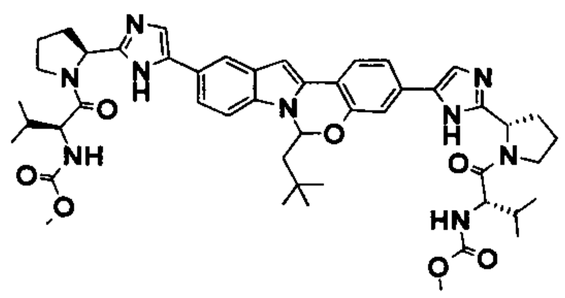
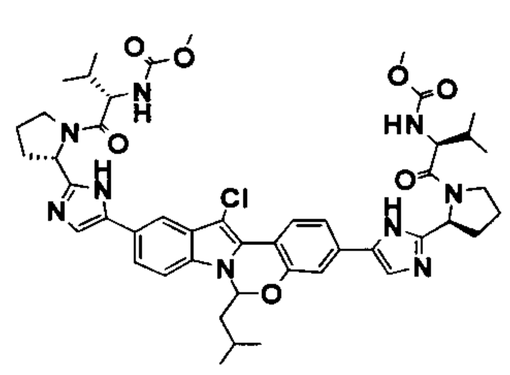
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1024		0.003	25.32	0.2	0.003	4.1	942.40	942.5	Single isomer
1025		0.003	0.68	0.31	0.002	0.2	942.20	942.2	Single isomer
1026		16.000	443				893.40	893.5	Mixture of isomers
1027							693.30	693.3	Mixture of isomers
1028		> 1	> 100	> 100	> 1	> 100	843.40	843.5	Mixture of isomers
1029		0.004	3.17	1	0.008	3.8	1007.40	1007.2	Mixture of isomers

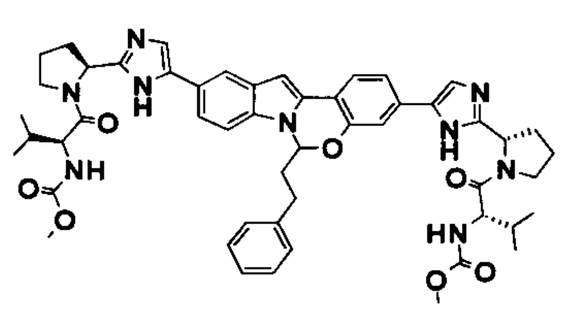
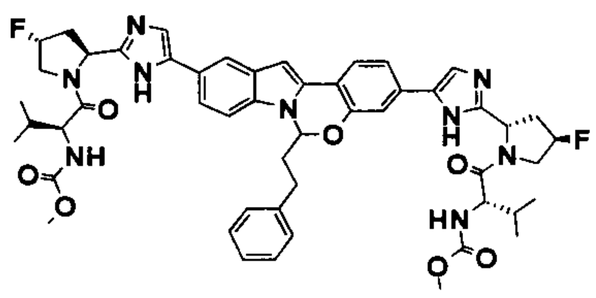
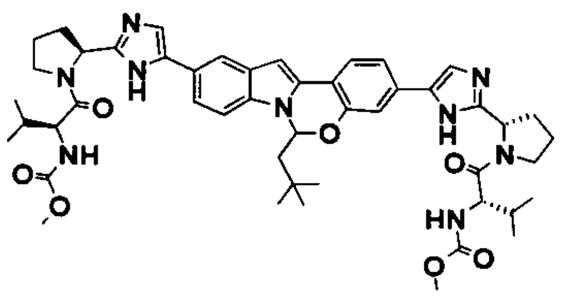
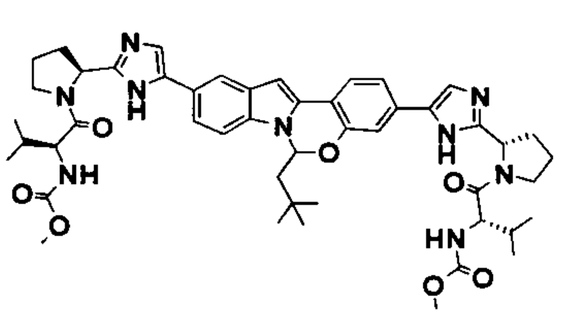
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1030		> 1	> 100	> 100	> 1	> 100	842.40	842.5	Mixture of isomers
1031		199.700	606				846.40	846.4	Mixture of isomers
1032		1.000	> 100	> 100	1.000	> 100	844.40	844.5	Mixture of isomers
1033		0.006	2	0.2	0.005	0.7	960.40	960.5	Mixture of isomers
1034		0.030	82	13	> 1	51.11	844.40	844.5	Single isomer
1035		0.247	11		0.066	6.15	844.40	844.4	Single isomer

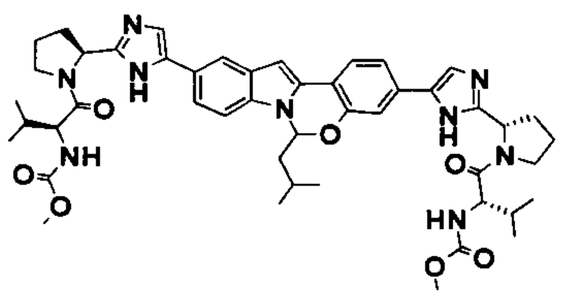
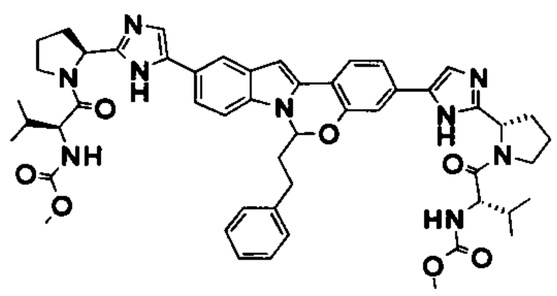
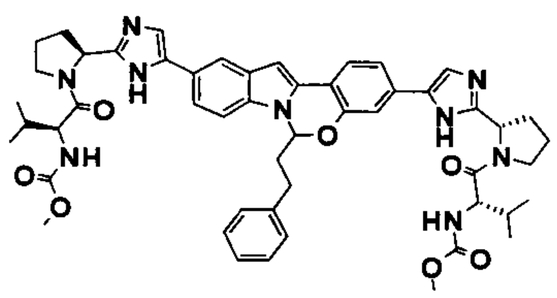
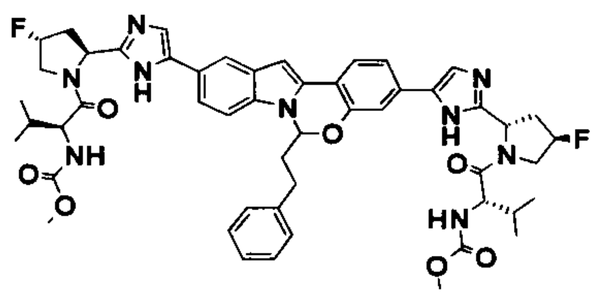
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1036		219.000	628				874.40	874.5	Mixture of isomers
1037		0.010	3.2		0.005	10.4	988.50	988.5	Mixture of isomers
1038		0.024	0.4		0.009	0.2	984.50	984.5	Mixture of isomers
1039		0.009	12.1		0.007	0.6	958.40	958.5	Mixture of isomers
1040							942.40	942.2	Mixture of isomers

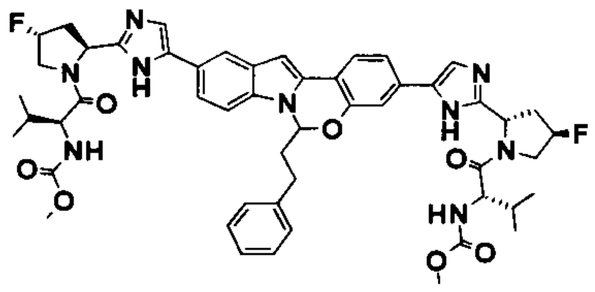
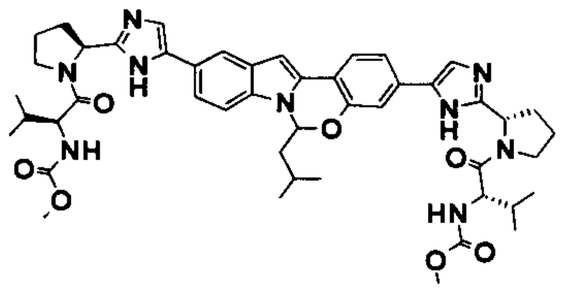
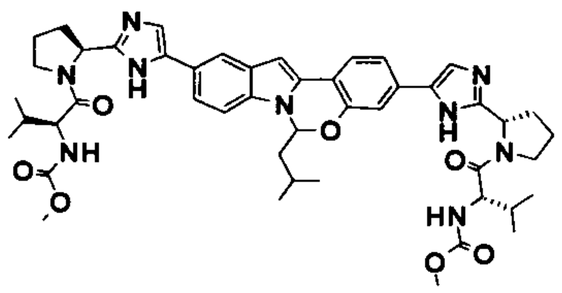
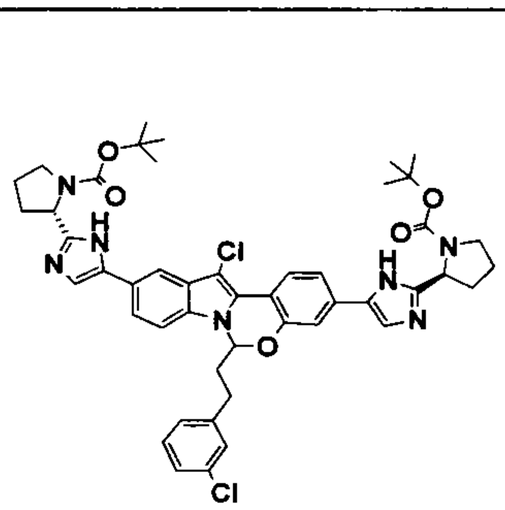
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1041			>100	39		74	884.40	884.2	Mixture of isomers
1042		0.020	58	0.96		19.80.	976.40	976.2	Mixture of isomers
1043		0.022	72.2	0.28			994.40	994.3	Mixture of isomers
1044		0.024	3.5	<0.195		<0.195	974.50	974.2	Mixture of isomers

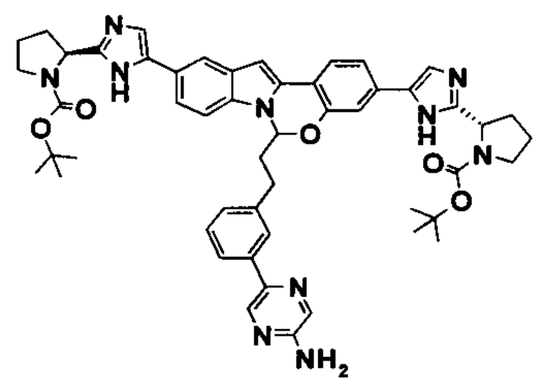
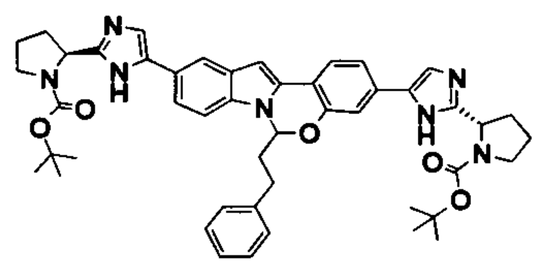
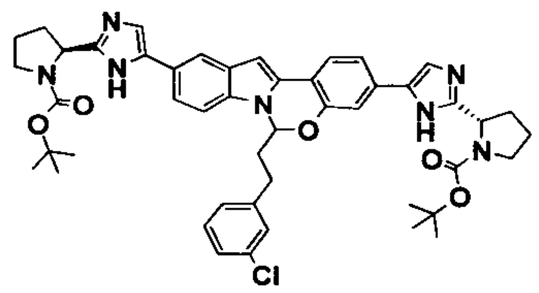
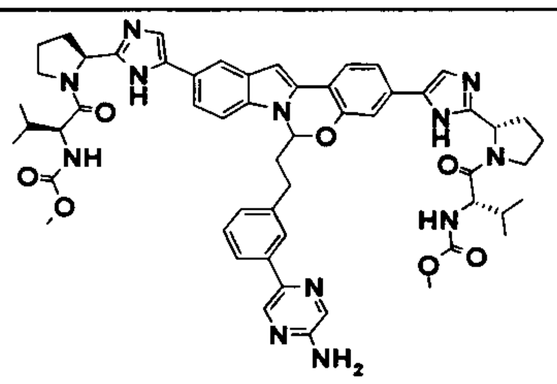
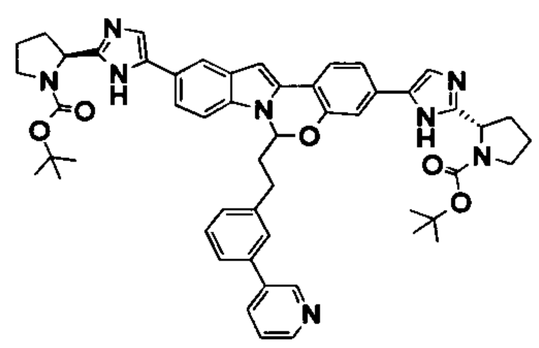
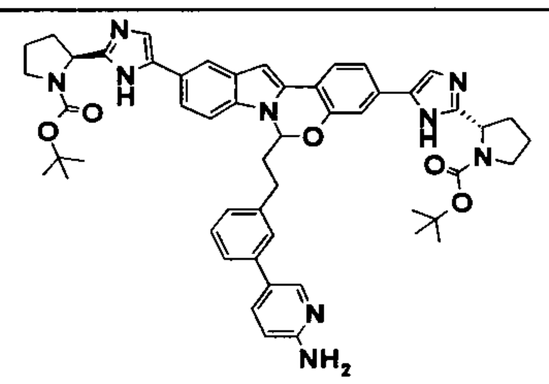
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1045		>1	>100	7.2		>100	914.40	914.4	Mixture of isomers
1046		330.000	325				864.40	864.3	Mixture of isomers
1047		319.000	527				780.40	780.3	Mixture of isomers
1048		0.030	0.43	0.03		0.13	1026.50	1026.6	Mixture of isomers
1049		0.004	10.5	1.1	0.001	21	944.50	944.5	Mixture of isomers

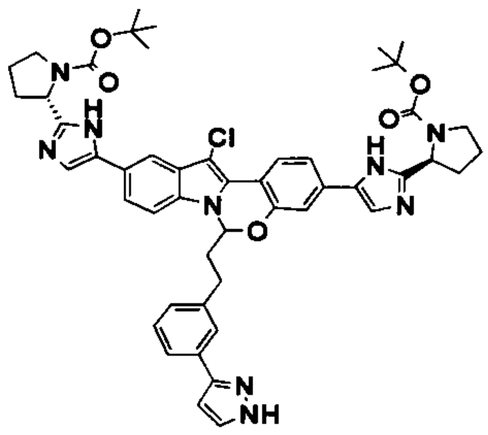
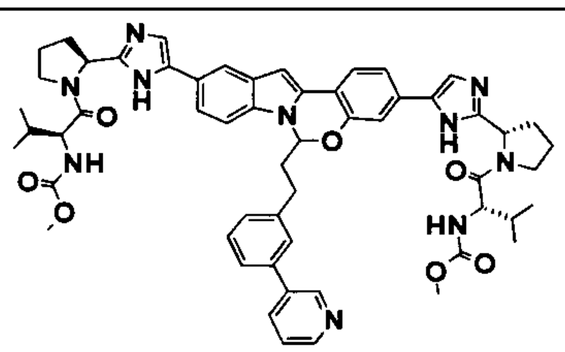
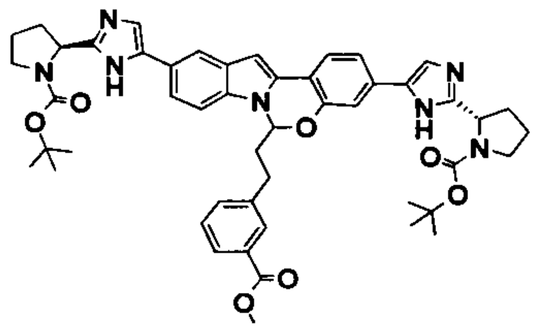
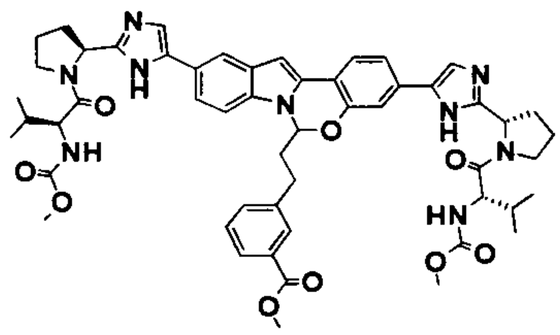
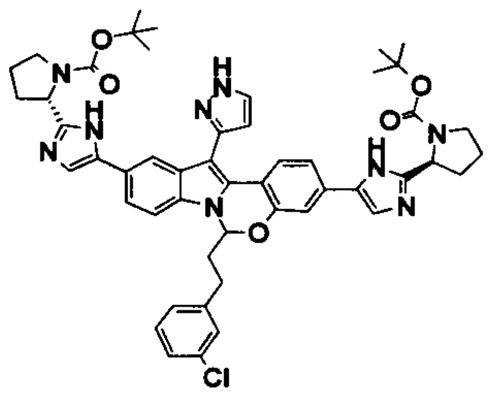
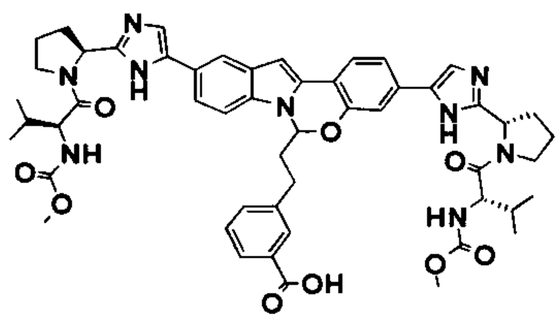
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1050		0.039	< 100	12	0.003	113	910.50	910.4	Mixture of isomers
1051		0.030	0.4	9	0.001	129	980.50	980.4	Mixture of isomers
1052		0.007	48	5.5	0.001	85	876.50	876.8	Mixture of isomers
1053		0.005	37.5	1.1	0.001	19	896.40	896.0	Mixture of isomers

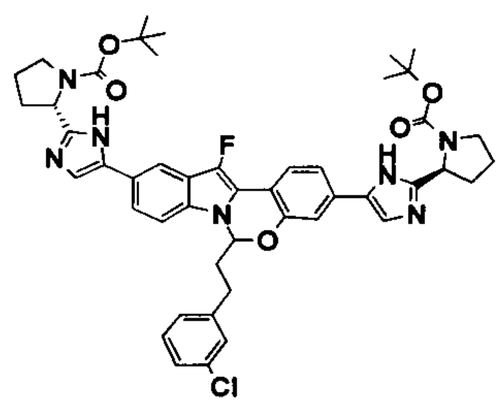
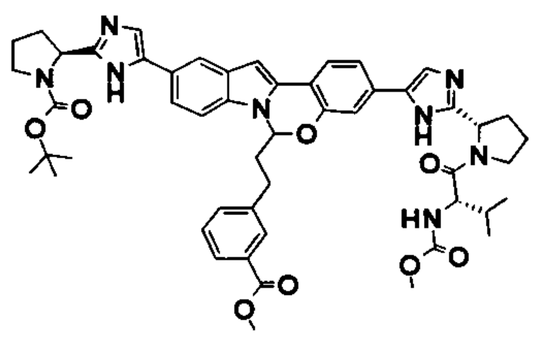
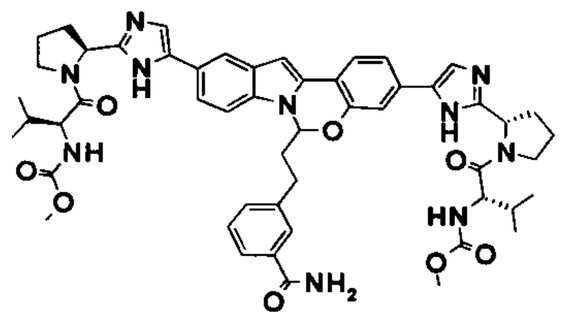
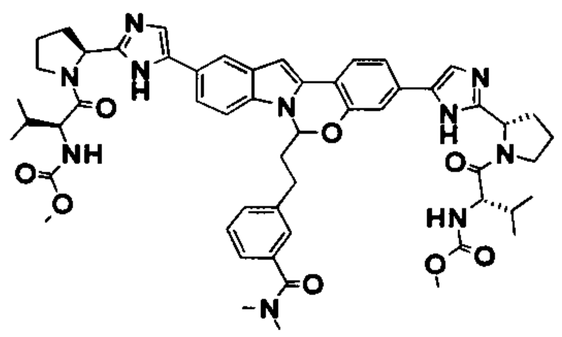
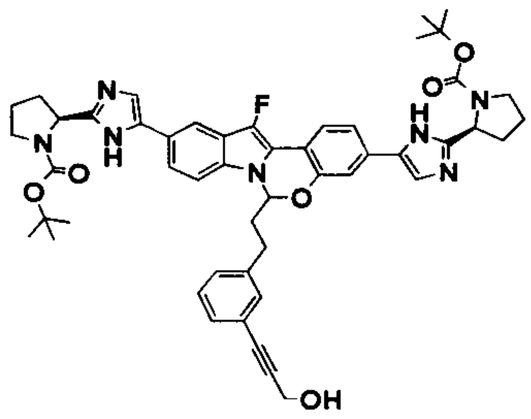
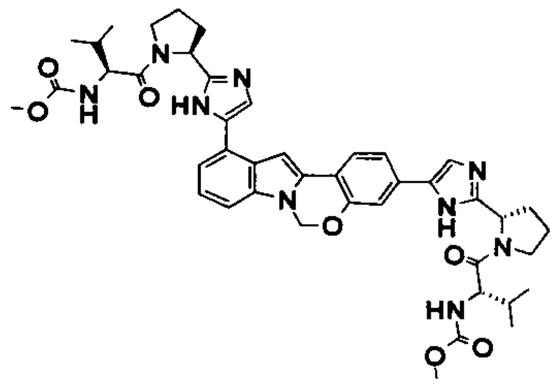
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1054		0.001	2.1	0.8	0.000	50.6	910.50	910.5	Mixture of isomers
1055		0.002	0.2	11	0.001	12	946.40	946.4	Mixture of isomers
1056		0.020	52.58	1.3	0.001	15	876.50	876.5	Single isomer
1057		0.004	5.11	2.5	0.002	81	876.50	876.5	Single isomer

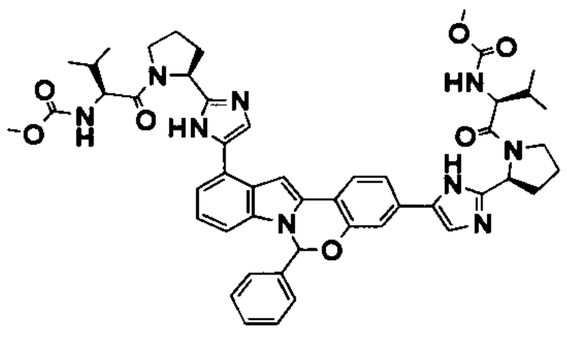
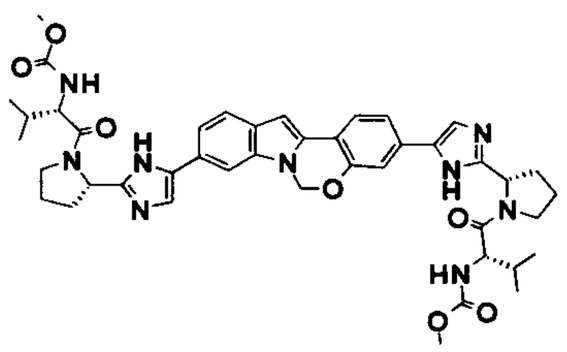
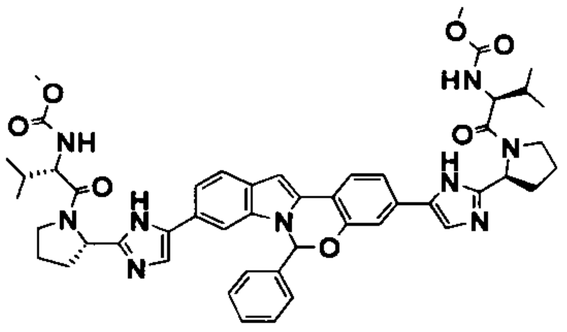
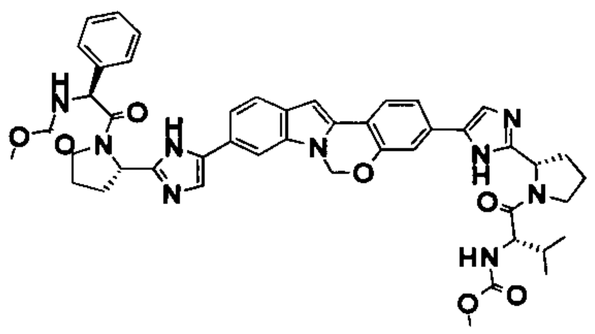
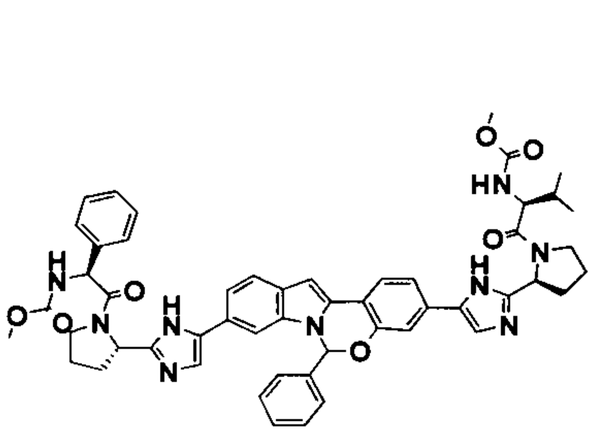
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1058		0.001	10.73	0.771	0.001	10	862.50	862.5	Mixture of isomers
1059		0.003	27	1	0.001	2	910.50	910.5	Single isomer
1060		0.002	1.5	0	0.001	2	910.50	910.5	Single isomer
1061		> 0.2	0.8	25	0.001	15	946.40	946.5	Single isomer

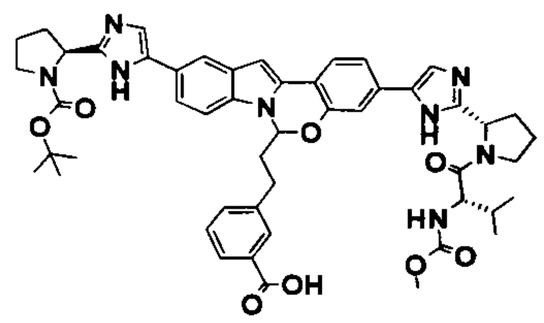
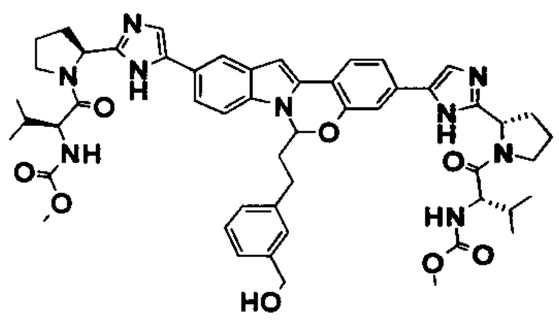
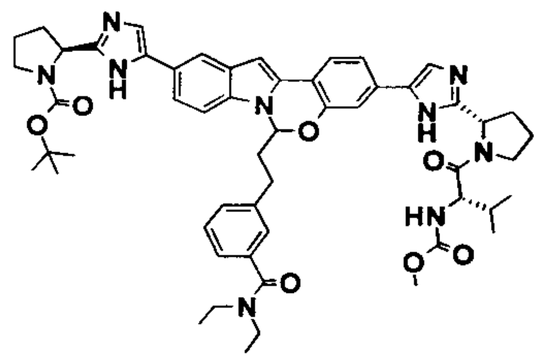
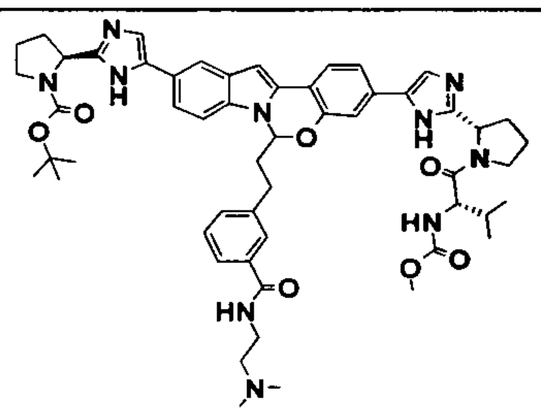
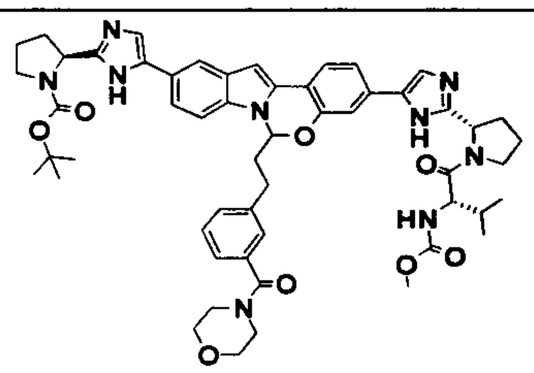
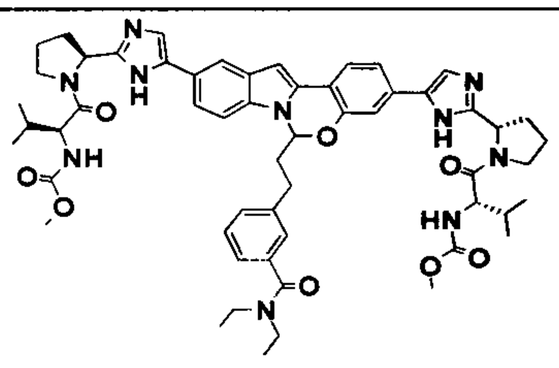
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1062		0.003	0.19	7	0.001	45	946.40	946.5	Single isomer
1063		0.010	90.3	4.85	0.001	11.1	862.50	862.5	Single isomer
1064		0.000	67.2	1.32	0.000	10.9	862.50	862.5	Single isomer
1065		130.383	494.969				864.30	864.2	Mixture of isomers

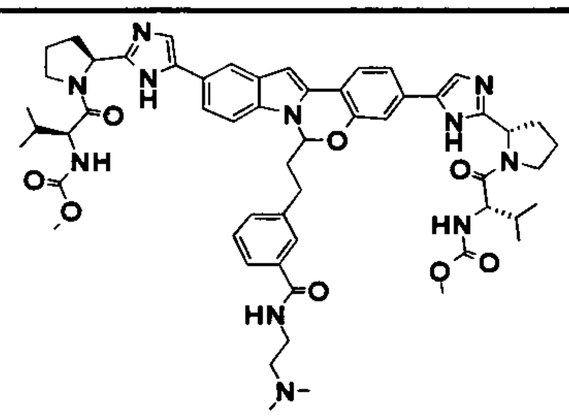
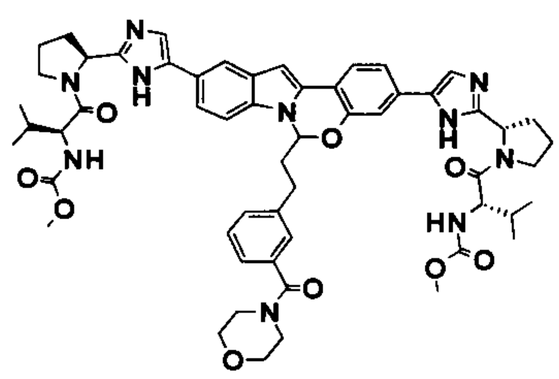
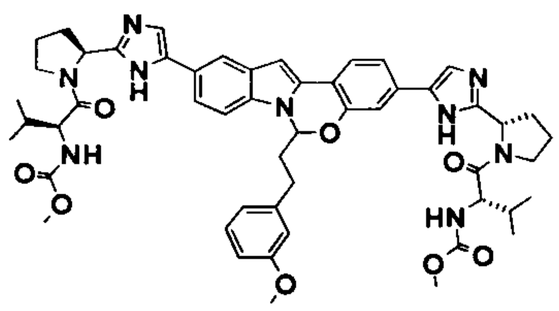
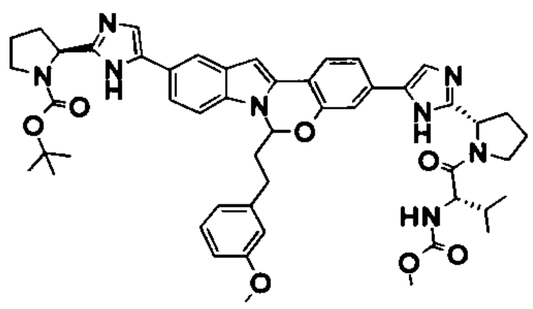
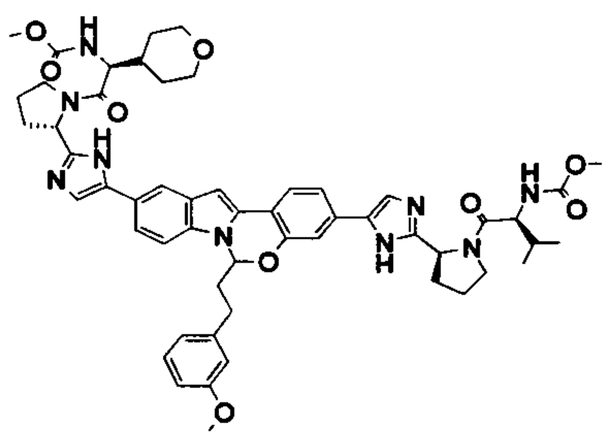
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1066		> 10	> 1000	> 1000	> 2	423.891	889.40	889.5	Mixture of isomers
1067		> 10	> 1000	> 1000	> 2	> 1000	796.40	796.4	Mixture of isomers
1068		> 10	415.367	> 1000	> 2	> 1000	830.40	830.3	Mixture of isomers
1069		1.950	13.99	1.95	0.200	2	1003.50	1003.2	Mixture of isomers
1070		> 2	4508	978		1179.3	873.40	873.4	Mixture of isomers
1071		> 2	4801	1681		1342.2	888.50	888.4	Mixture of isomers

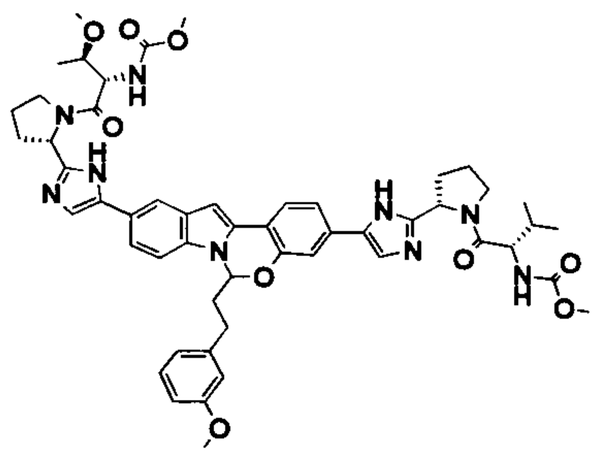
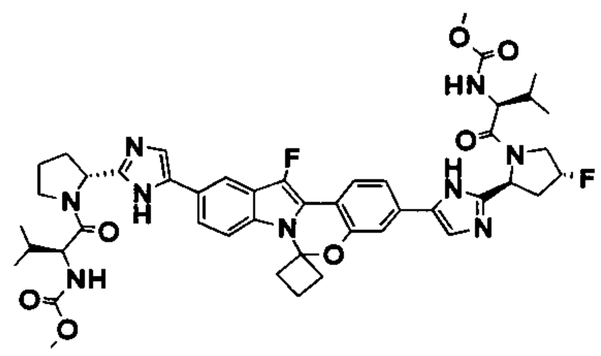
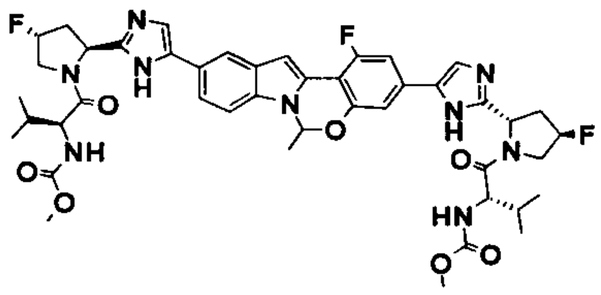
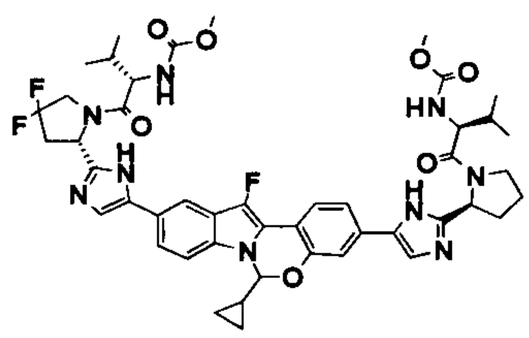
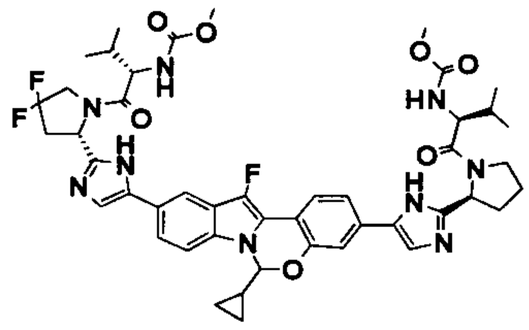
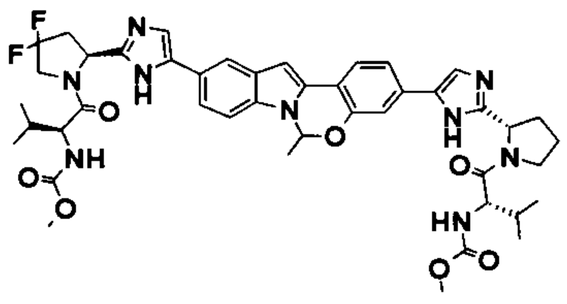
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1072		7.301	642.739				896.40	896.3	Mixture of isomers
1073		0.006	19	9.11	0.005	9	987.50	987.4	Mixture of isomers
1074		267.000	777.33				854.40	854.3	Mixture of isomers
1075		0.008	36.28	148.08	0.003	> 5000	968.50	968.4	Mixture of isomers
1076		27.260	45.888				898.20	898.2	Mixture of isomers
1077		0.628	> 200	200	> 2	200	955.50	955.3	Mixture of isomers

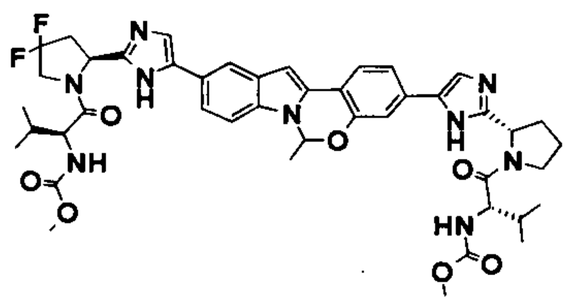
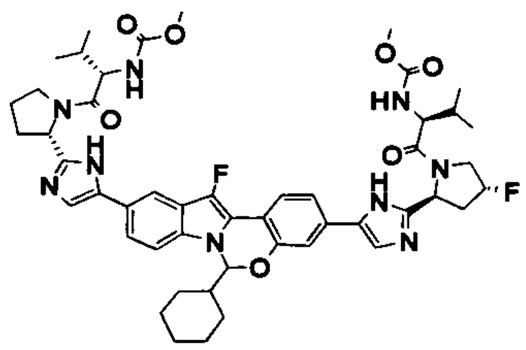
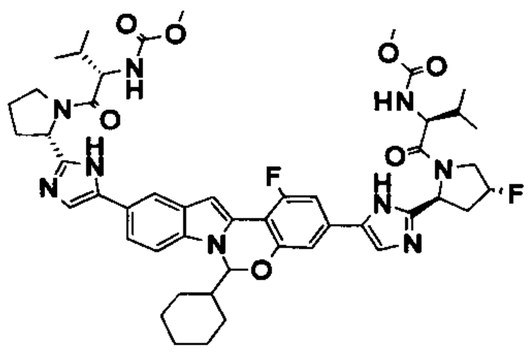
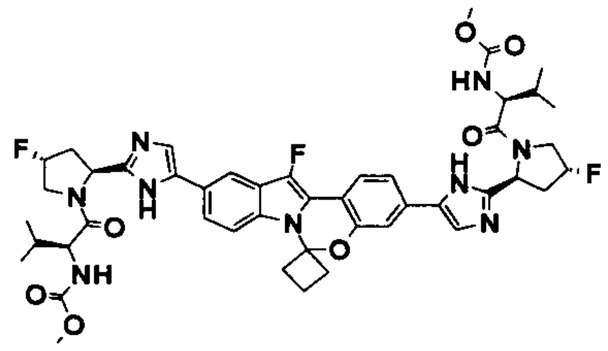
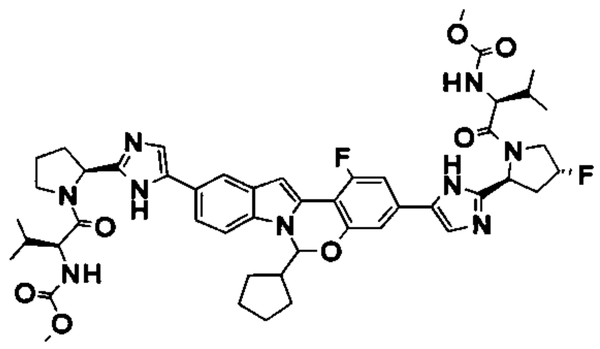
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1078		455.503	1819.04				848.40	848.3	Mixture of isomers
1079		156.944	831.55				911.40	911.4	Mixture of isomers
1080		0.061	> 200	10.5	0.009	14	953.50	953.4	Mixture of isomers
1081		0.010	87.6	4.6	0.015	2.1	981.50	981.2	Mixture of isomers
1082		33.936	30.1				868.40	868.1	Mixture of isomers
1083		1.000	> 100	> 100	1.000	> 100	806.40	806.4	Mixture of isomers

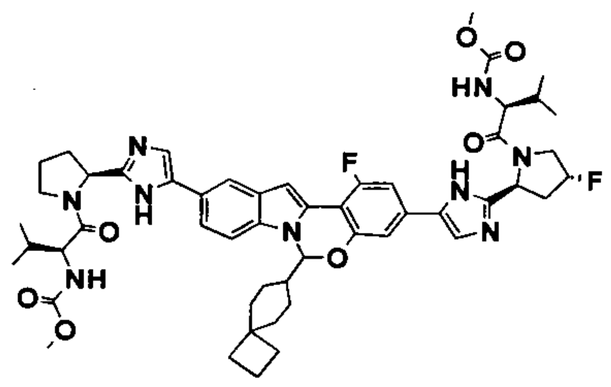
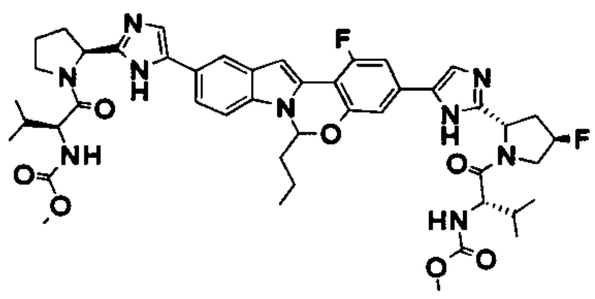
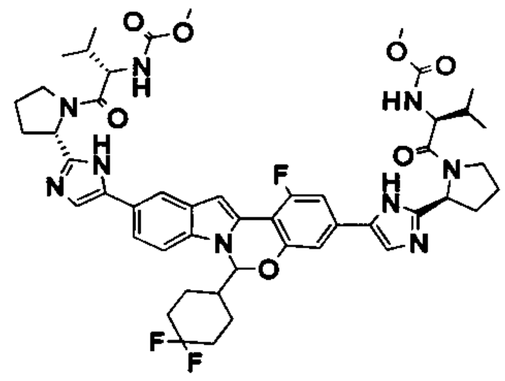
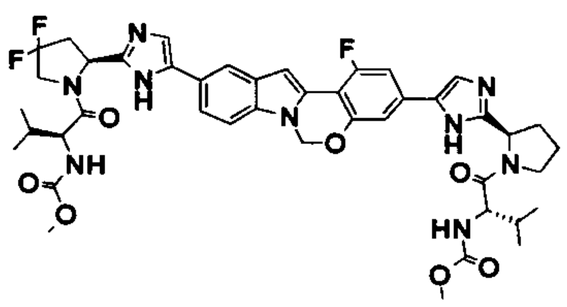
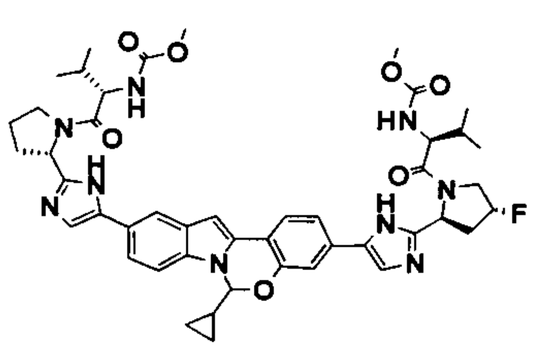
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1084		1.000	> 100	97	0.188	97.3	882.40	882.5	Mixture of isomers
1085		1.000	> 100	> 100	0.159	> 100	806.40	806.7	Mixture of isomers
1086		0.074	> 100	45.5	0.010	22.24	882.40	882.7	Mixture of isomers
1087		0.478	> 100	> 100	0.430	> 100	841.40	841.3	Mixture of isomers
1088		0.417	> 100	94	0.237	> 100	916.40	916.4	Mixture of isomers

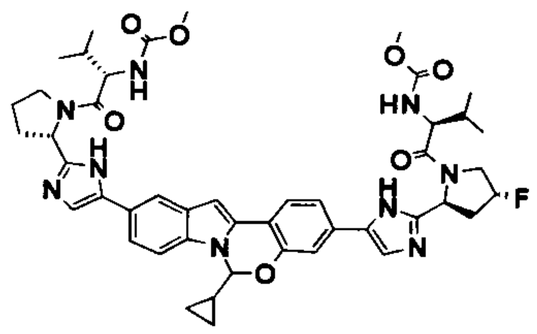
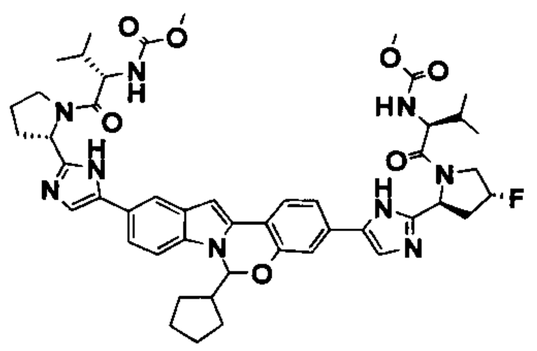
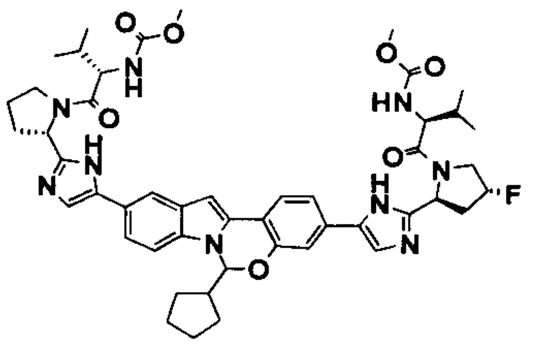
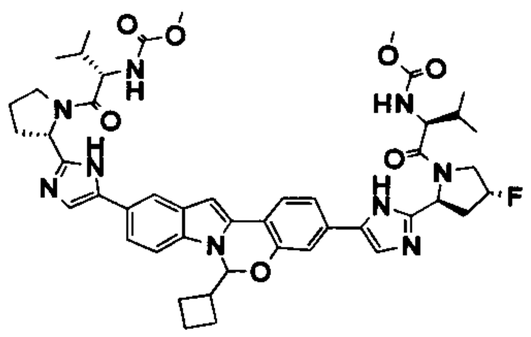
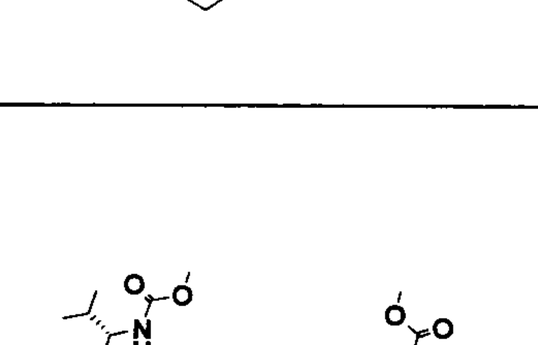
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1089		194.000	2153				897.40	897.4	Mixture of isomers
1090		0.028	5.99	2.9	0.011	9.181	940.50	940.5	Mixture of isomers
1091			549				952.50	952.5	Mixture of isomers
1092		409.900	2306				967.50	967.5	Mixture of isomers
1093		74.178	1252				966.50	966.2	Mixture of isomers
1094		0.013	21	2.7	0.013	2.2	1009.50	1009.5	Mixture of isomers

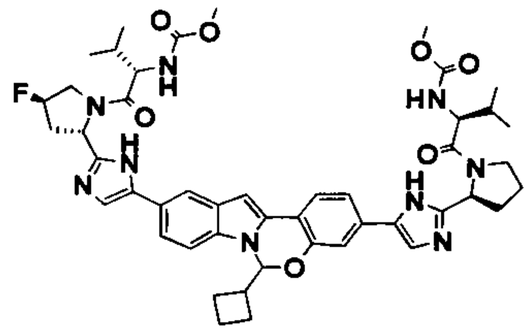
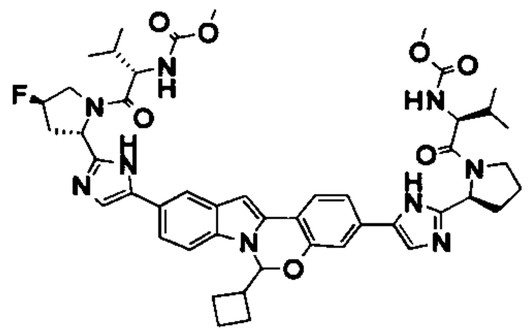
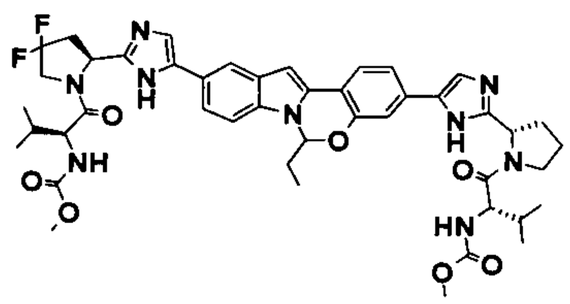
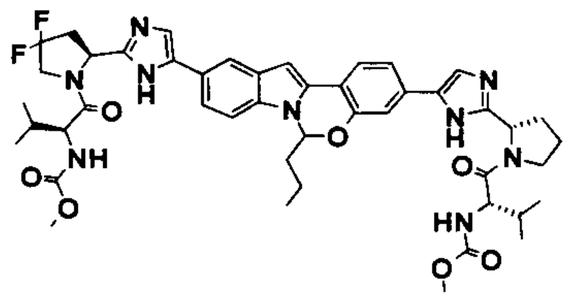
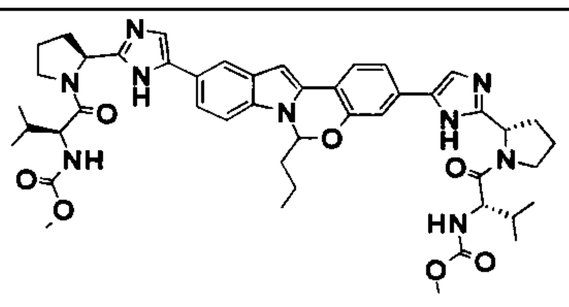
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1095		0.041	> 100	2.8	0.016	2.1	1024.50	1024.5	Mixture of isomers
1096		1.000	> 100	77.9	0.127	> 100	1024.50	1024.5	Mixture of isomers
1097		0.008	> 100	0.8	0.005	6.9	940.50	940.5	Mixture of isomers
1098		2.020	196				883.40	883.5	Mixture of isomers
1099		0.012	3.2			0	983.50	983.4	Mixture of isomers

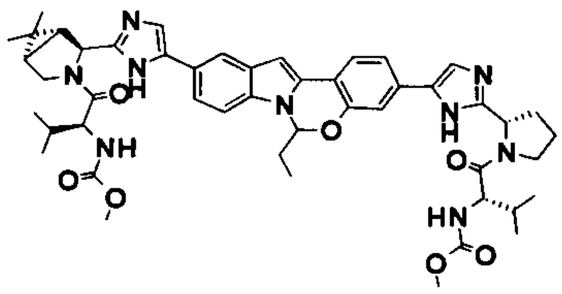
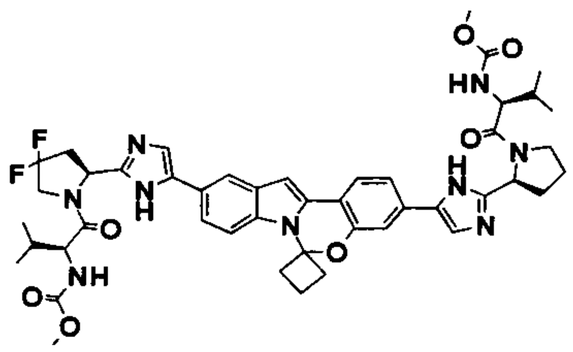
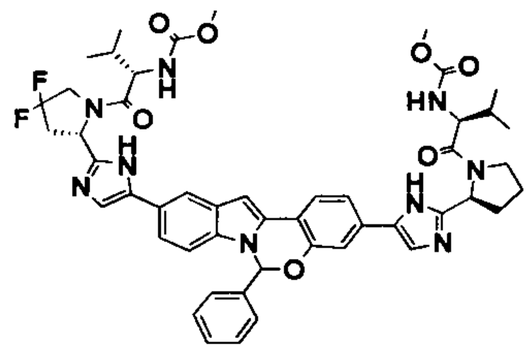
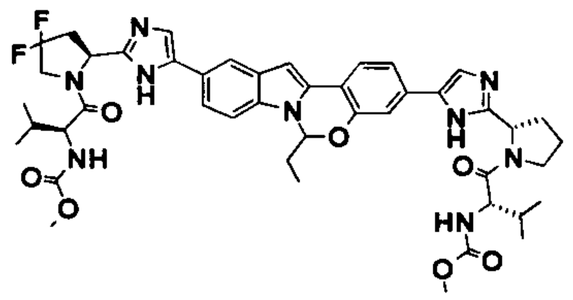
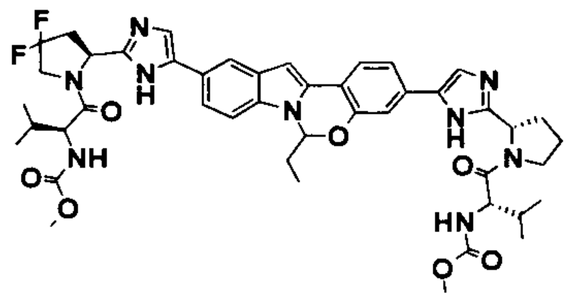
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1100		0.010	19.2	1.56	0.006	3.51	956.50	956.5	Mixture of isomers
1101		0.002	1.26	7.719	0.001	50.2	881.40	882.4	Single isomer
1102		0.002	1.95	19.68	0.002	> 100	873.40	874.4	Single isomer
1103		0.007	17.1	1.542	0.006	23.4	899.40	900.4	Single isomer
1104		0.004	2.26	0.588	0.003	23.7	899.40	900.4	Single isomer
1105		0.003	2.97	3.046	0.005	17	855.40	856.4	Single isomer

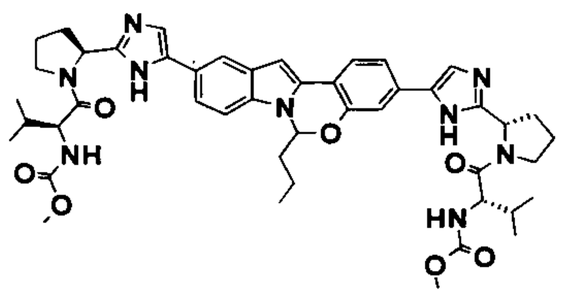
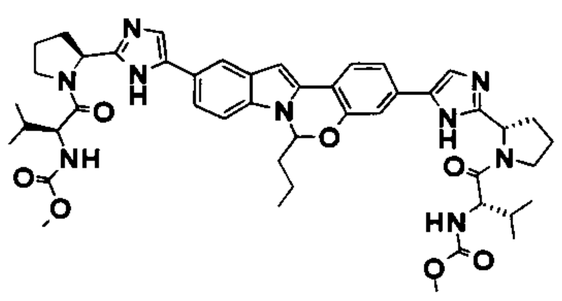
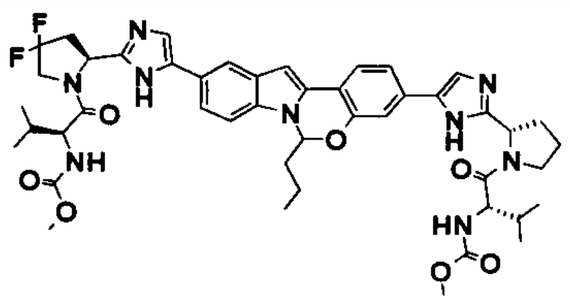
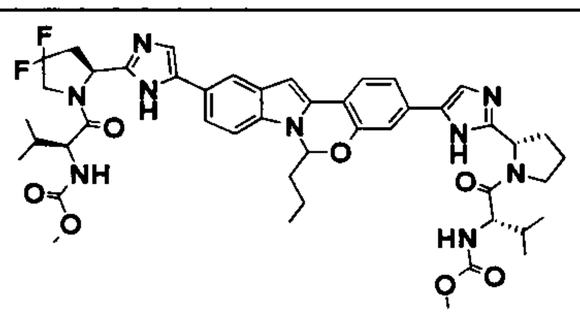
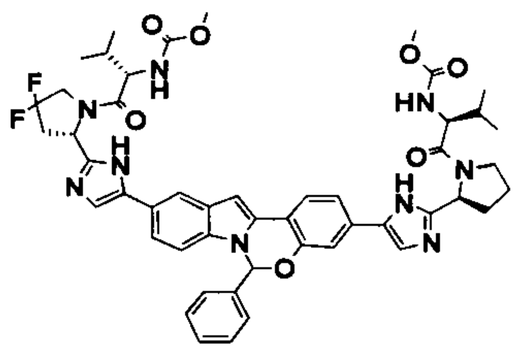
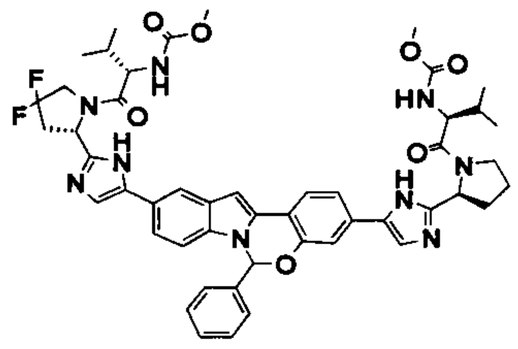
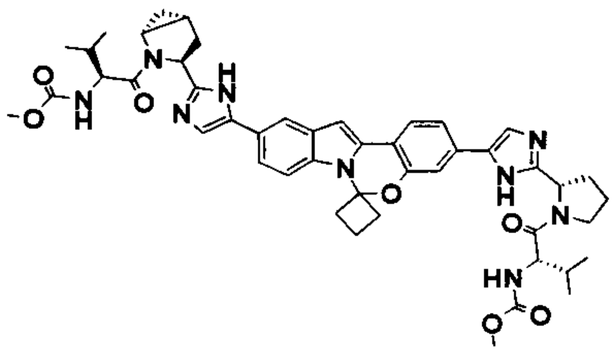
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1106		0.002	1.95	0.637	0.001	31	855.40	856.4	Single isomer
1107		0.005	1.95	1.591	0.001	18.3	923.50	924.5	Mixture of isomers
1108		0.003	1.95	1.521	0.001	19.3	923.50	924.5	Mixture of isomers
1109		0.020	43	0.3	0.001	52	899.40	900.3	Single isomer
1110		0.001	1.1	0.9	0.001	9.4	909.40	910.4	Mixture of isomers

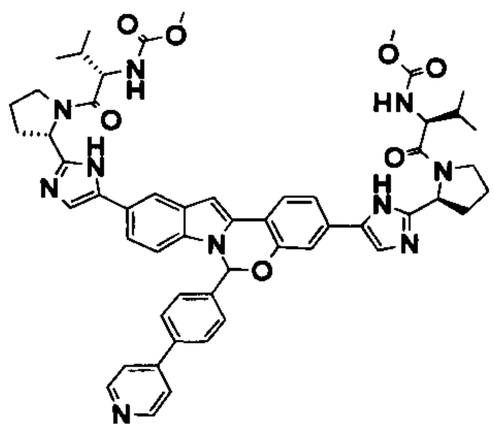
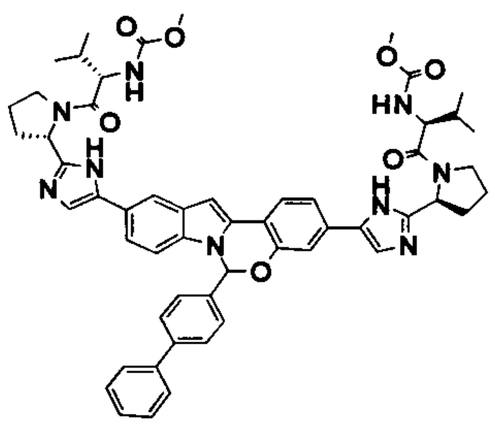
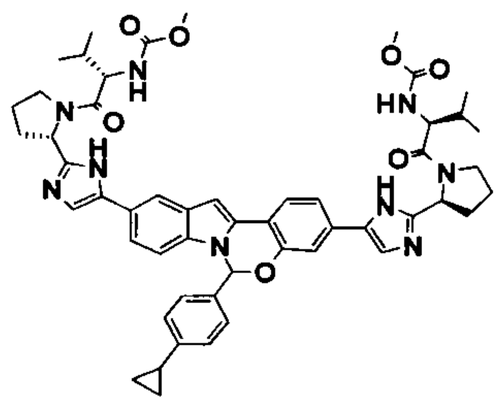
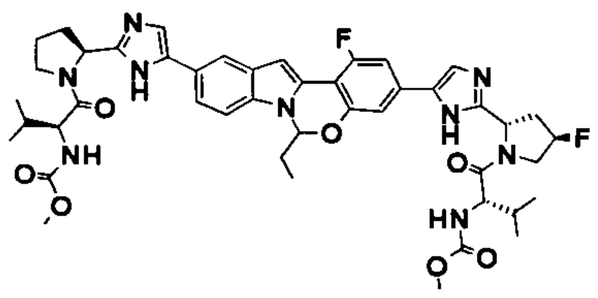
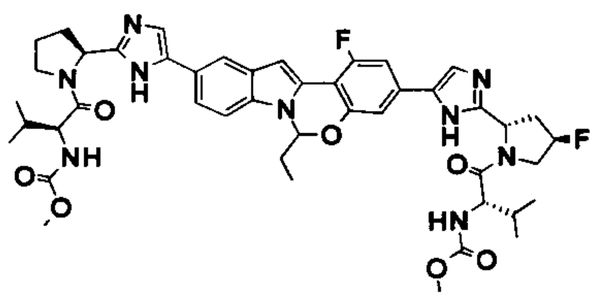
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1111		0.002	0.8	1	0.001	9.7	963.50	964.7	Mixture of isomers
1112		0.003		4.108	0.001	8.5	883.40	884.4	Mixture of isomers
1113		0.003	11	1.2	0.001	12	941.40	942.8	Mixture of isomers
1114		0.002	1.2	0.4	0.001	76	859.40	860.4	Single isomer
1115		0.064	92.5	64	0.004	64	863.40	863.7	Single isomer

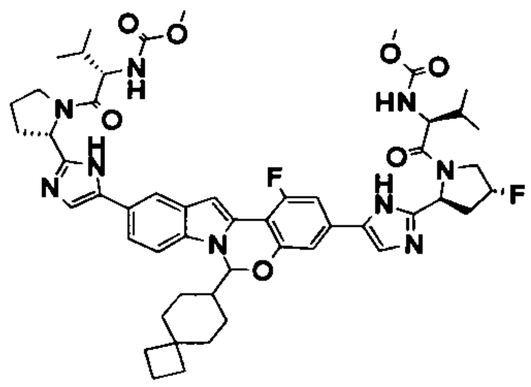
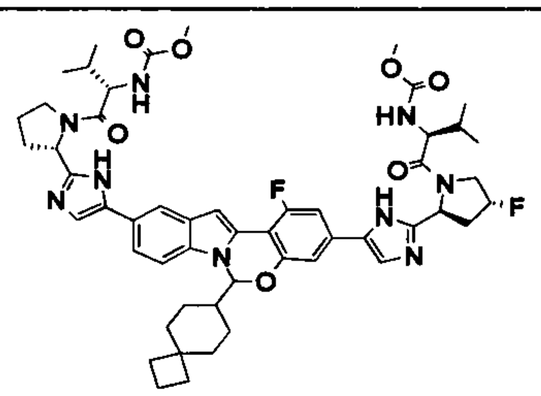
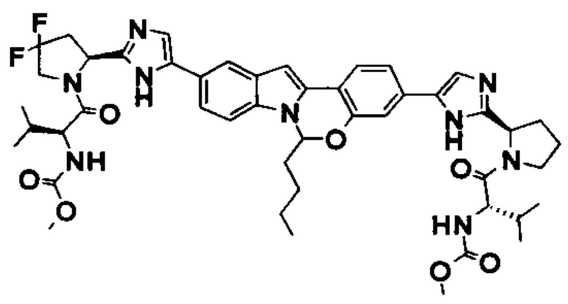
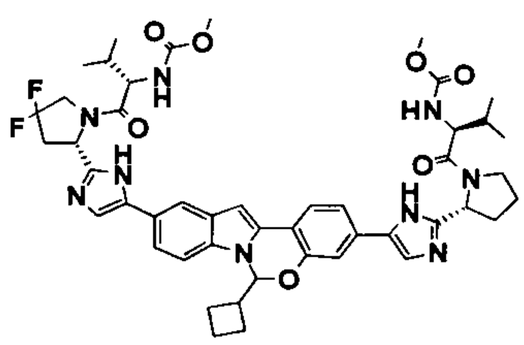
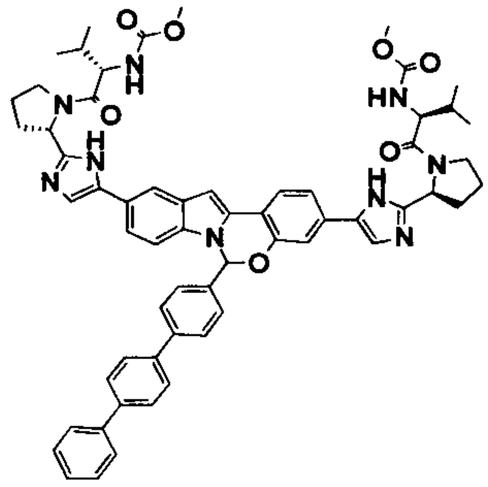
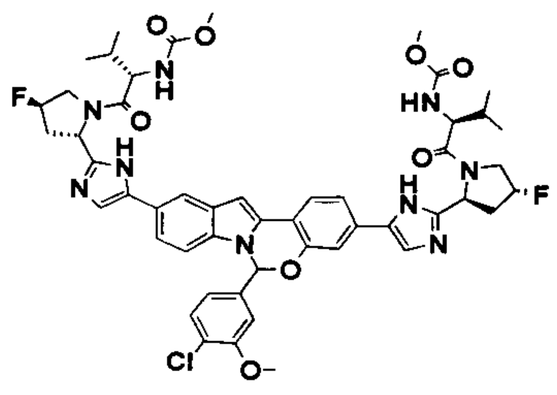
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1116		0.010	0.8	2.4	0.020	20.9	863.40	863.7	Single isomer
1117		0.023	19.7	4.8	0.001	7	891.40	892.7	Single isomer
1118		0.003	0.5	2	0.001	23	891.40	892.7	Single isomer
1119		0.011	8.8	10	0.001	31	877.40	877.7	Single isomer
1120		0.003	0.5	4.8	0.001	21	877.40	877.7	Single isomer

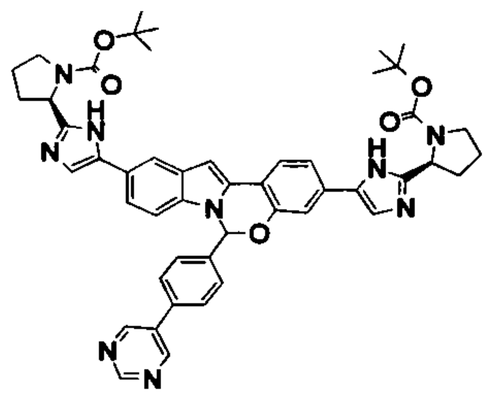
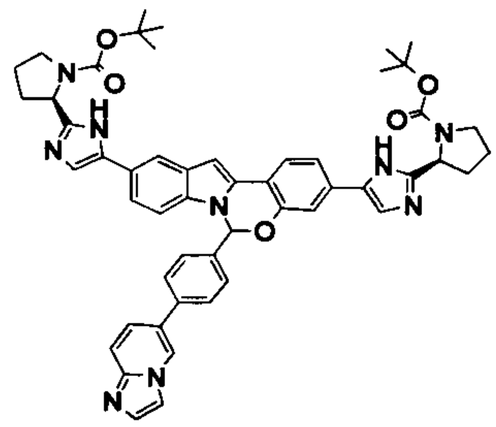
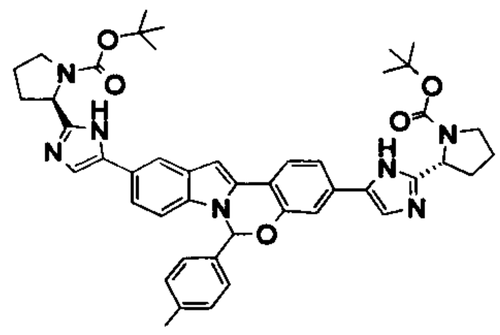
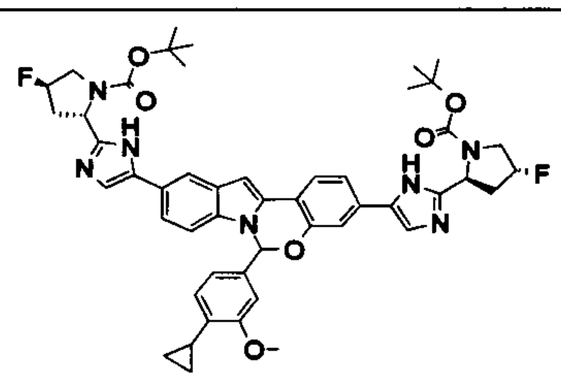
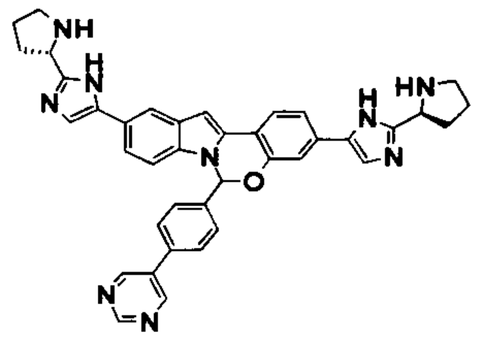
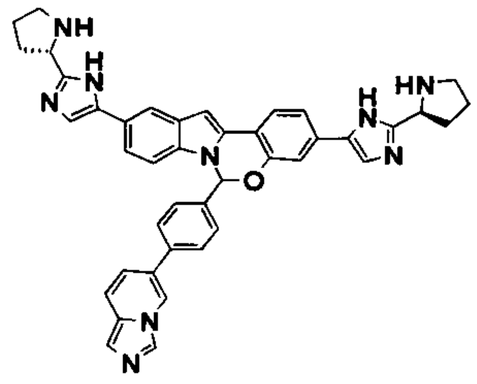
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1121		0.030	20.2	17.5	0.001	23	877.40	877.7	Single isomer
1122		0.002	0.8	4.9	0.001	27	877.40	877.7	Single isomer
1123		0.002	6.4	2.9	0.001	22	869.40	870.2	Mixture of isomers
1124		0.002	2.8	1	0.001	6	883.40	884.2	Mixture of isomers
1125		0.002	13.5	1.2	0.001	5	847.40	848.2	Mixture of isomers

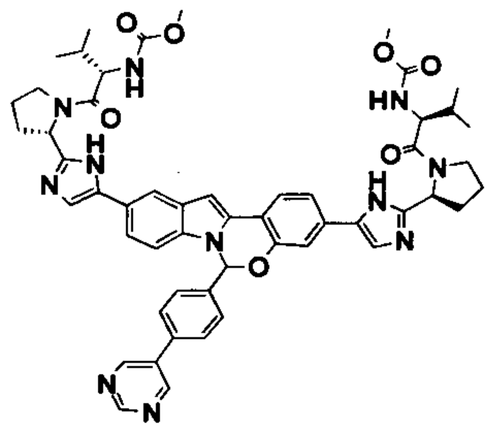
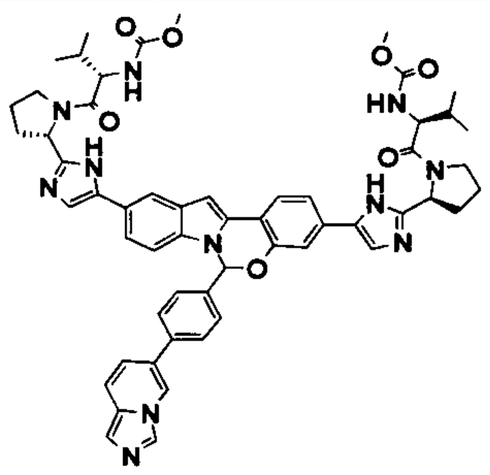
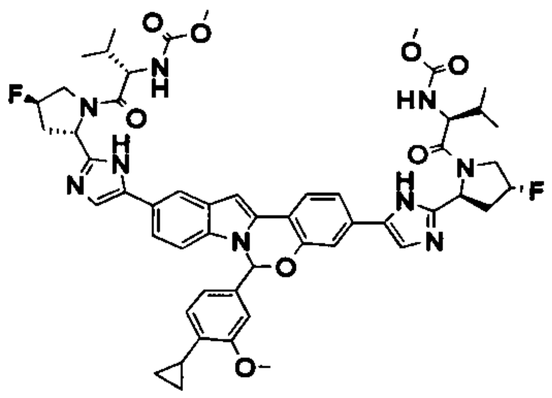
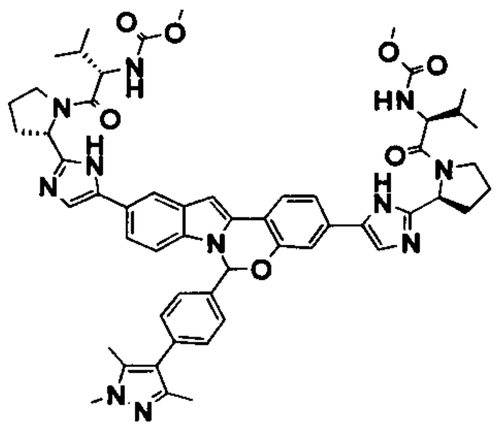
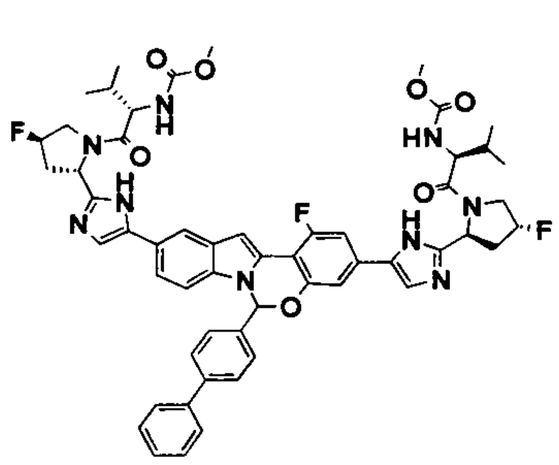
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1126		0.018	46.74	26.5	0.001	142	873.50	874.5	Mixture of isomers
1127		0.003	12	12	0.001	49	881.40	882.5	Single isomer
1128		0.002	0.8	0	0.001	9	917.40	918.5	Mixture of isomers
1129		0.003	3	2	0.002	14	869.40	870.3	Single isomer
1130		0.001	2	1	0.001	37	869.40	870.3	Single isomer

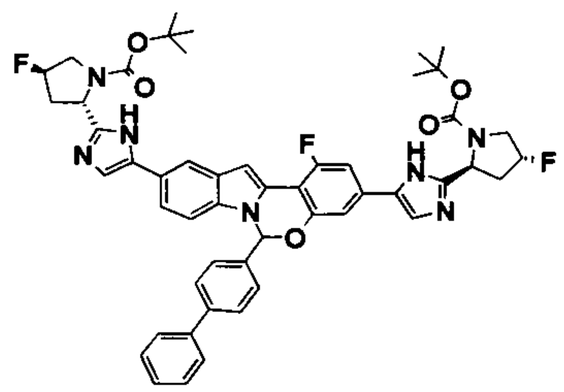
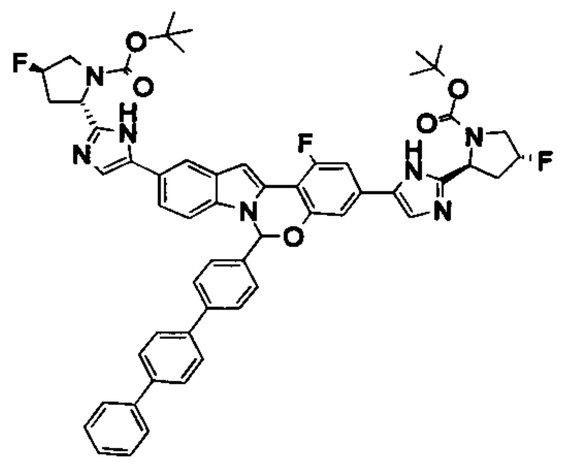
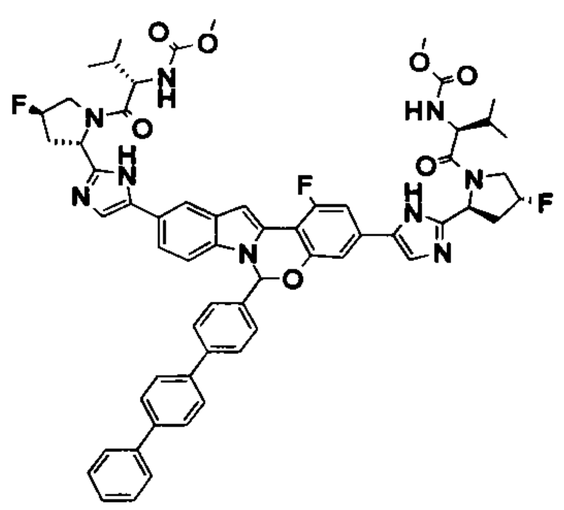
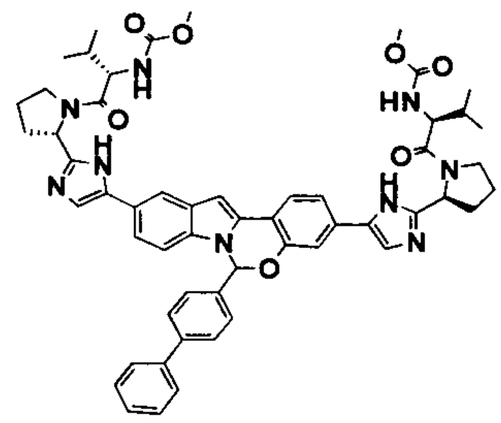
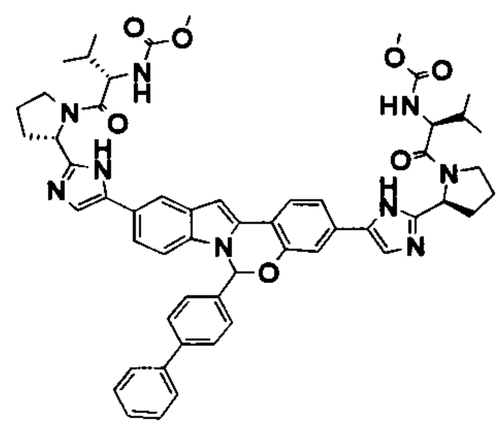
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1131		0.003	29	2	0.002	5	847.40	848.4	Single isomer
1132		0.003	3	1	0.002	3	847.40	848.4	Single isomer
1133		0.004	27	1	0.002	16	883.40	884.4	Single isomer
1134		0.001	1	1	0.001	17	883.40	884.4	Single isomer
1135		0.003	17	0	0.001	26	917.40	918.4	Single isomer
1136		0.002	1	0	0.001	11	917.40	918.4	Single isomer
1137		0.002	19.1	4.23	0.001	40.6	857.40	858.5	Single isomer

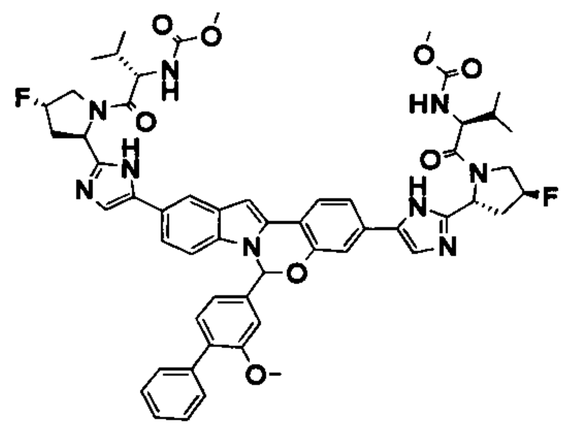
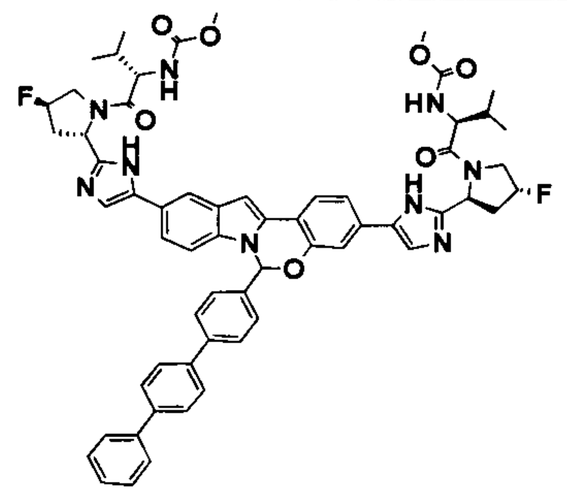
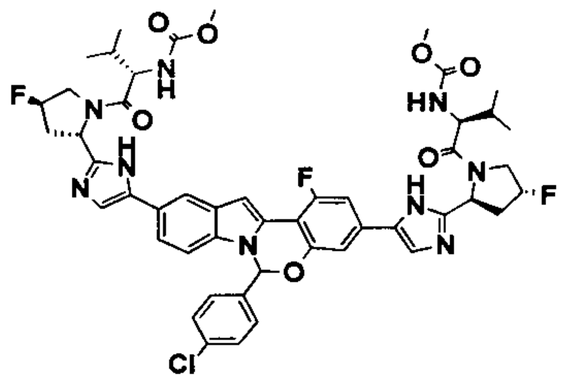
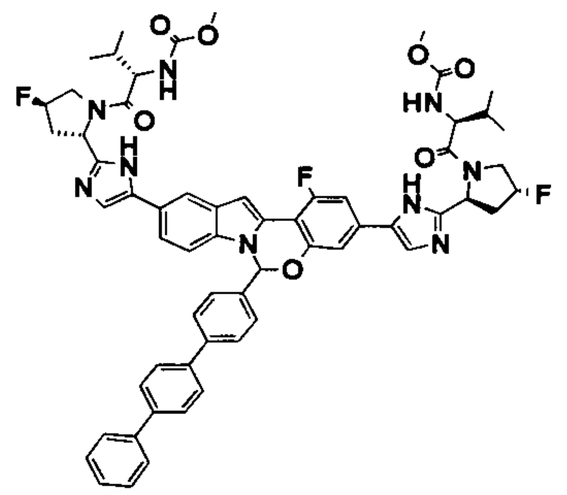
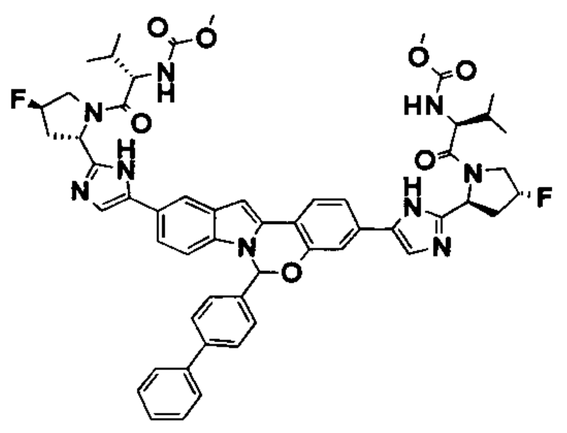
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1138		0.003	18.7	0.26	0.004	2	958.50	959.2	Mixture of isomers
1139		0.010	1	1.1	0.020	1.1	957.50	958.5	Mixture of isomers
1140		1.100	2	1.1	0.020	1.1	921.50	922.5	Mixture of isomers
1141		0.010	2	13	0.020	12.4	869.40	870.5	Single isomer
1142		1.100		11.2	0.020	45.1	869.40	870.5	Single isomer

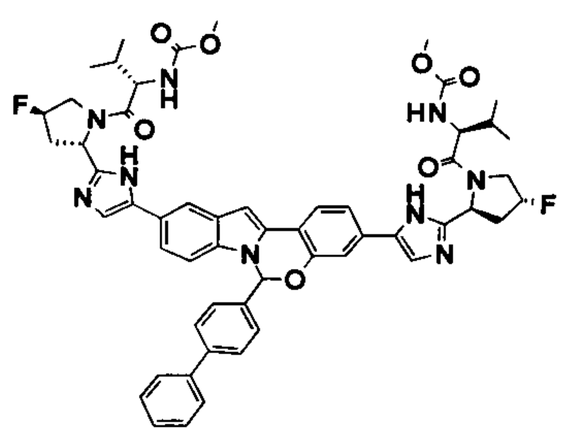
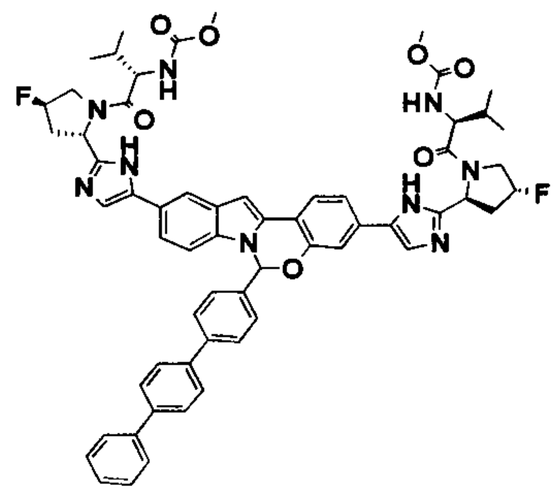
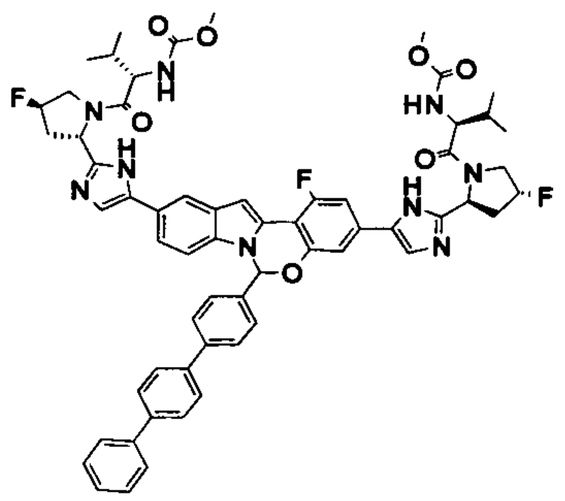
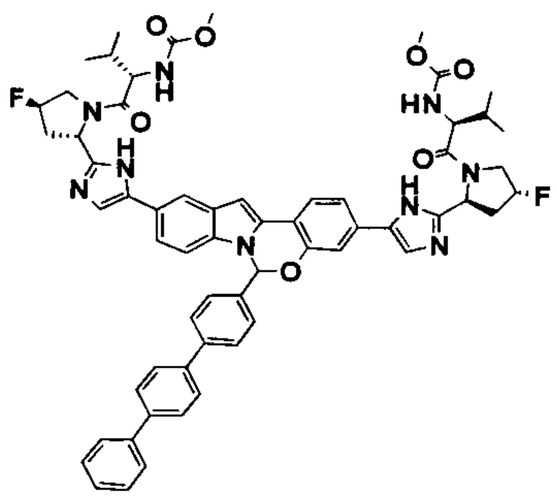
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1143		0.010	> 100	7.7	0.020	10.2	963.50	**964**.5	Single isomer
1144		0.010	2	1.1	0.020	26.5	963.50	**964**.5	Single isomer
1145		0.019	5.764	2.511	0.054	457.395	897.40	**898**.4	Mixture of isomers
1146		0.019	4.6	2.4	0.070	318.37	895.40	**896**.4	Mixture of isomers
1147		0.019	1.9555	1.9555	0.002	1.9555	1033.50	**1034**.4	Mixture of isomers
1148		0.019	1.9555	5.39248	0.002	67.2647	981.40	**982**.4	Mixture of isomers

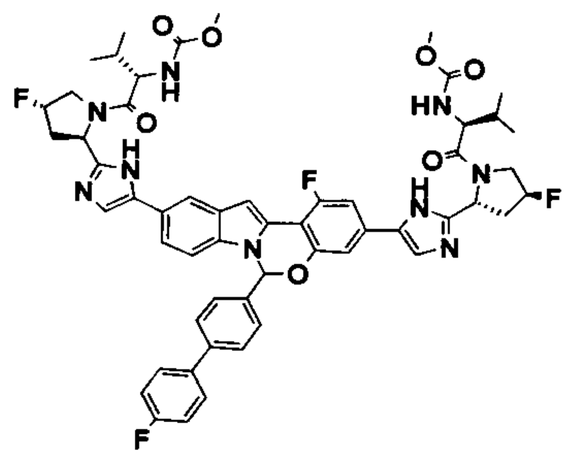
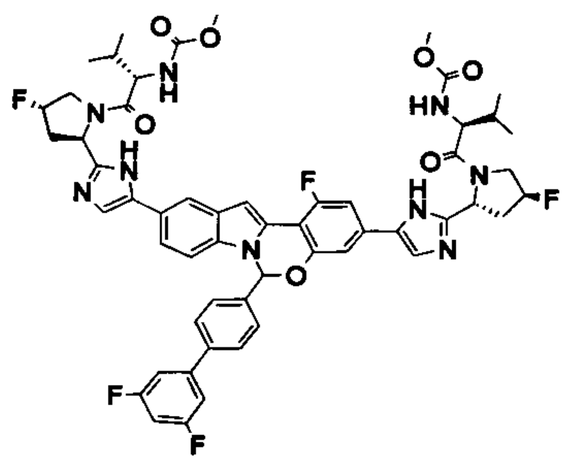
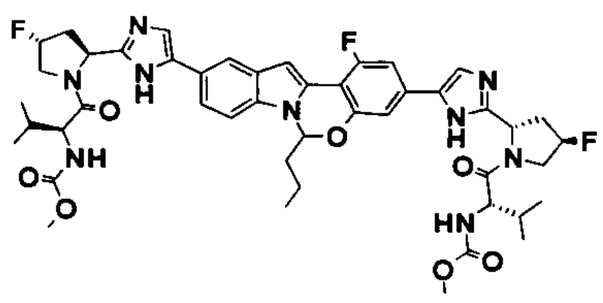
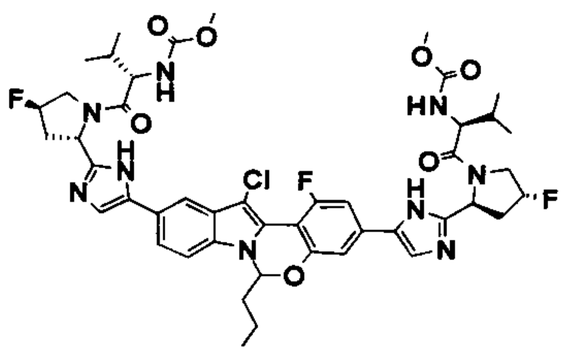
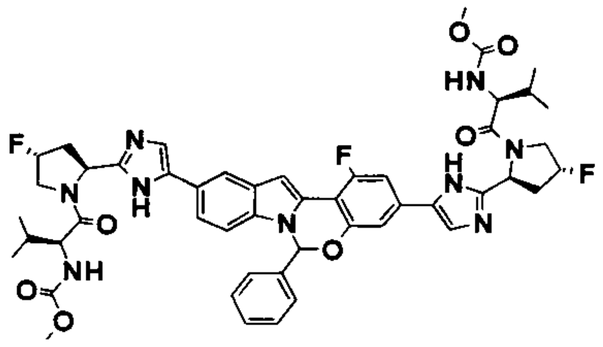
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1149		124.000	640				845.40	846.3	Mixture of isomers
1150		298.500	> 5000				883.40	884.3	Mixture of isomers
1151		53.000	248				781.40	782.3	Mixture of isomers
1152		488.700	764				873.40	874.3	Mixture of isomers
1153		245.000	> 5000				645.30	646.3	Mixture of isomers
1154		9.300	> 5000				683.30	684.3	Mixture of isomers

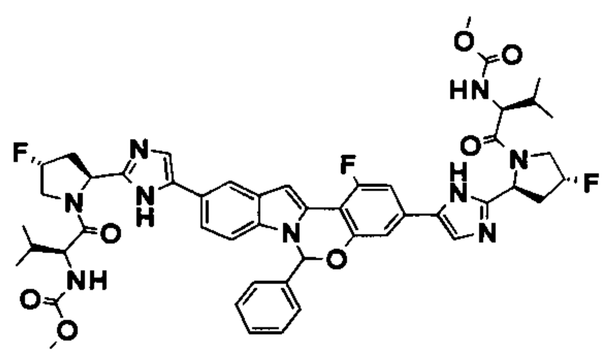
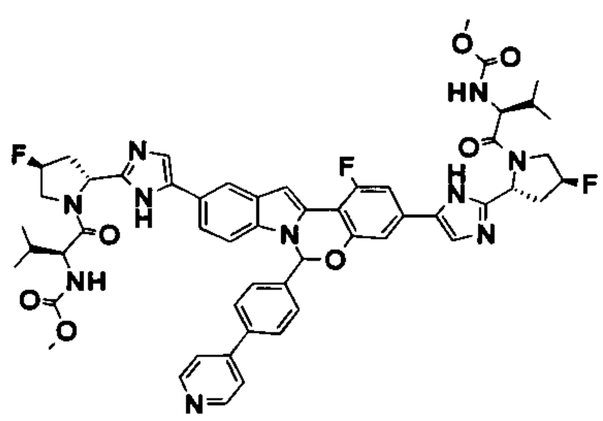
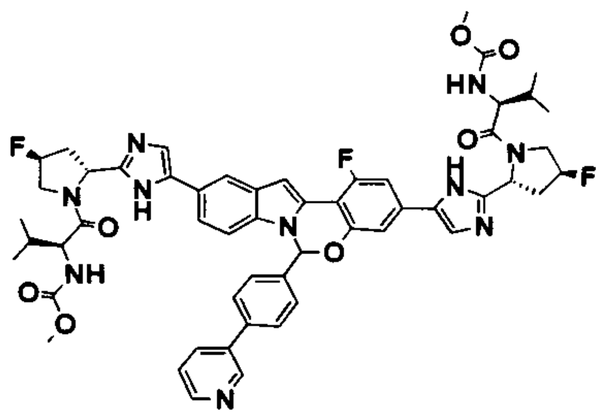
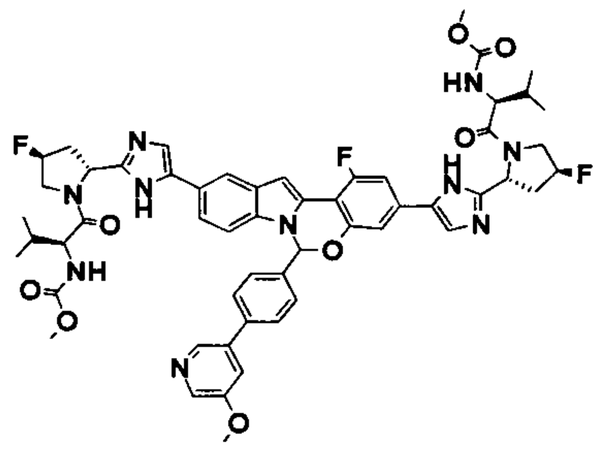
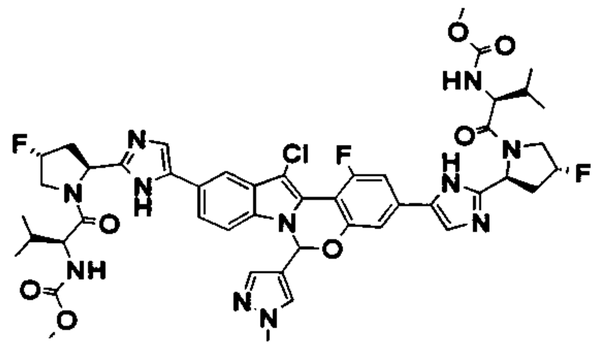
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1155		0.030	16.31	3.4	0.023	11.75	959.40	960.4	Mixture of isomers
1156		0.016	26.75	2.4	0.011	4.4	997.50	998.4	Mixture of isomers
1157		0.007	0.27	6.6	0.004	32	987.50	988.5	Mixture of isomers
1158		0.032	15.22	1	0.021	4.92	989.50	990.5	Mixture of isomers
1159		0.005	0.2	4.6	0.005	20.1	1012.40	1013.3	Mixture of isomers

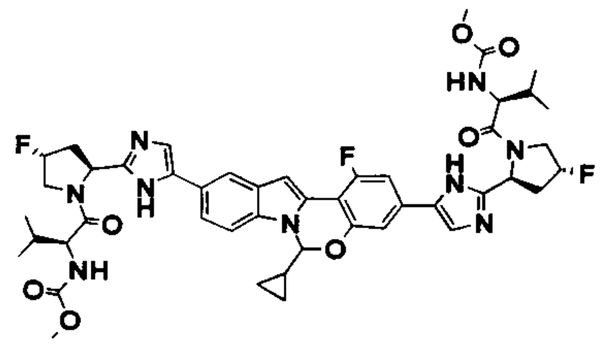
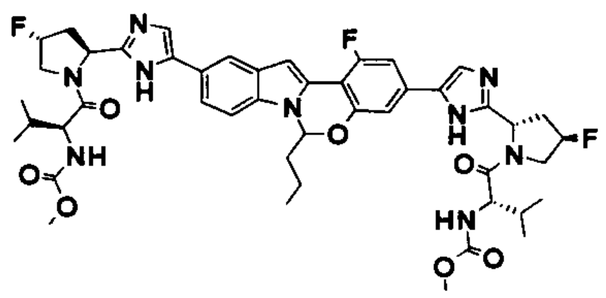
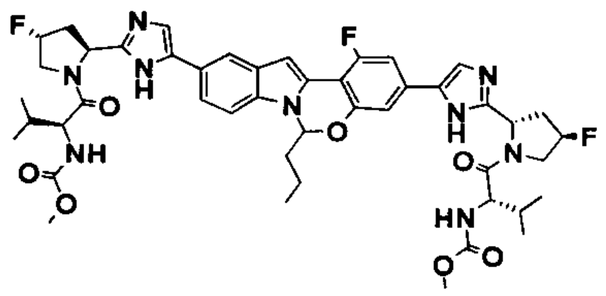
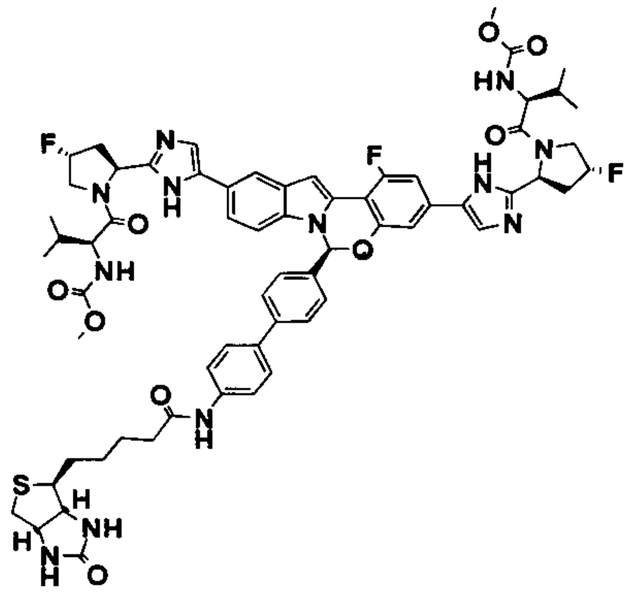
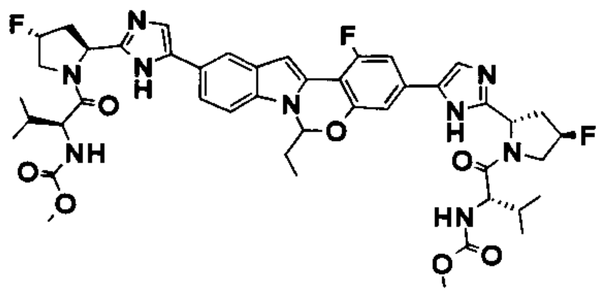
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1160		922.301	724.584				897.40	898.3	Mixture of isomers
1161		8.766	5099				973.40	974.3	Mixture of isomers
1162		0.006	9.111	9.111	0.005	14.818	1087.50	1088.3	Mixture of isomers
1163		0.004	58.732	9.111	0.004	9.111	957.50	958.5	Single isomer
1164		0.006	9.111	9.111	0.005	9.111	957.50	958.5	Single isomer

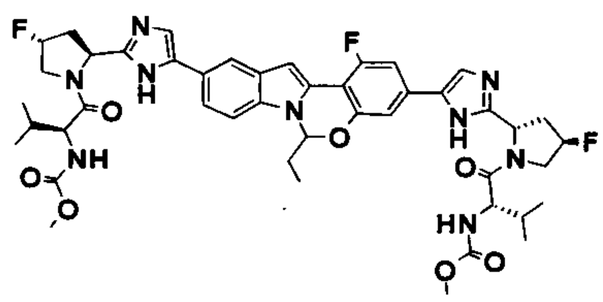
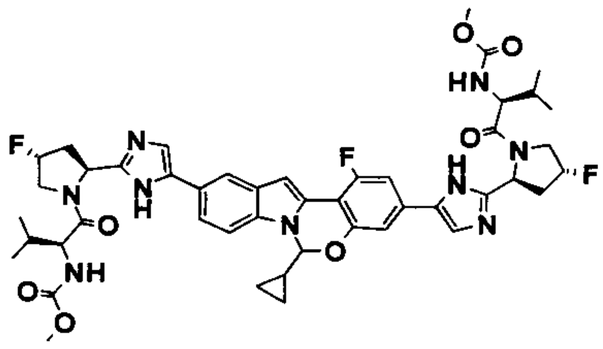
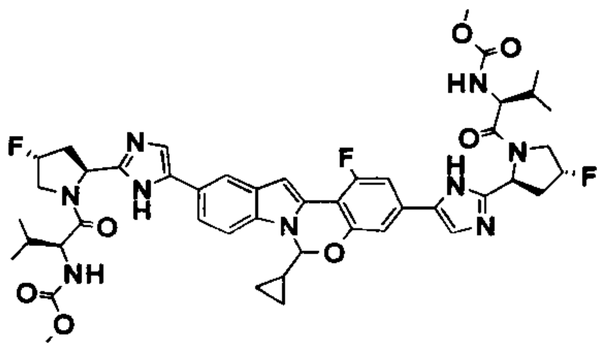
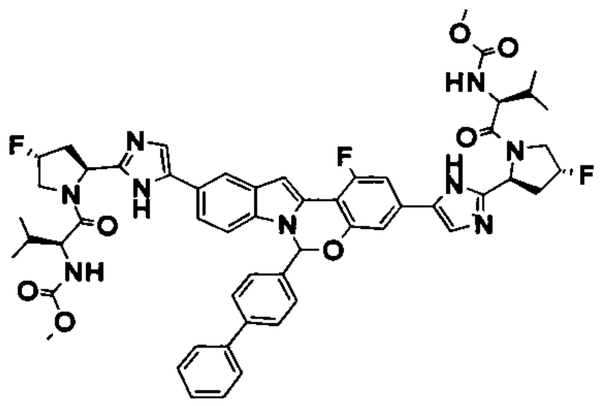
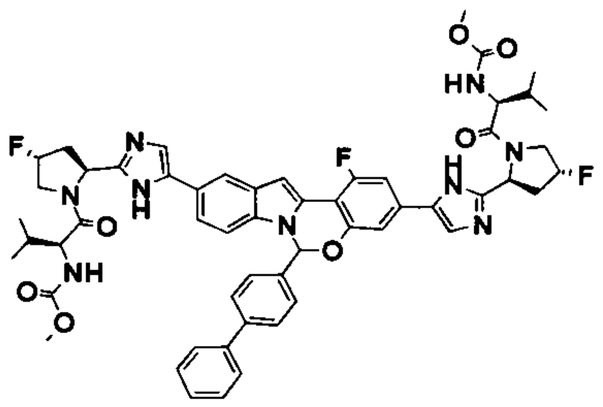
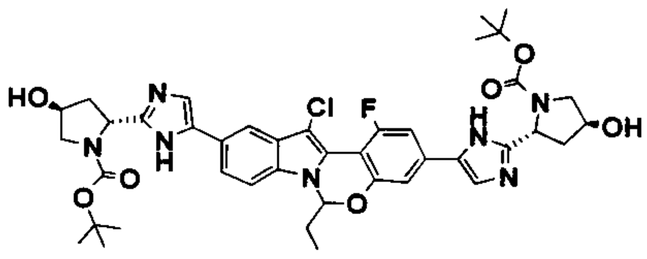
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1165		0.005	0.13	889.65	0.003	99.34	1023.50	1024.4	Mixture of isomers
1166		0.005	0.09	9.11	0.003	25.34	1069.50	1070.4	Mixture of isomers
1167		0.015	0.2	685.23	0.002	> 5000	969.40	970.3	Single isomer
1168		0.005	0.19	0.9	0.006	8.6	1087.50	1088.4	Single isomer
1169		0.049	0.64	9	0.002	49.8	993.40	994.5	Single isomer

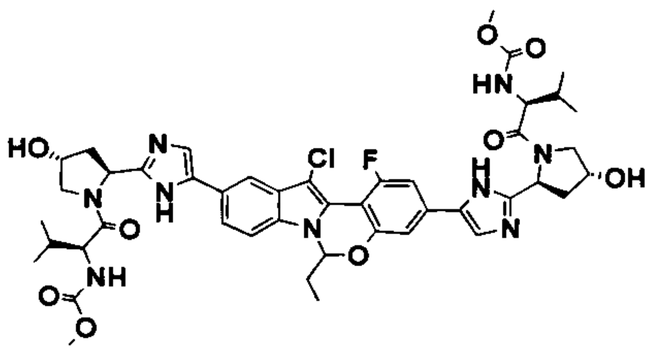
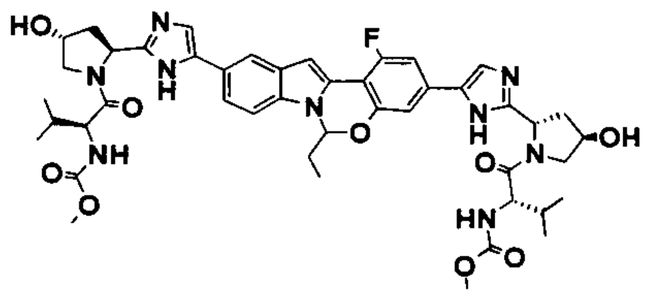
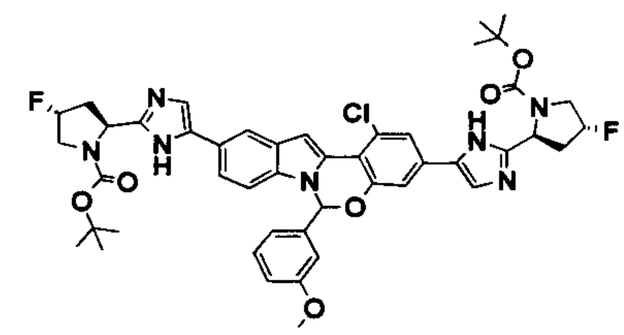
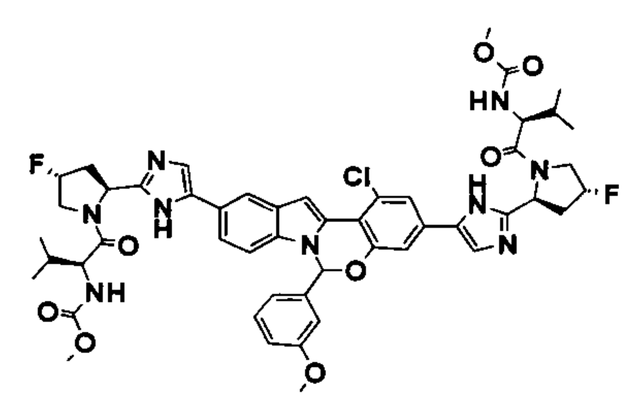
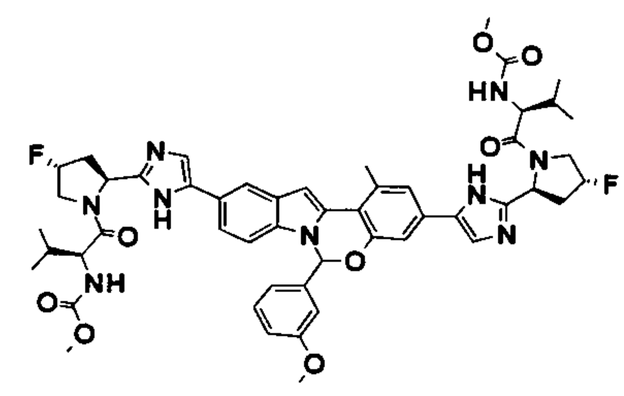
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1170		0.002	0.2	2.3	0.003	25.3	993.40	994.5	Single isomer
1171		0.015	0.67	5.5	0.003	51	1069.50	1070.4	Single isomer
1172		0.025	0.76	10.7	0.005	37.6	1087.50	1088.4	Single isomer
1173		0.002	0.19	0.6	0.003	11.5	1087.50	1088.4	Single isomer

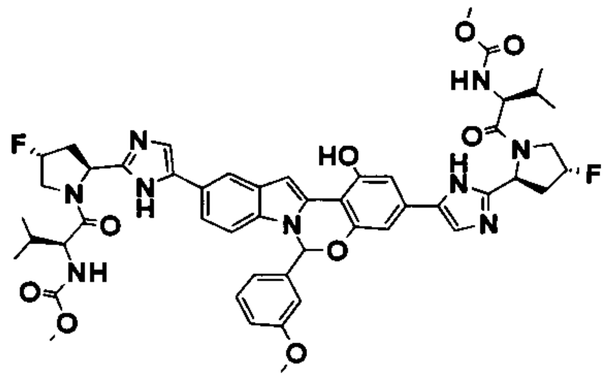
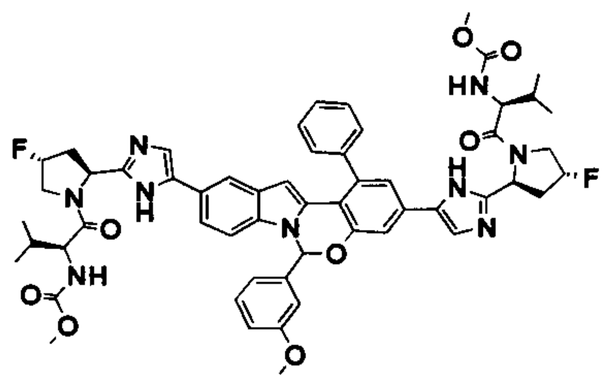
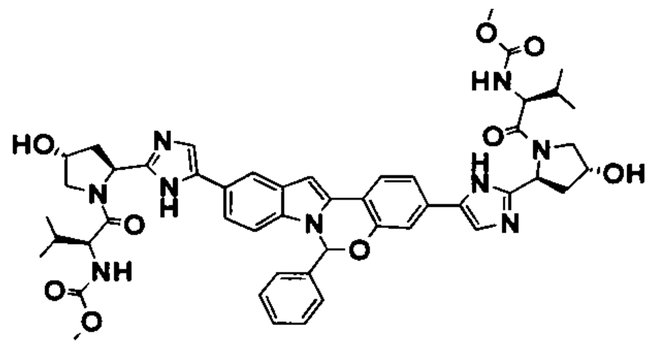
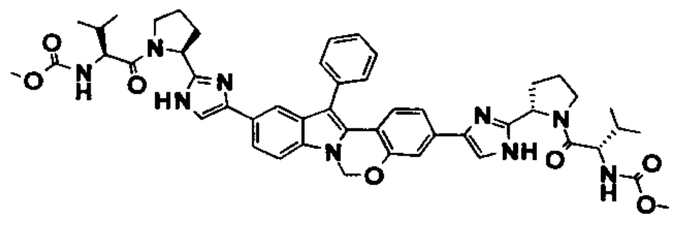
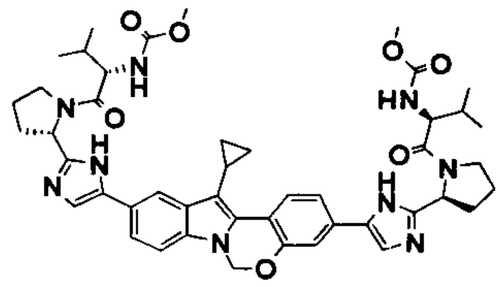
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1174		0.016	0.38	6.5	0.004	61	1029.40	1030.3	Single isomer
1175		0.022	0.25	6.9	0.002	36.5	1047.40	1048.3	Single isomer
1176		0.004	0.2	21.3	0.002	90	901.40	902.4	Mixture of isomers
1177		0.065	0.3	23.8		> 200	935.40	936.3	Mixture of isomers
1178		0.007	0.4	5.1	0.002	28.8	935.40	936.1	Single isomer

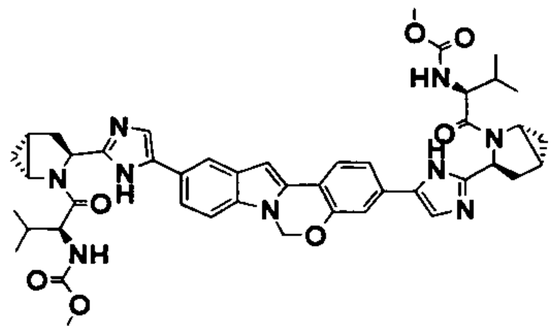
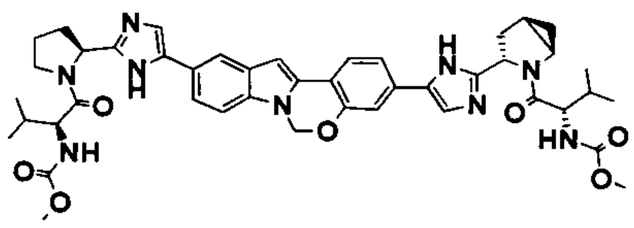
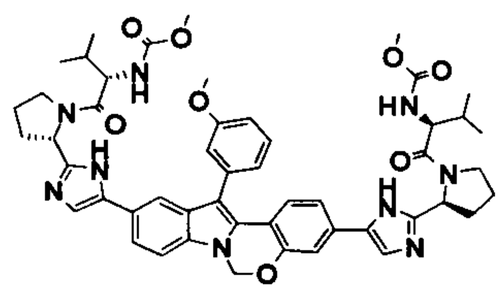
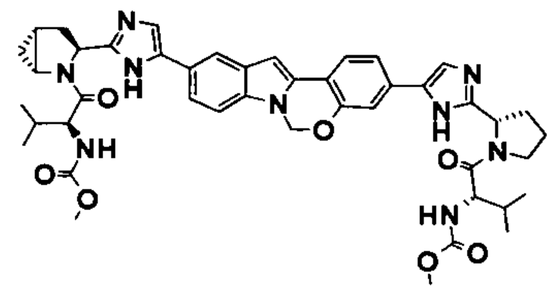
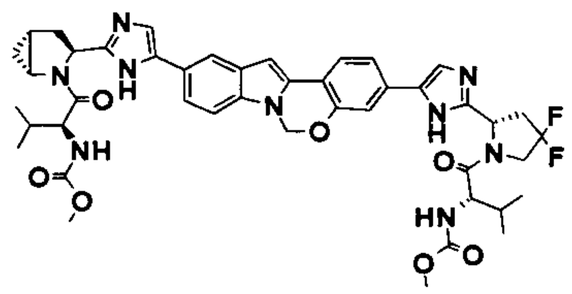
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1179		0.002	0.1	4	0.002	27.9	935.40	936.1	Single isomer
1180		0.002		5.4	0.004	39.9	1012.40	1013.0	Single isomer
1181		0.003		2.71	0.005	20.8	1012.40	1013.9	Single isomer
1182		0.003		1.245	0.004	27.4	1042.40	1043.0	Single isomer
1183		0.250	>100			>100	973.40	974.3	Mixture of isomers

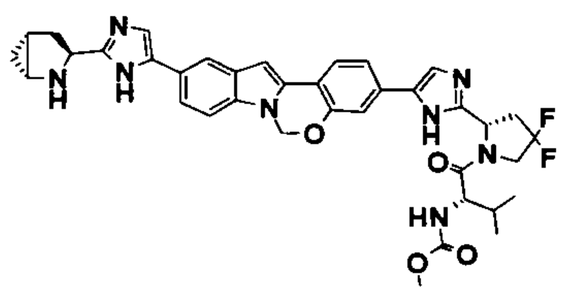
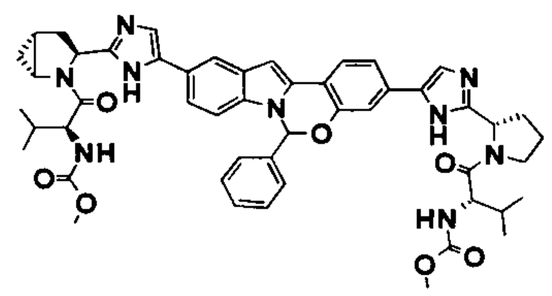
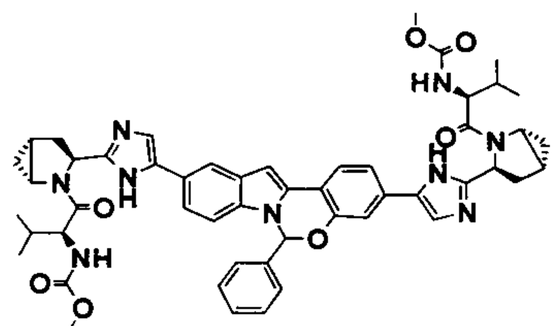
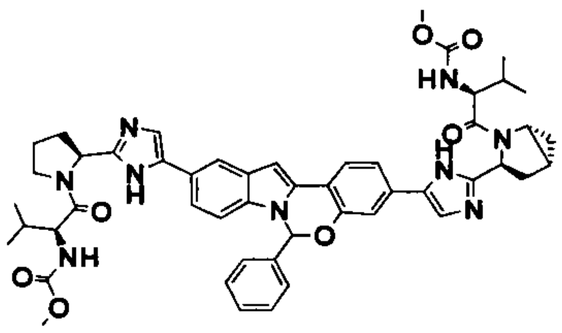
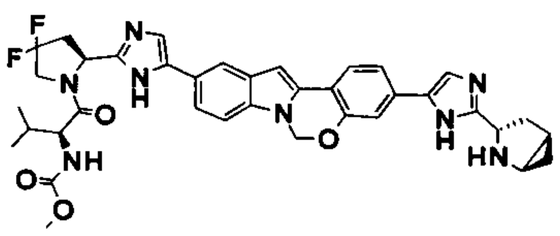
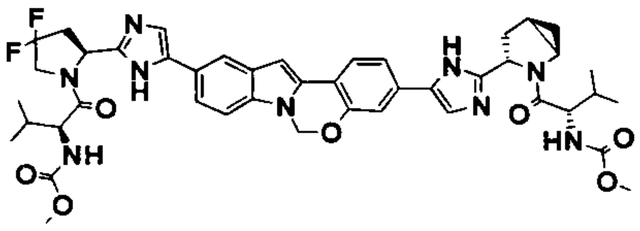
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1184		0.011	0.2	28.29	0.009	53	899.40	900.5	Mixture of isomers
1185		0.045	0.59	39	0.005	61.2	901.40	902.4	Single isomer
1186		0.008	0.19	22	0.005	61	901.40	902.4	Single isomer
1187		0.164	3.5	16	0.043	> 100	1252.50	1253.8	Single isomer
1188		0.014	0.2	49	0.005	41	887.40	888.4	Single isomer

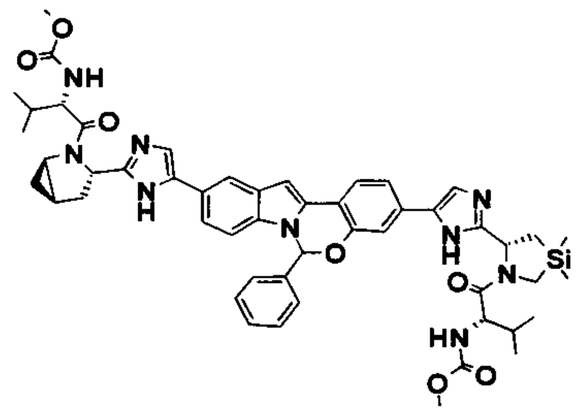
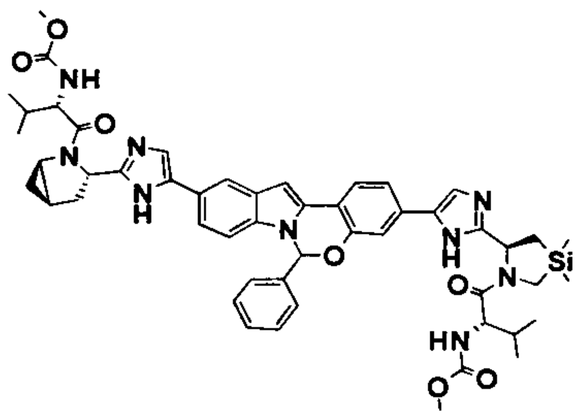
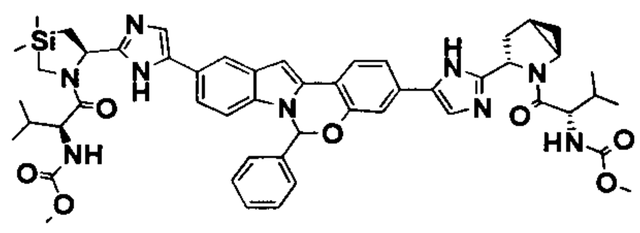
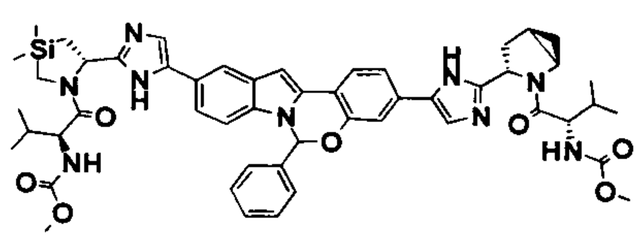
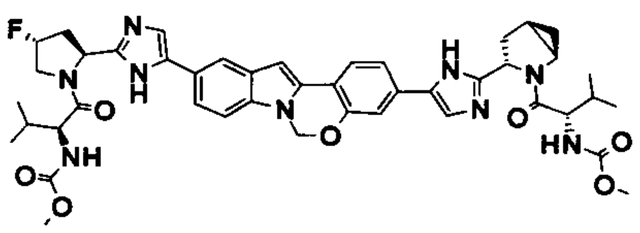
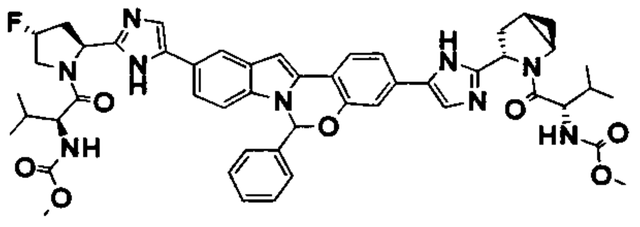
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1189		0.006	0.2	28	0.004	82	887.40	888.4	Single isomer
1190		0.220	> 100	71	0.006	74.4	899.40	900.4	Single isomer
1191		0.008	0.3	17.9	0.005	56	899.40	900.4	Single isomer
1192		0.007		2.365	0.005	48	1011.40	1012.4	Single isomer
1193		0.037	0.9	11.514	0.004	60	1011.40	1012.4	Single isomer
1194		533.000	943				803.30	804.4	Mixture of isomers

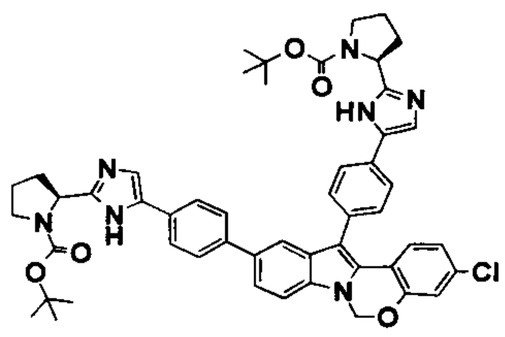
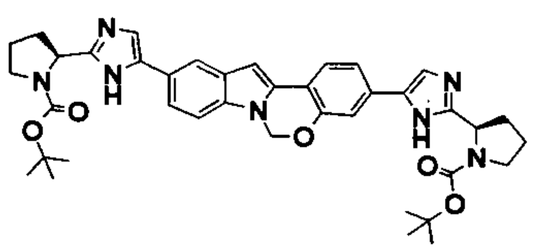
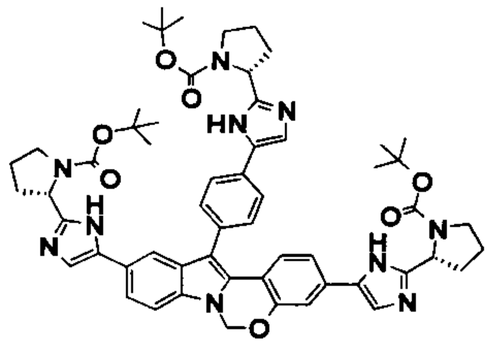
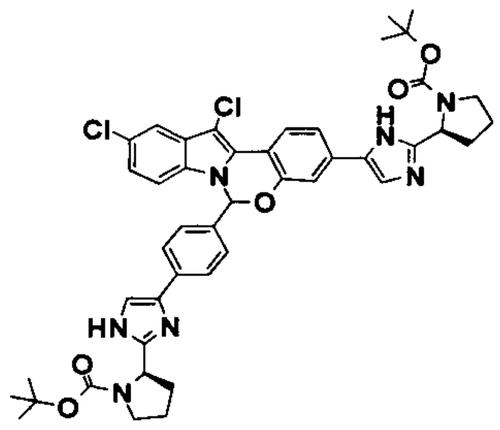
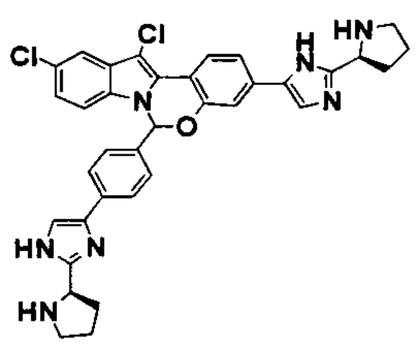
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1195		0.135	1	68.9	0.010	> 100	917.40	918.4	Mixture of isomers
1196		0.150	8.2	95		>100	883.40	884.4	Mixture of isomers
1197		608.000	>1000				867.30	868.3	Mixture of isomers
1198		0.058	0.75	4.7		95	981.40	982.2	Mixture of isomers
1199		0.130	0.92	2.9		85	961.43	962.4	Mixture of isomers

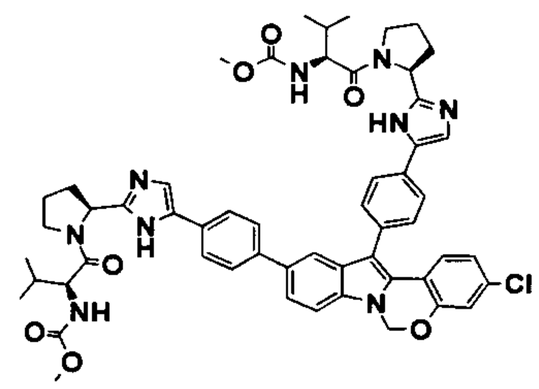
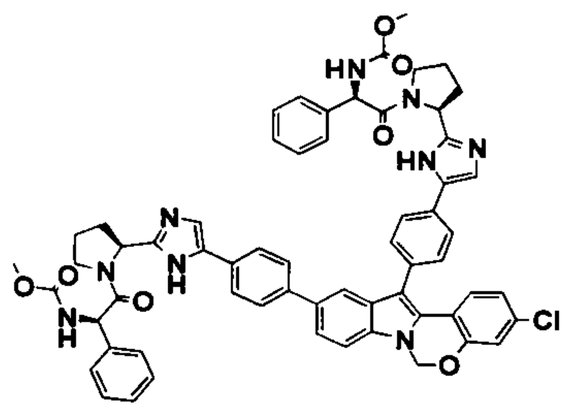
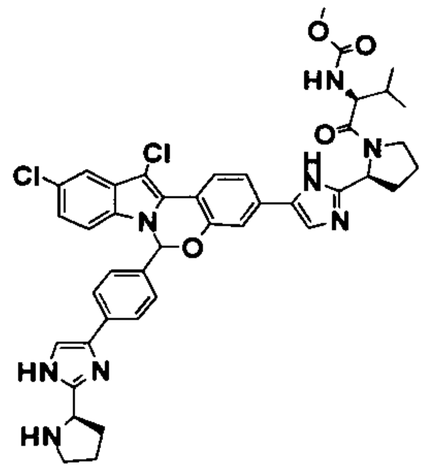
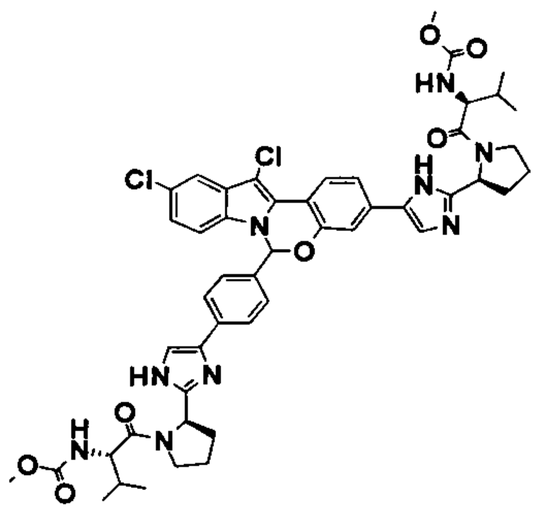
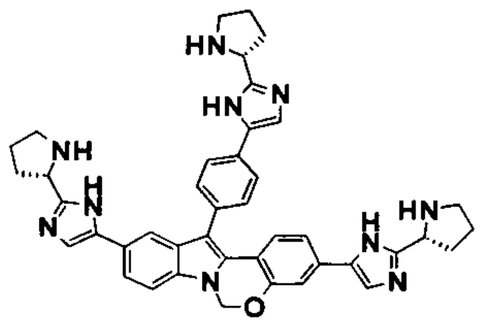
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1200		2.500	25	432		498	963.40	964.2	Mixture of isomers
1201		0.320	4.3	4.7		37	1023.50	1024.6	Mixture of isomers
1202		0.360	32	66		>1000	913.40	914.4	Single isomer
1203		0.002	98	2	0.000	6.5	881.40	881.7	Single isomer
1204		0.011	26.4	3.8	0.001	36	845.40	845.8	Single isomer

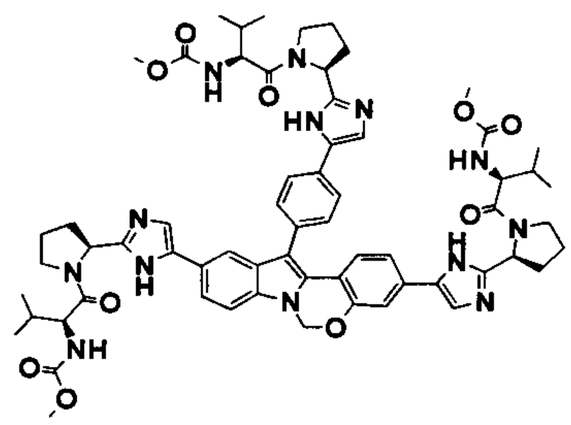
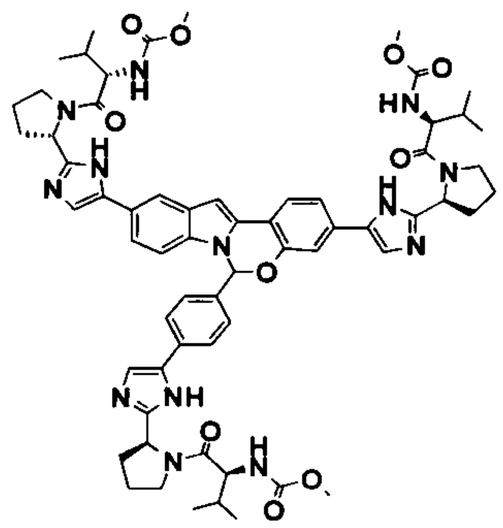
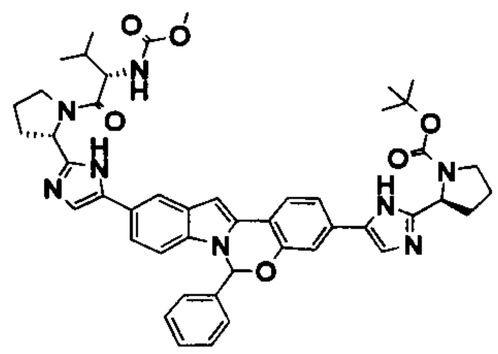
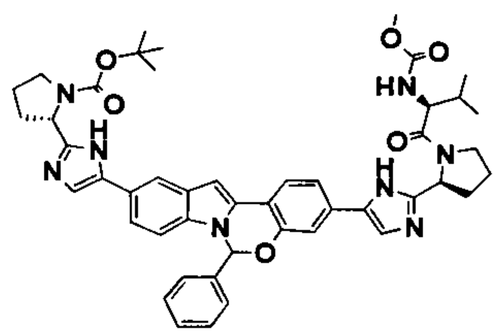
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1205		0.002	0.65	0.195	0.001	12	829.40	830.2	Single isomer
1206		0.001	1.16	0.222	0.001	9	817.40	818.2	Single isomer
1207		0.007	51	8	0.001	48	911.40	913.2	Single isomer
1208		0.004	1	1	0.002	22	817.40	819.2	Single isomer
1209		0.002	0.48	2.9	0.000	98	853.40	854.2	Single isomer

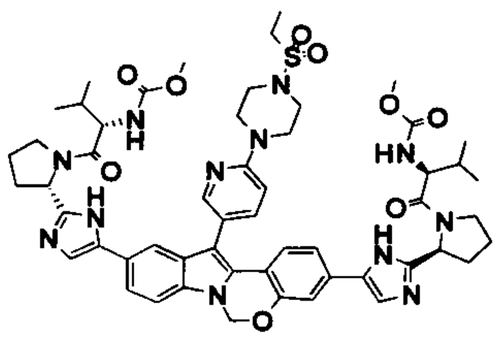
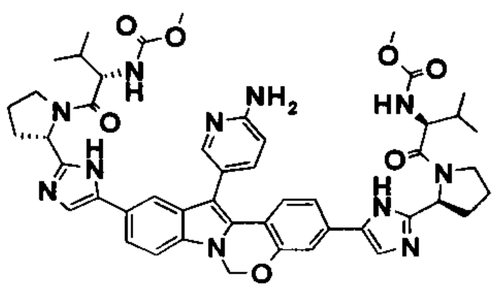
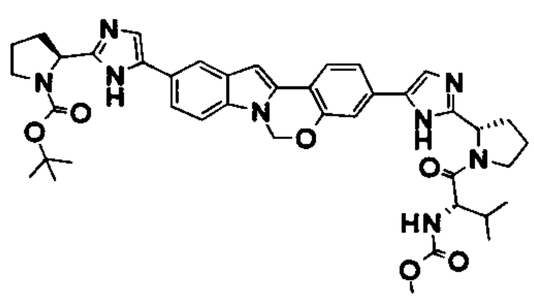
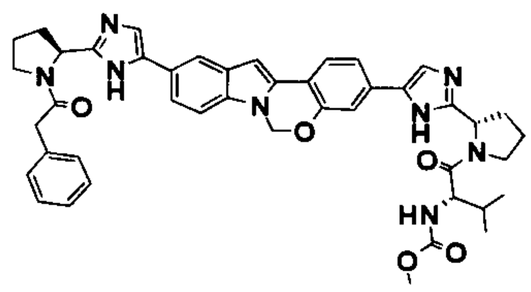
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1210		> 0.2	46.31	24	0.098	374	696.30	698.2	Single isomer
1211		1.100	2	1.1	0.020	5	893.40	894.4	Mixture of isomers
1212		1.100	2	1.1	0.020	44.2	905.40	906.5	Mixture of isomers
1213		1.100	2	1.1	0.020	3.1	893.40	894.4	Single isomer
1214		0.010	134	123.5	0.760	982.1	697.30	697.2	Single isomer
1215		0.010	8.48	1.1	0.020	82.3	853.40	854.3	Single isomer

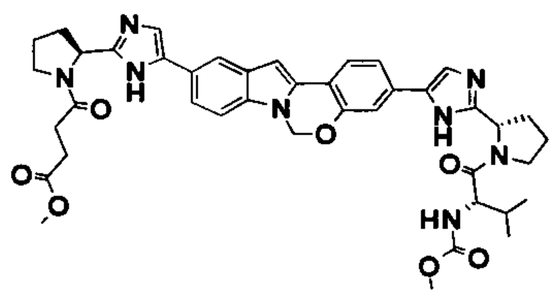
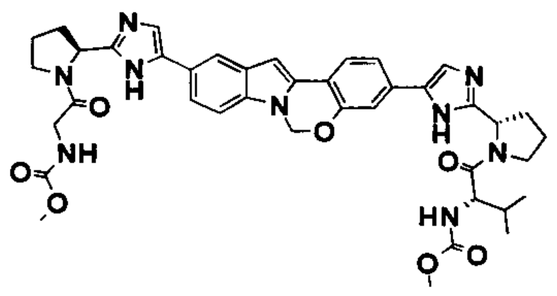
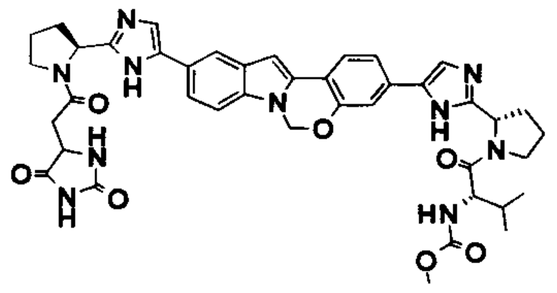
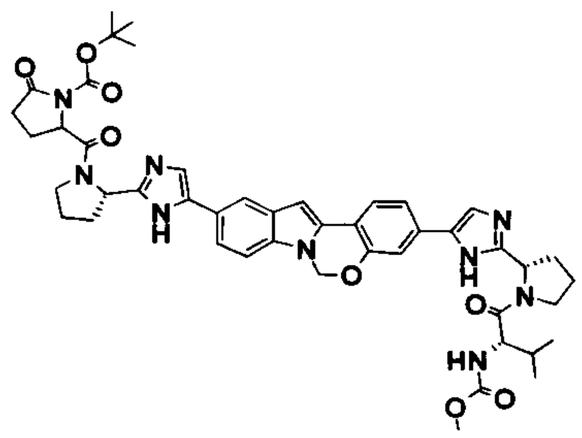
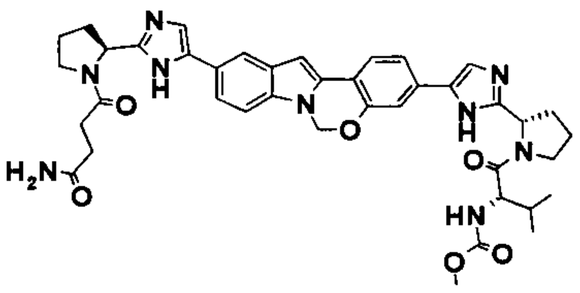
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1216		0.019	2.16	1.95	0.002	32	937.40	938.2	Mixture of isomers
1217		0.019	4.366	1.95	0.003	29	937.40	938.6	Mixture of isomers
1218		0.019	8.242	1.95	0.003	76.7234	937.40	939.4	Mixture of isomers
1219		0.019	50.879	3.065	0.002	58	937.40	938.4	Mixture of isomers
1220		0.019	1.9555	1.9555	0.002	36.2983	835.40	836.2	Single isomer
1221		0.019	1.9555	1.9555	0.002		911.40	912.2	Mixture of isomers

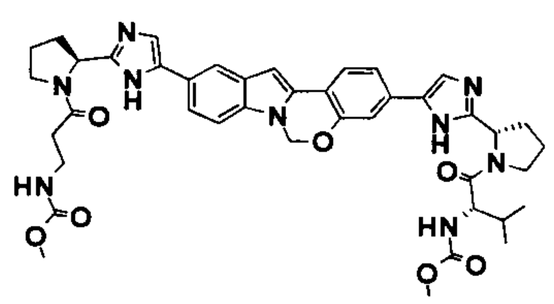
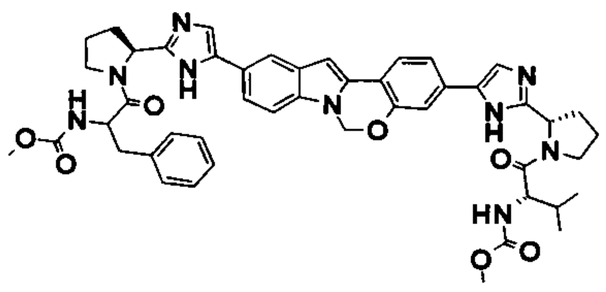
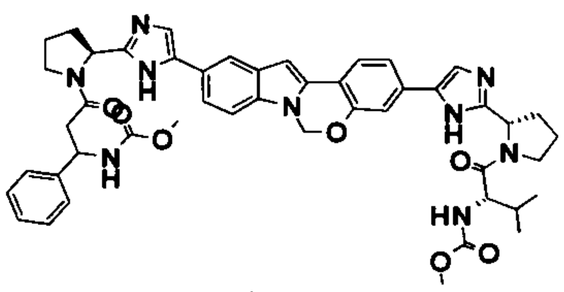
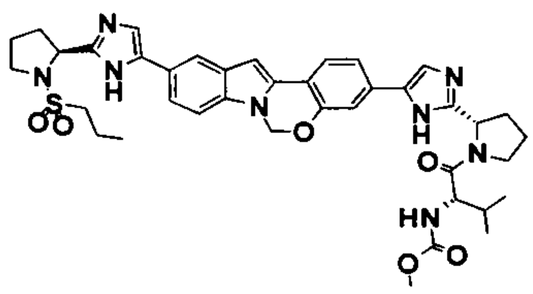
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1222		4.725	352.297	50.7592	0.301	> 1000	877.40	878.0	Single isomer
1223		502.760	1000	1000	> 100	1000	691.40	692.3	Single isomer
1224		180.440	1000	1000	15.920	510	1002.50	1004.0	Single isomer
1225		########	645.63	1000	> 100	1000	835.30	836.3	Mixture of isomers
1226		129.300	> 5000				635.20	636.2	Mixture of isomers

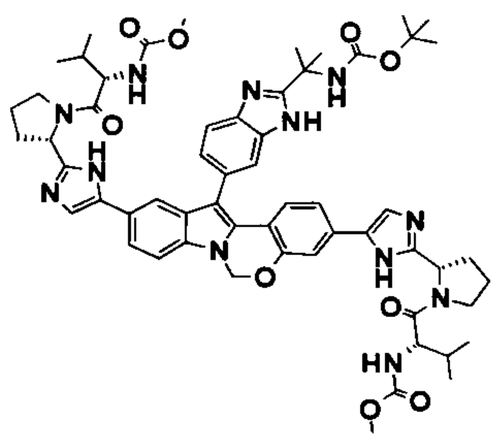
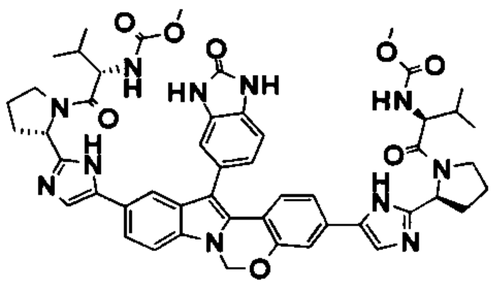
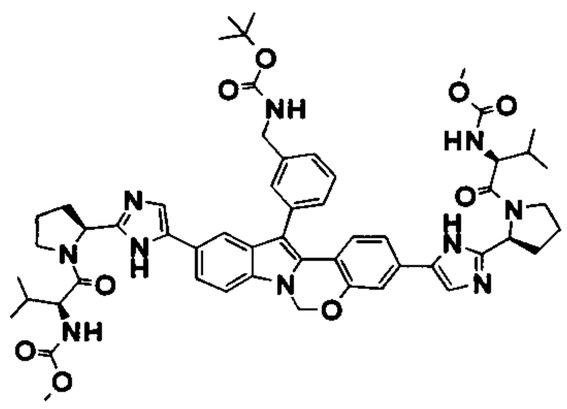
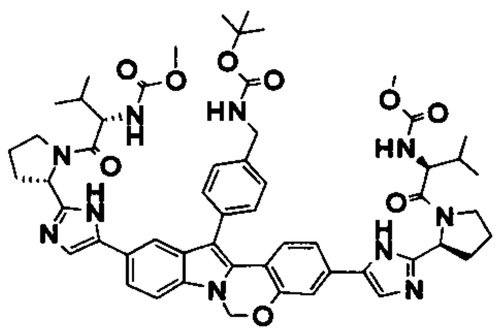
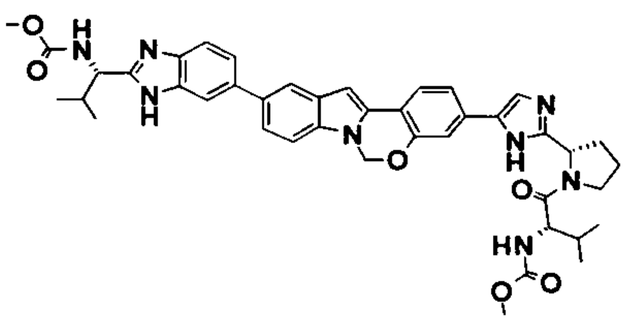
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1227		> 2	> 5000	3844		4709	991.40	992.0	Single isomer
1228		> 2	> 5000	4660		> 5000	1059.40	1061.0	Single isomer
1229		8.600	1254				792.30	793.2	Mixture of isomers
1230		> 2	1827	404		948.6	951.30	952.1	Mixture of isomers
1231		501.958	5099				702.30	703.3	Single isomer

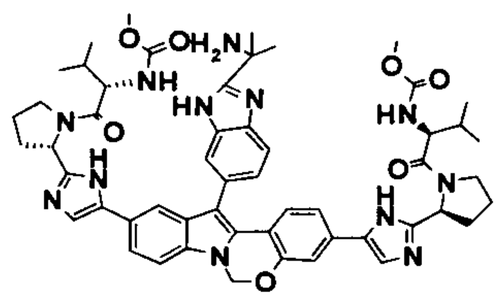
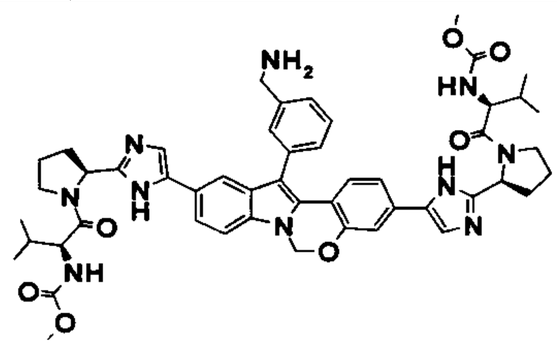
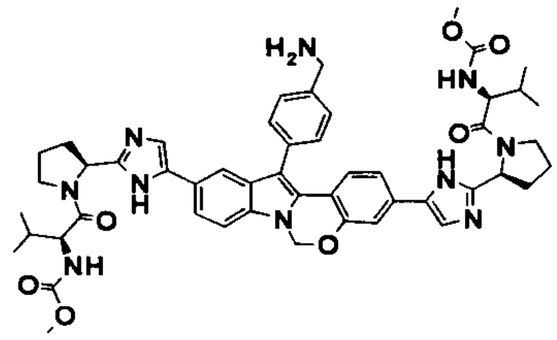
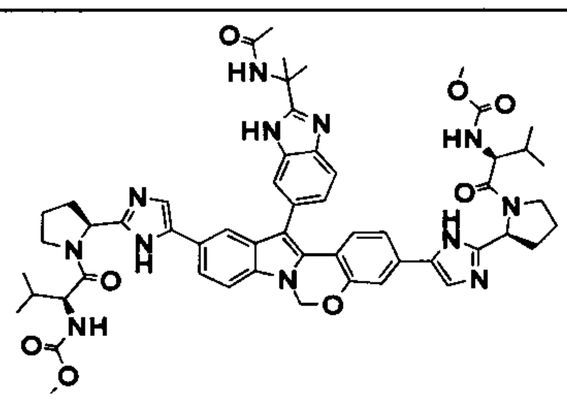
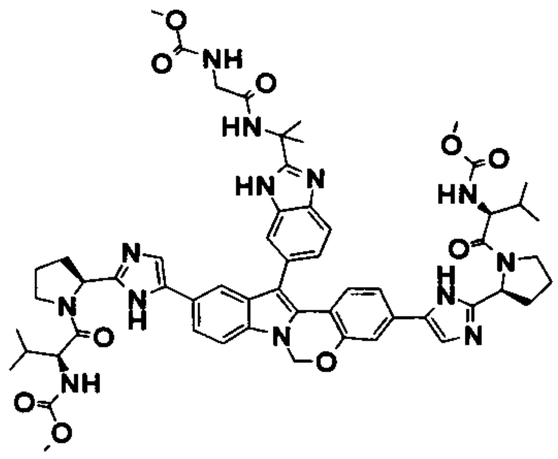
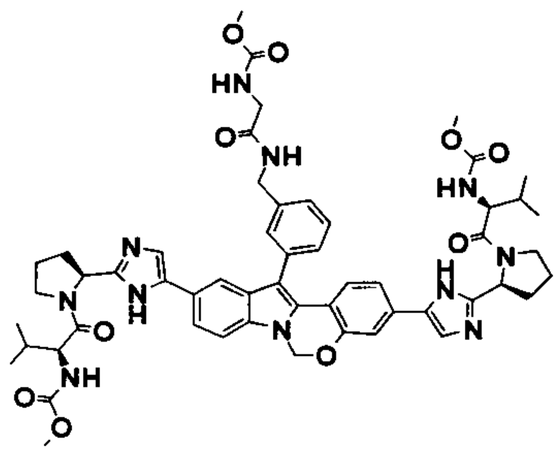
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1232		0.025	> 10	9.11	0.020	9.11	1173.60	1174.5	Single isomer
1233		0.059	29.393	9.111	0.029	9.111	1173.60	1175.4	Mixture of isomers
1234		> 2	381.08	156.186	0.075	211.543	824.40	825.3	Mixture of isomers
1235		0.270	155.87	65.774	0.025	81.879	824.40	825.4	Mixture of isomers

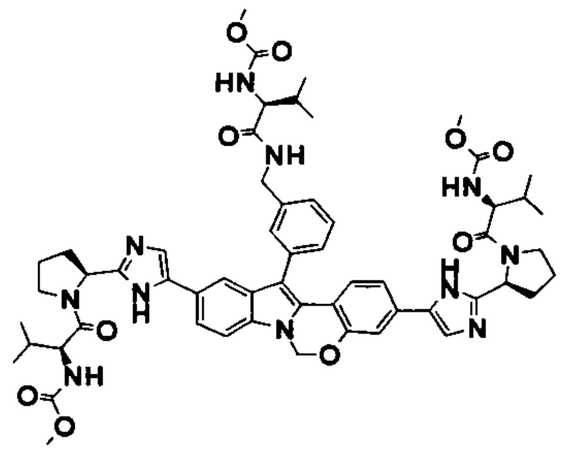
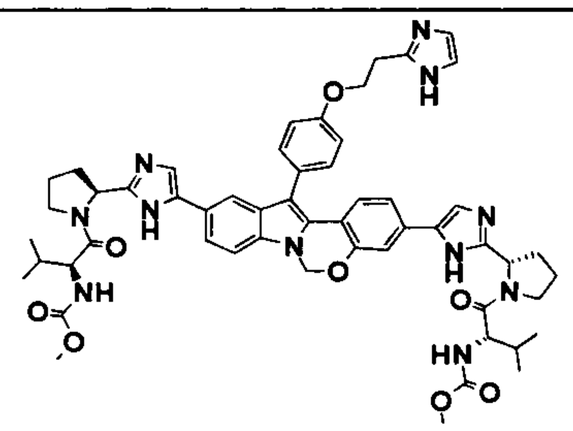
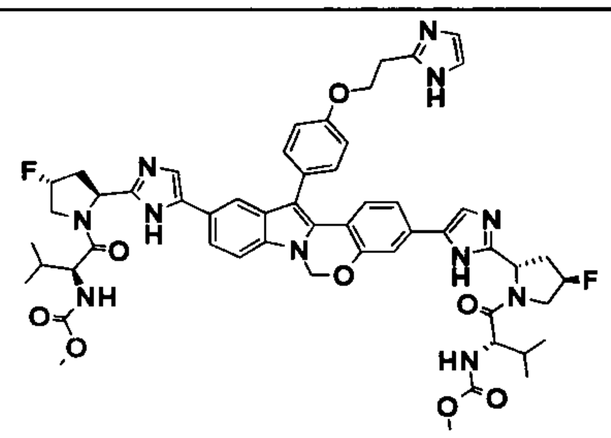
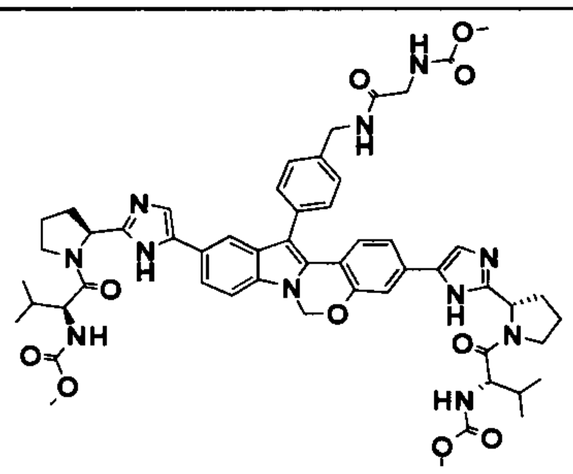
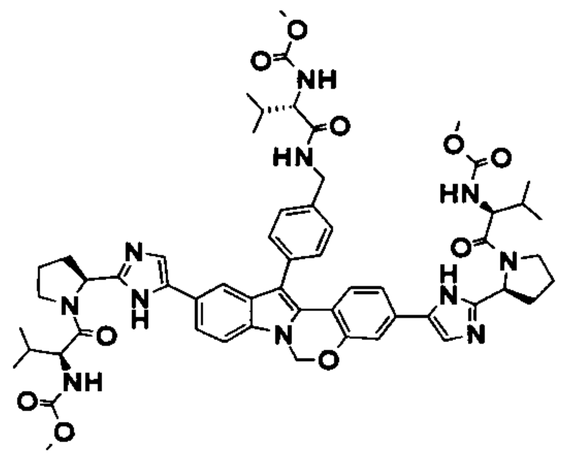
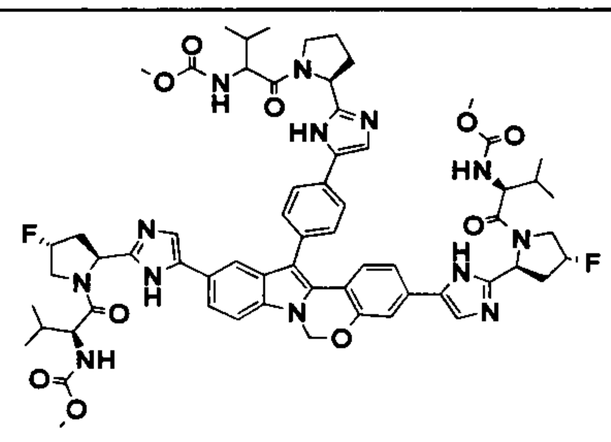
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1236		0.037	49	11	0.019	28	1058.50	1060.3	Single isomer
1237		0.203	13	83	0.008	219	897.40	898.3	Single isomer
1238		> 1	> 50	76.7	0.036	987.75	748.40	749.3	Single isomer
1239		0.112	> 50	> 5000	0.004	164.09	766.40	767.2	Single isomer

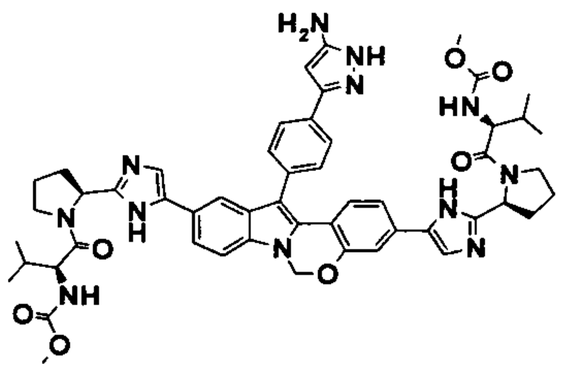
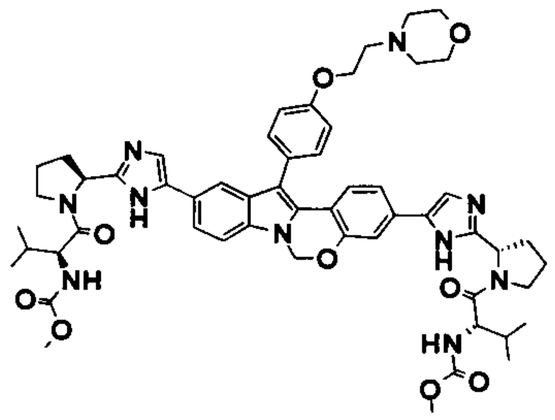
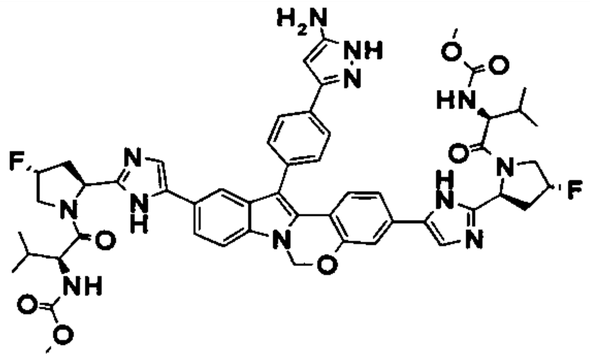
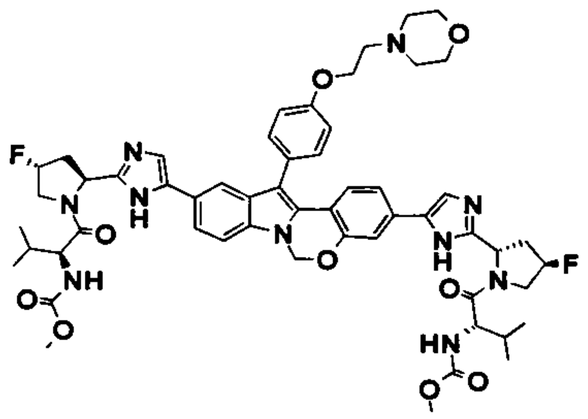
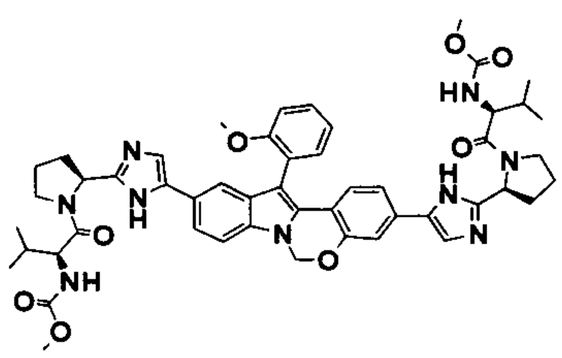
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1240		0.606	> 50	> 5000	0.039	745.66	762.40	763.2	Single isomer
1241		0.071	> 50	> 5000	0.014	325.09	763.30	764.2	Single isomer
1242		0.510	> 50	9.11	0.024	1248.86	788.30	789.2	Mixture of isomers
1243		0.320	> 50	9.11	0.021	1564.83	859.40	860.2	Mixture of isomers
1244		0.366	> 50	> 5000	0.025	1457.91	747.40	748.3	Single isomer

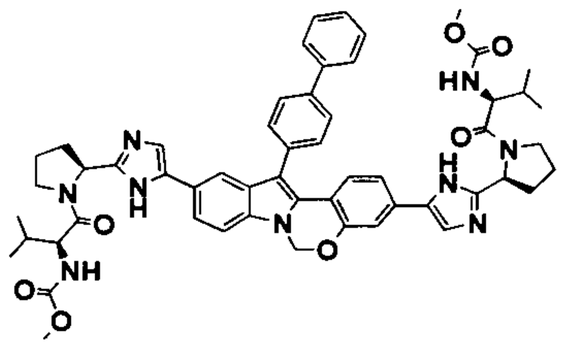
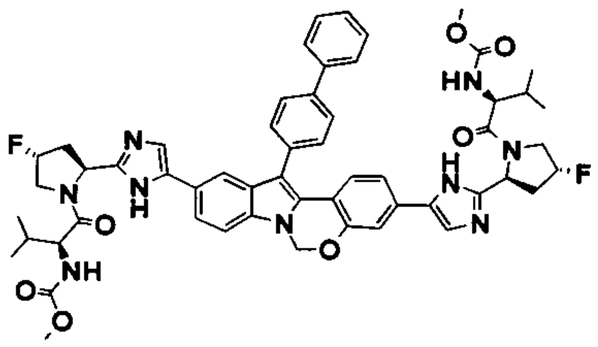
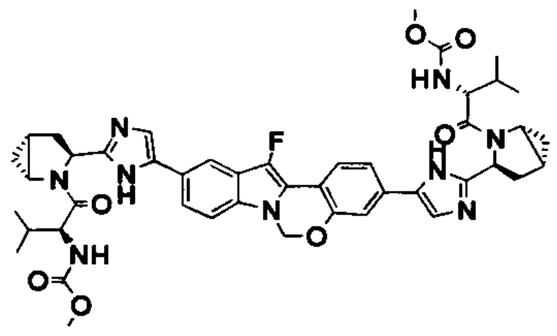
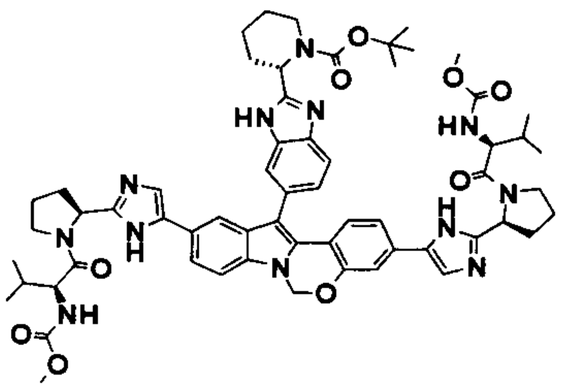
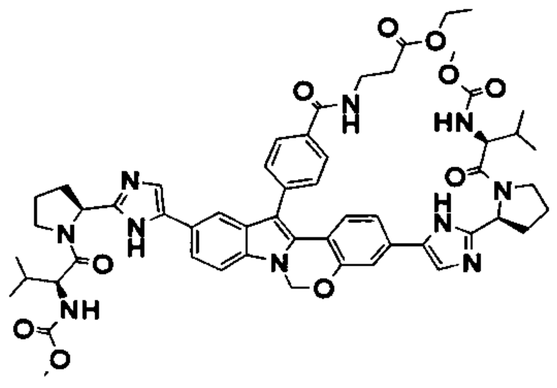
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1245		0.266	> 50	> 5000	0.019	614.1	777.40	778.3	Single isomer
1246		0.023	> 50	9.11	0.004	103.13	853.40	854.3	Mixture of isomers
1247		> 2	> 50	612.51	0.012	217.17	853.40	854.4	Mixture of isomers
1248		> 1	> 50	9.11	0.053	281.25	754.30	755.3	Single isomer

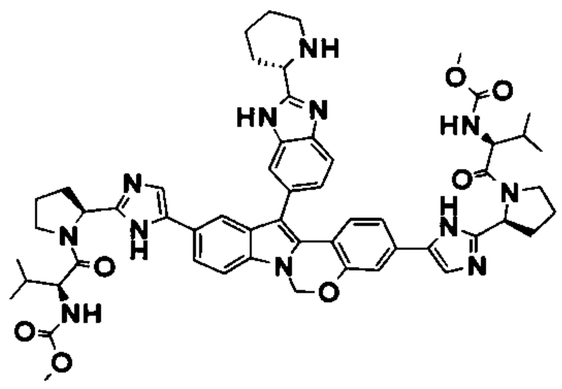
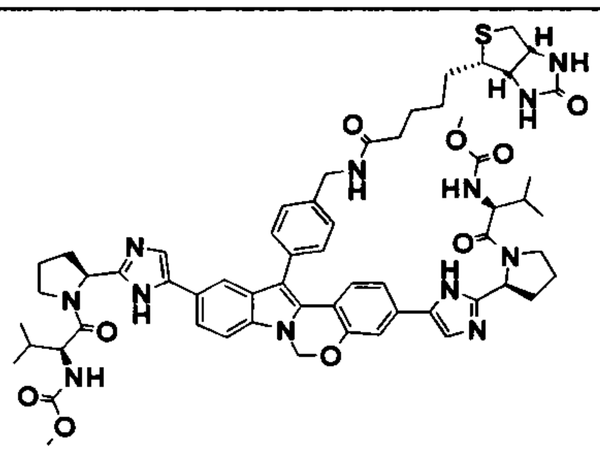
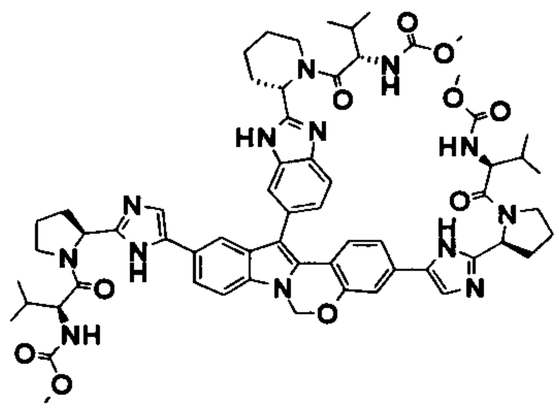
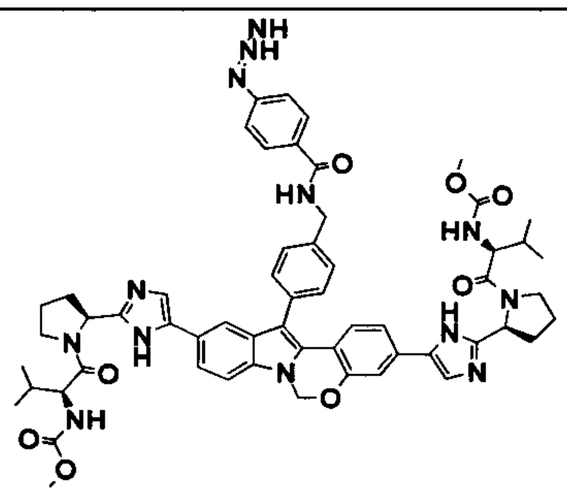
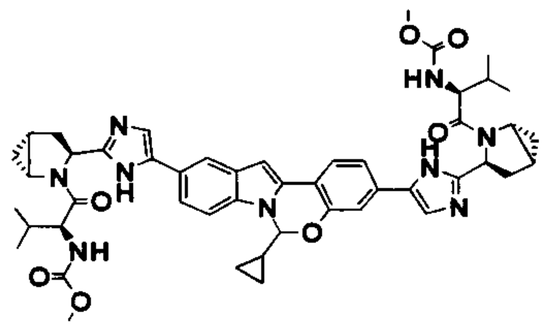
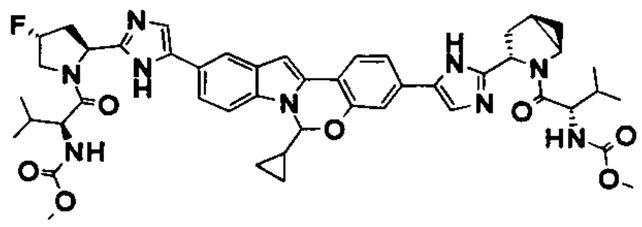
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1249		0.045	> 200	43.2	0.004	57.81	1078.50	1060.4	Single isomer
1250		2.633	> 20000	> 200	0.192	> 200	937.40	938.5	Single isomer
1251		0.037	> 200	10.1	0.004	> 200	1010.50	1012.4	Single isomer
1252		0.019	> 200	17.8	0.004	> 200	1010.50	1011.5	Single isomer
1253		3.974	359.7	> 200	> 2	> 200	758.40	759.3	Single isomer

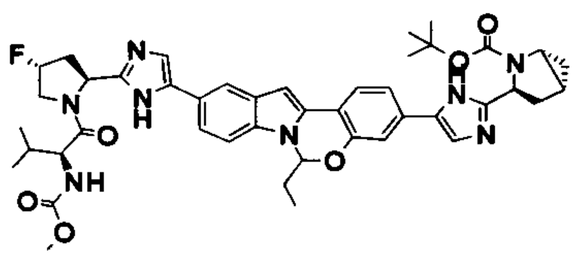
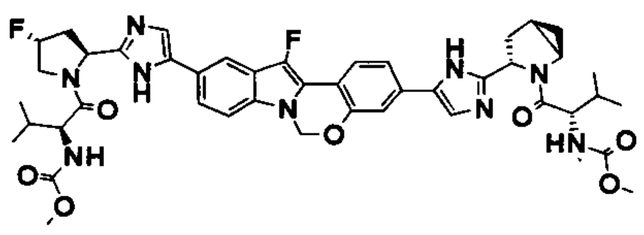
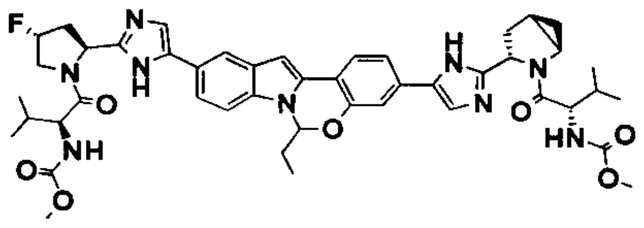
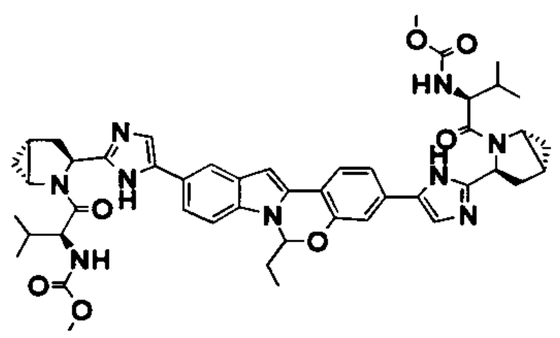
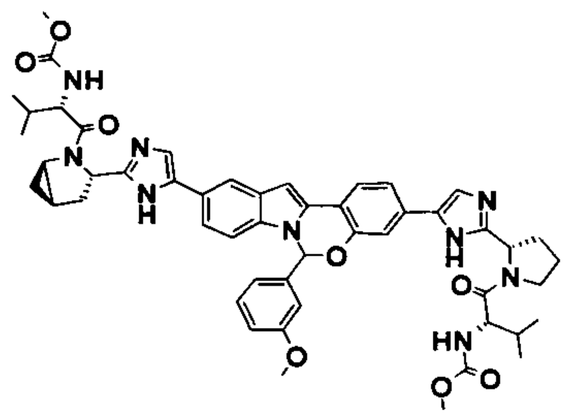
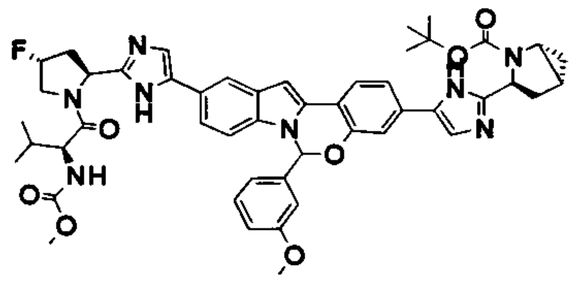
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1254		4.765	1234.4	> 200	0.177	> 200	978.50	979.4	Single isomer
1255		0.043	46.8	200	0.022	> 200	910.50	911.2	Single isomer
1256		0.100	> 200	> 200	0.014	> 200	910.50	911.1	Single isomer
1257		0.020	> 200	200	0.092	> 200	1020.50	1023.0	Single isomer
1258		0.041	> 200	56.12	0.028	12.5	1093.50	1094.9	Single isomer
1259		0.064	> 200	20	0.005	12.7	1025.50	1026.0	Single isomer

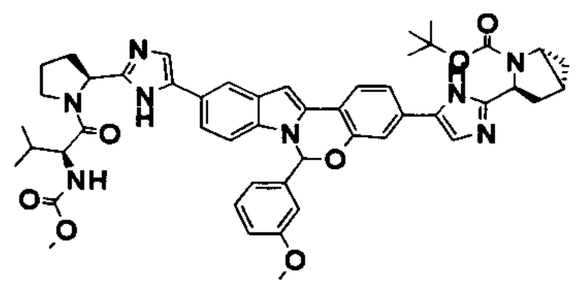
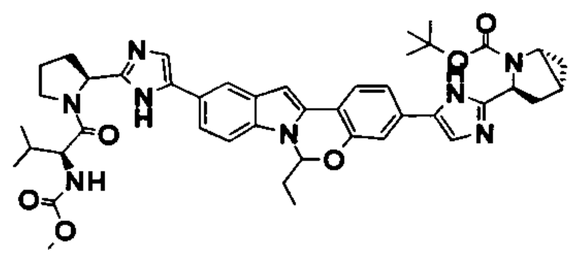
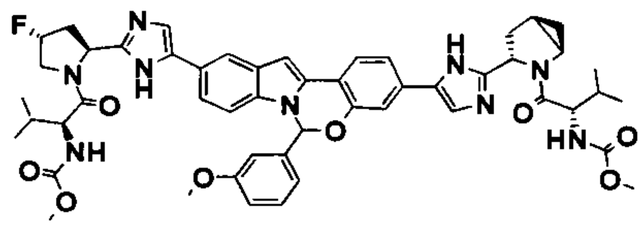
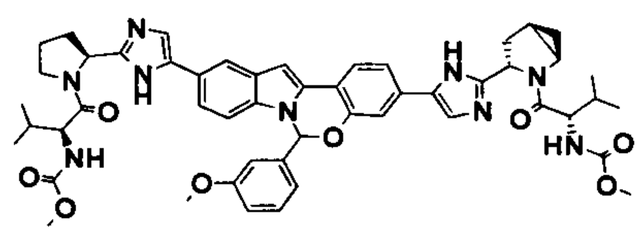
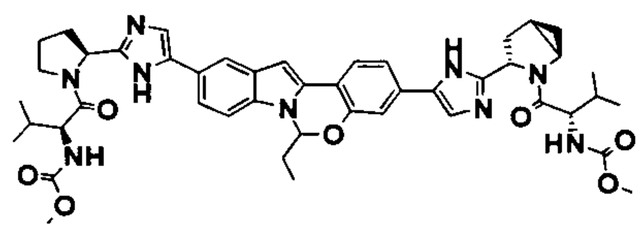
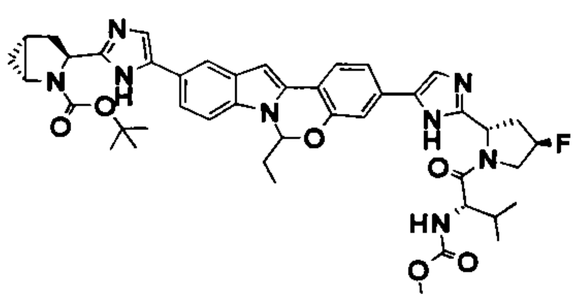
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1260		0.119	5.7	> 200	0.013	> 200	1067.50	1068.1	Single isomer
1261		0.030	82	8	0.008		991.50	992.5	Single isomer
1262		0.300	59	>100	0.030		1027.50	1028.4	Single isomer
1263		0.130	>100	>100	0.005		1025.50	1026.5	Single isomer
1264		0.020	74	20	0.007		1067.50	1069.3	Single isomer
1265		0.116	0.6	0.31	0.080	1	1209.60	1210.0	Single isomer

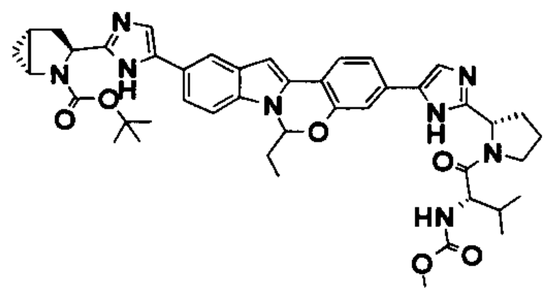
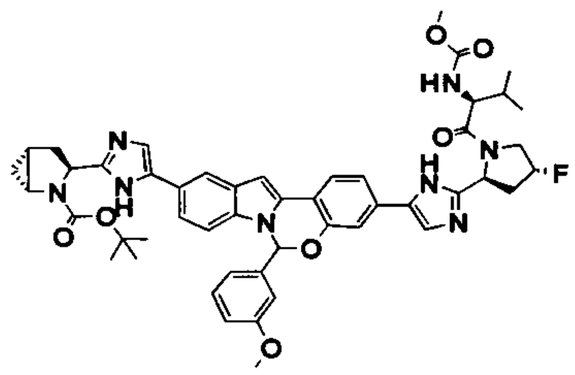
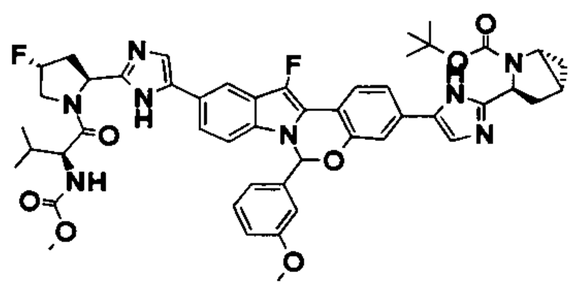
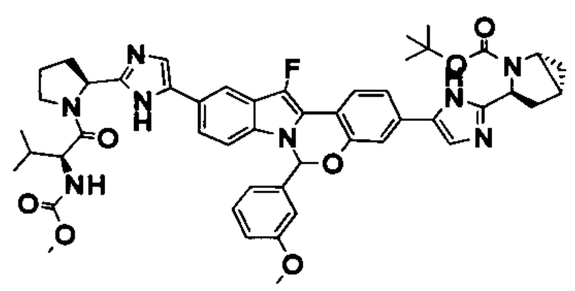
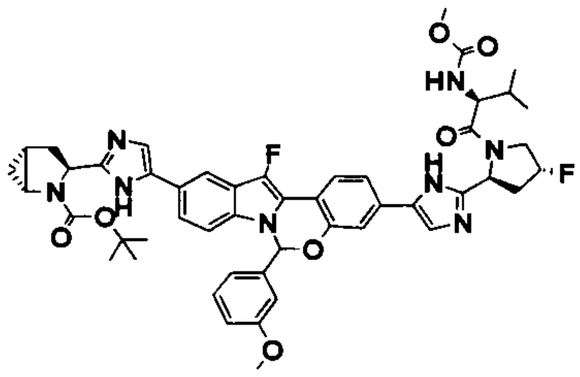
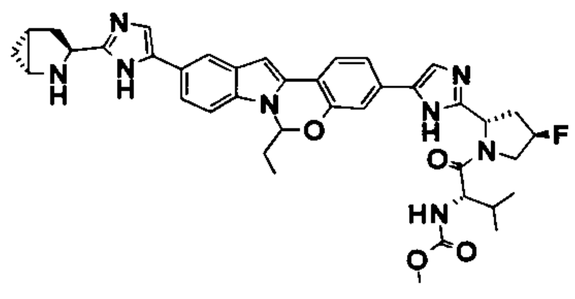
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1266		0.458	24	37.72	0.103	47.239	962.50	963.5	Single isomer
1267		0.079	82	8	0.013	1.875	1010.50	1011.0	Single isomer
1268		1.000	> 100	> 100	0.423	> 100	998.40	999.0	Single isomer
1269		0.093	3.57	19.5	0.006	107	1046.50	1047.6	Single isomer
1270		0.039	60.65	18	0.010	34.6	911.40	912.4	Single isomer

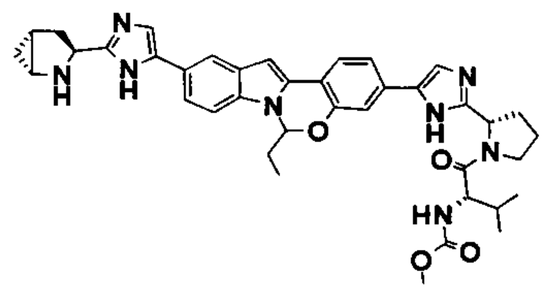
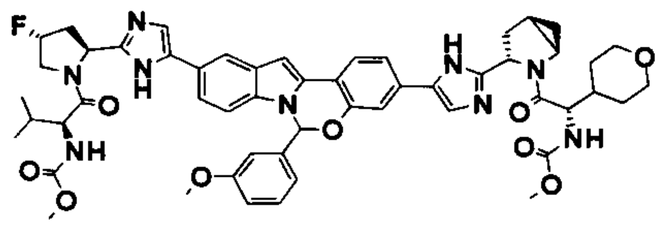
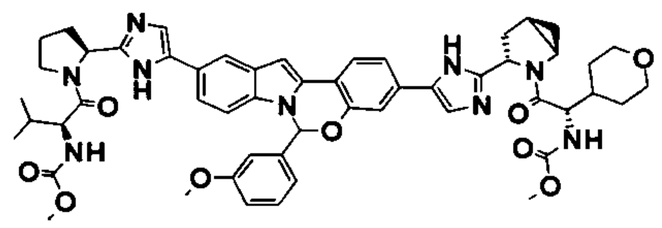
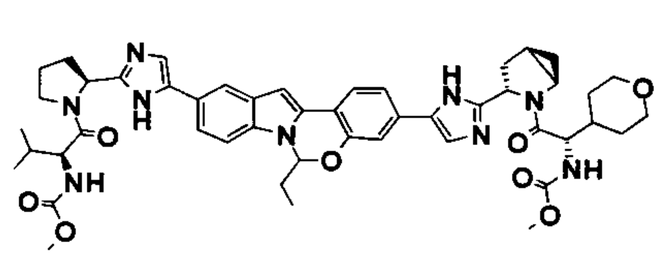
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1271		0.094	50.63	25.7	0.009	58.827	957.50	958.5	Single isomer
1272		0.005		1.826	0.004	5.138	993.40	994.4	Single isomer
1273		0.002	3	0.789	0.003	27.939	847.40	849.3	Single isomer
1274		0.056	72	7.5	0.013	29.2	1104.60	1105.4	Single isomer
1275		0.044	99	0.9	0.013	15.1	1024.50	1026.4	Single isomer

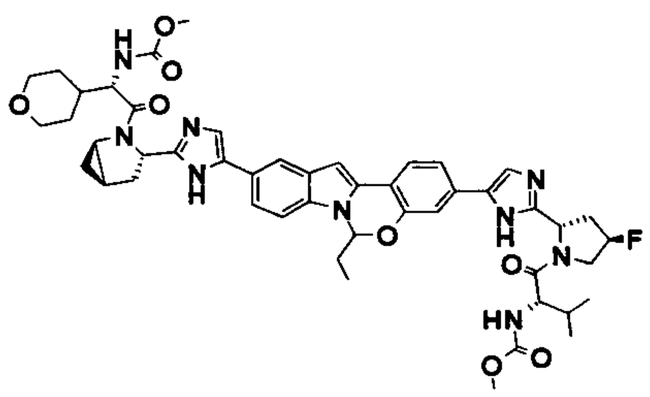
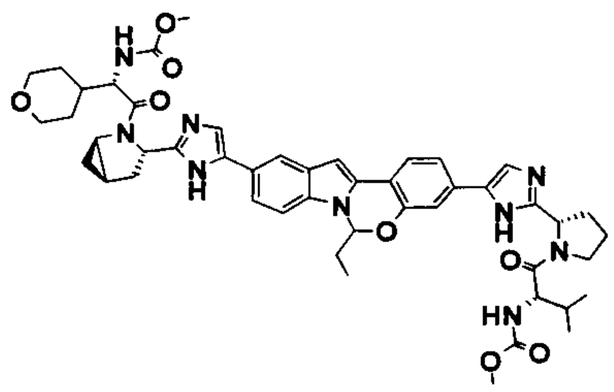
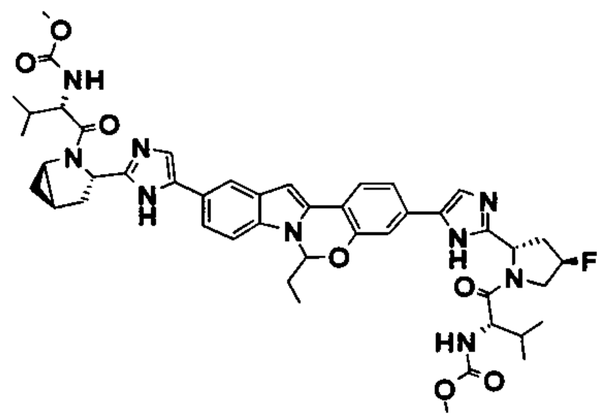
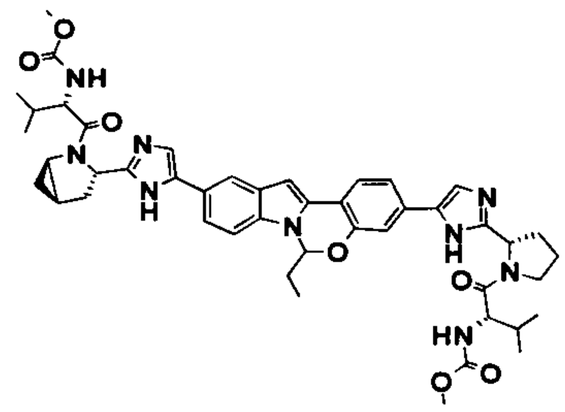
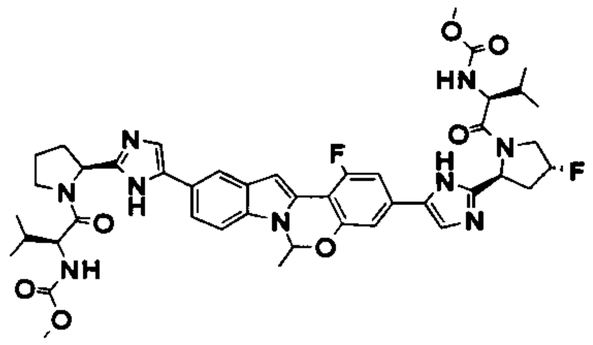
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1276		> 1	> 100	> 100	> 1	> 100	1004.50	1005.4	Single isomer
1277		> 1	> 100	> 100	0.597	> 100	1136.50	1138.5	Single isomer
1278			> 100	> 100	0.023		1161.60	1163.0	Single isomer
1279		0.052	34.3	15.803	0.026	84	1056.50	1057.3	Single isomer
1280		0.011	21.3	4.007	0.020	110	869.40	871.4	Mixture of isomers
1281		0.026	2.3	13.4	0.009	> 100	875.40	877.5	Mixture of isomers

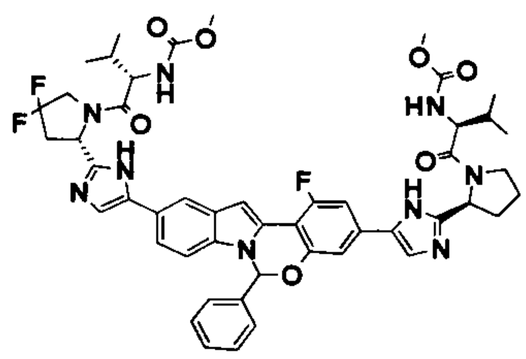
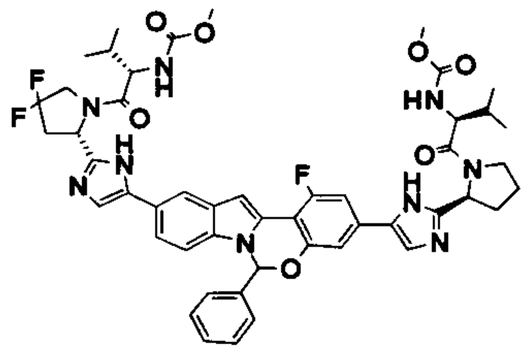
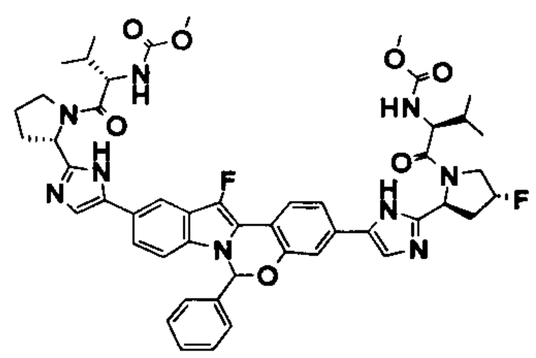
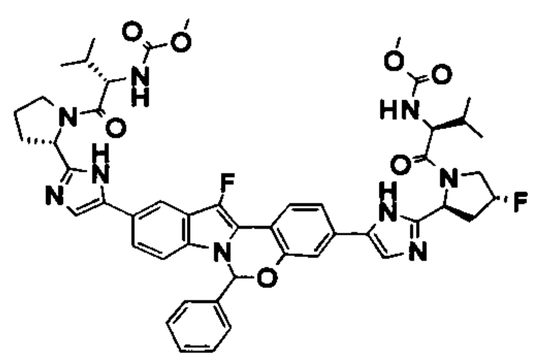
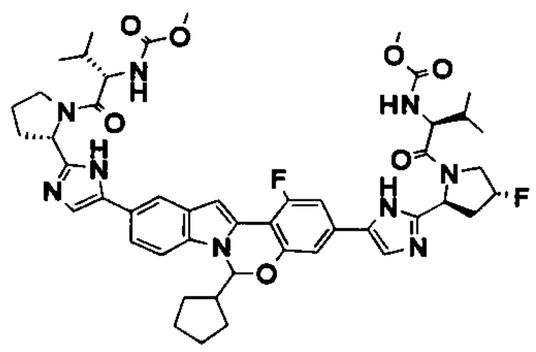
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1282		> 1	> 100	> 100	0.177	> 100	806.40	807.4	Mixture of isomers
1283		>1		>100		>100	853.40	854.3	Single isomer
1284		0.020		1.2		10	863.40	864.4	Mixture of isomers
1285		0.010		1.9		1.3	857.40	858.4	Mixture of isomers
1286		0.002		1.2		0.2	923.40	924.5	Mixture of isomers
1287		24.000		110		217	884.40	884.7	Mixture of isomers

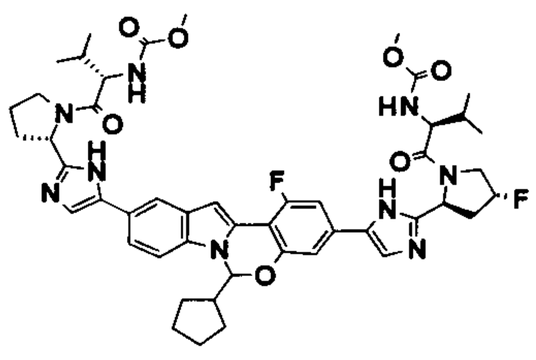
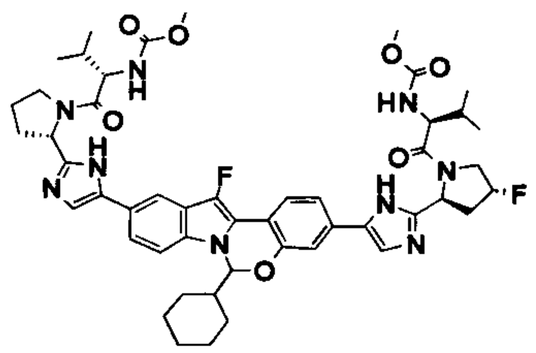
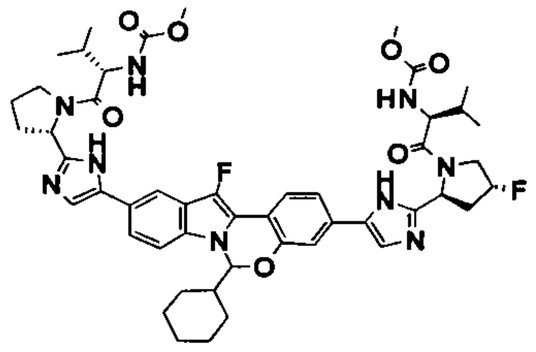
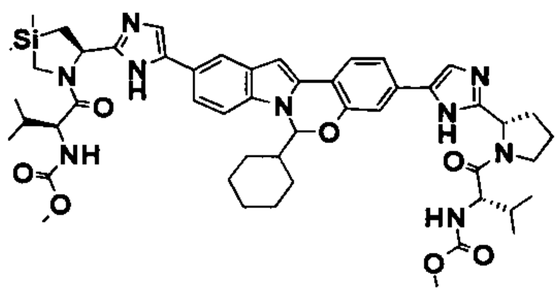
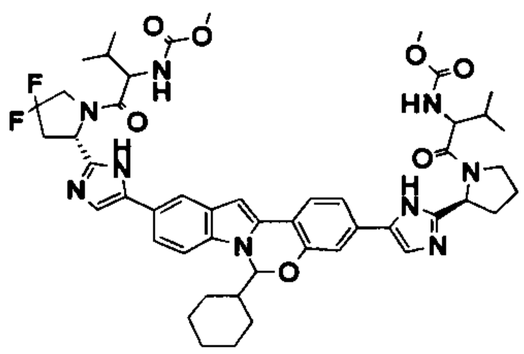
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1288		3.000		202		125	866.40	866.8	Mixture of isomers
1289		13.000		408		378	788.40	788.8	Mixture of isomers
1290		0.010		0.23		0.31	941.40	942.6	Mixture of isomers
1291		0.020		1		0.14	923.40	924.7	Mixture of isomers
1292		0.010		7		1	845.40	845.8	Mixture of isomers
1293							806.40	806.8	Mixture of isomers

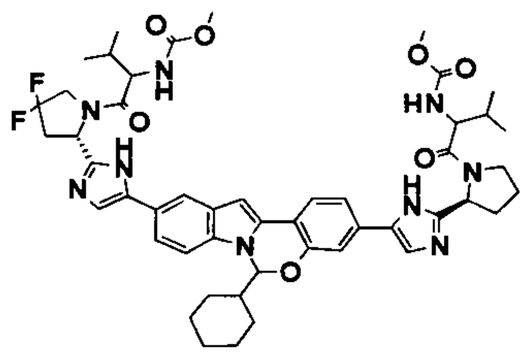
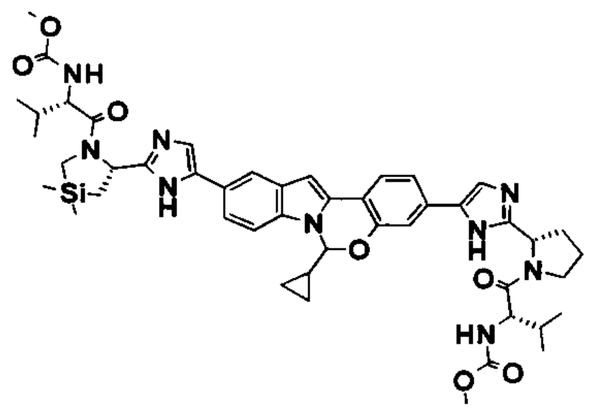
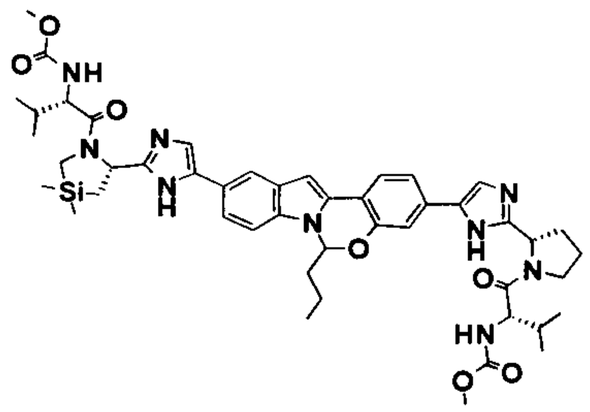
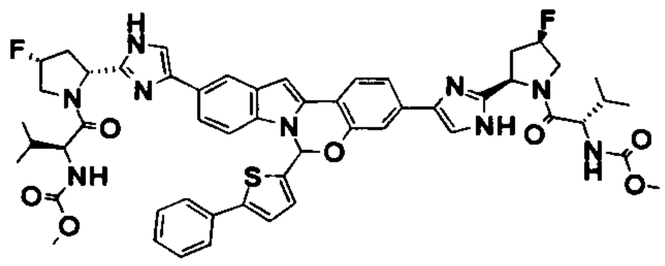
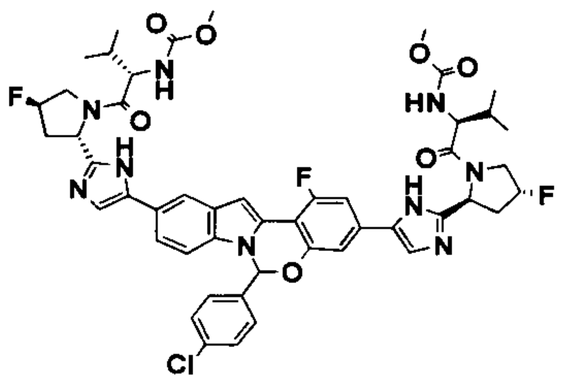
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1294							788.40	788.8	Mixture of isomers
1295							884.40	884.8	Mixture of isomers
1296							902.40	902.6	Mixture of isomers
1297							884.40	884.8	Mixture of isomers
1298							902.40	902.8	Mixture of isomers
1299							706.30	706.8	Mixture of isomers

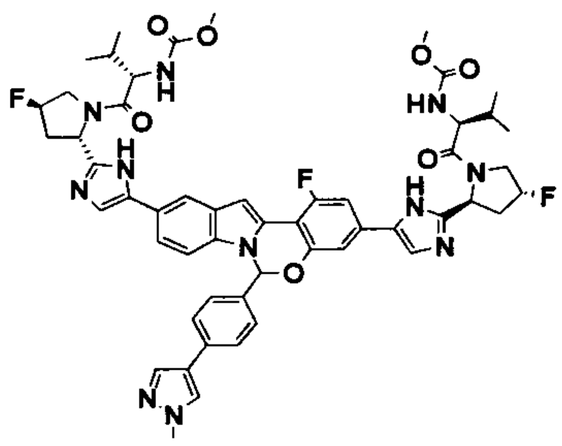
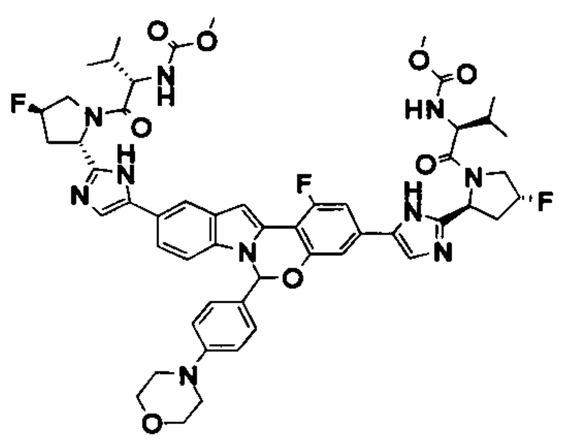
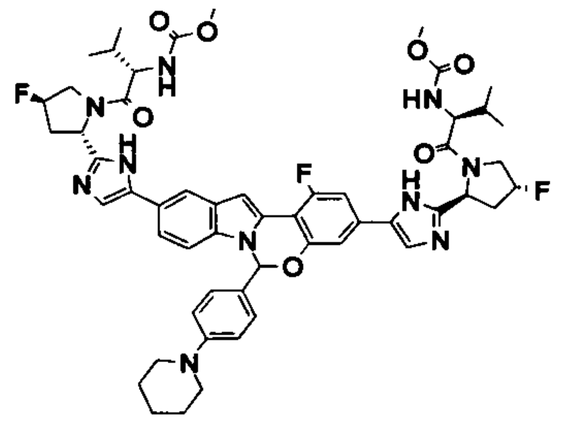
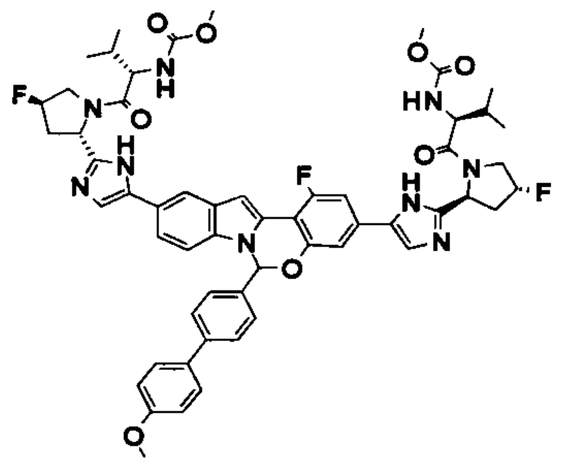
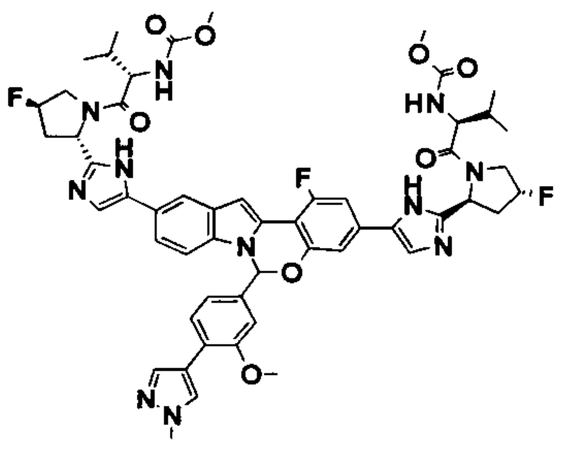
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1300							688.40	688.8	Mixture of isomers
1301		0.080	0.14	0.19		11	983.40	983.6	Mixture of isomers
1302		0.060	1	0.02		0.3	965.40	965.6	Mixture of isomers
1303		0.060	1.8	2.3		1.3	887.40	887.8	Mixture of isomers

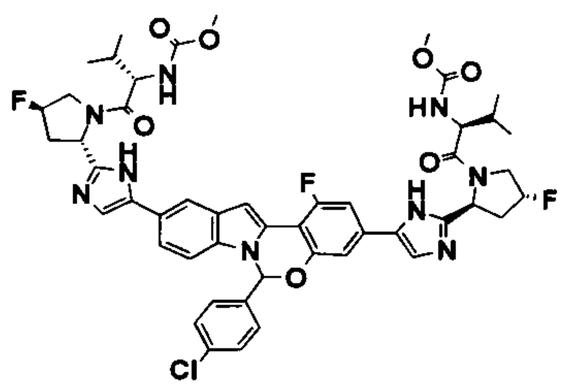
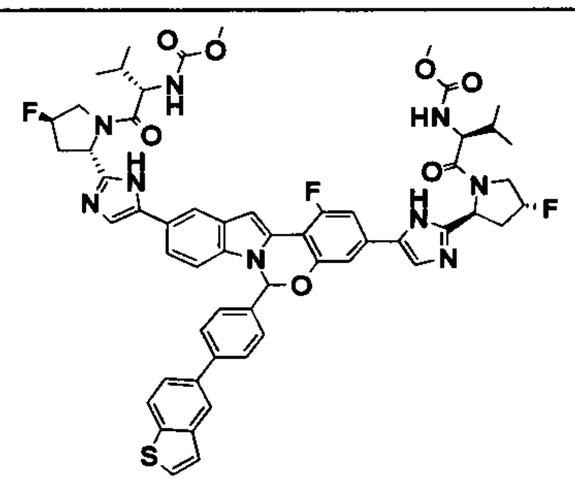
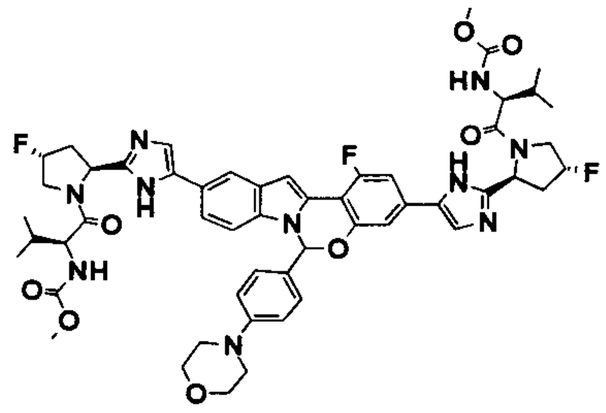
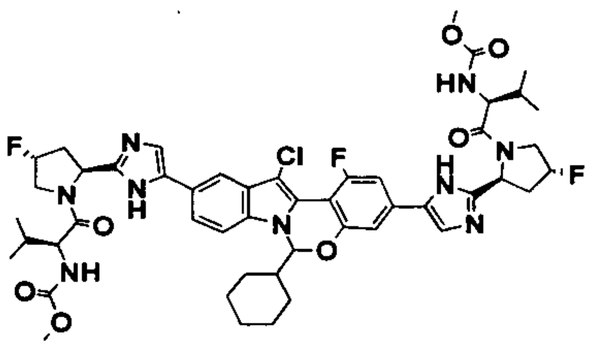
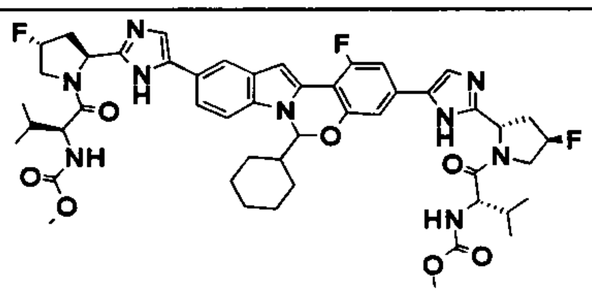
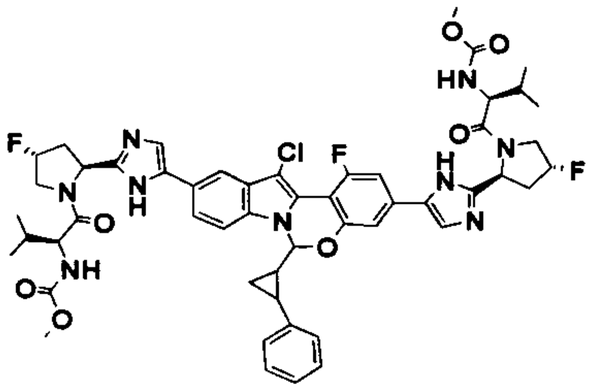
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1304		0.020	0.18	0.7		2.7	905.40	905.7	Mixture of isomers
1305		0.020	1	0.2		1.7	887.40	887.8	Mixture of isomers
1306		0.010	0.4	2.1		13	863.40	863.8	Mixture of isomers
1307		0.010	7	1.6		11	845.40	845.8	Mixture of isomers
1308		0.004	20	1.11	0.003		855.95	857.0	Mixture of isomers

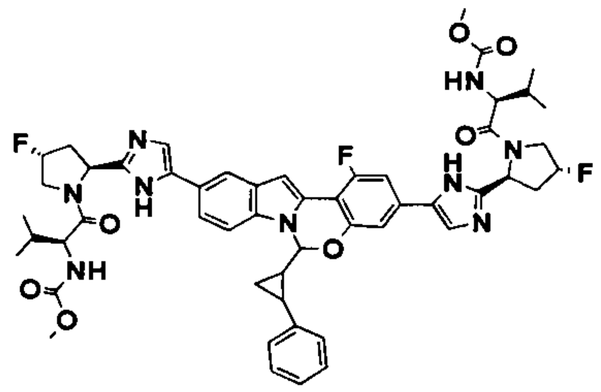
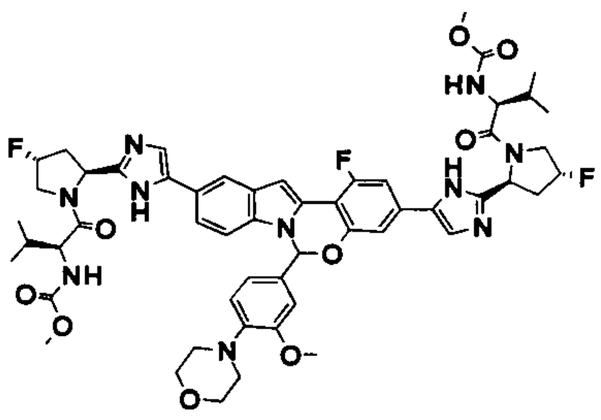
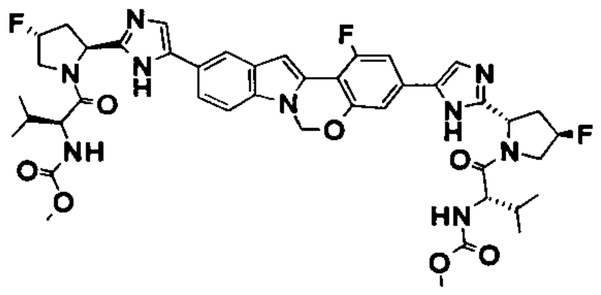
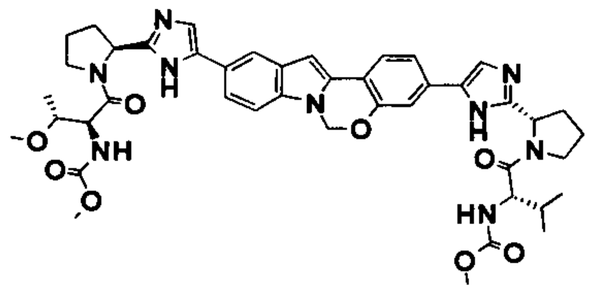
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1309		0.002	4.03	0.1997	0.001	24.3	936.012	937.0	Mixture of isomers
1310		0.001	0.46	0.019	0.001	12.3	936.012	937.0	Mixture of isomers
1311		0.001	0.2	0.6	0.001	9	918.022	919.0	Mixture of isomers
1312		0.004	5.4	0.7	0.001	42	918.022	919.0	Mixture of isomers
1313		0.016	7.6	3.8	0.001	10	910.042	911.0	Mixture of isomers

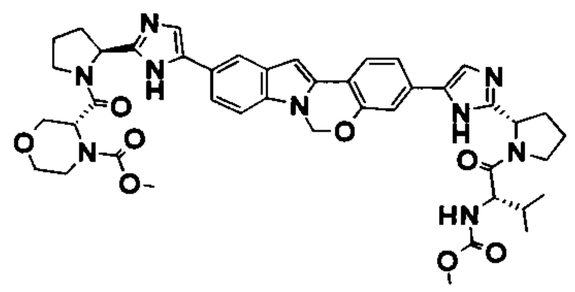
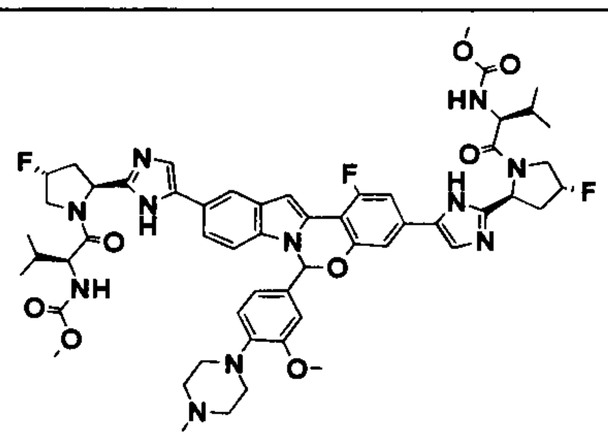
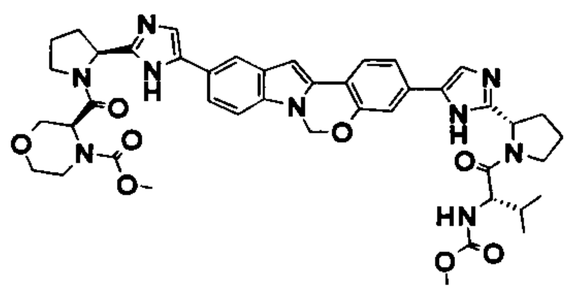
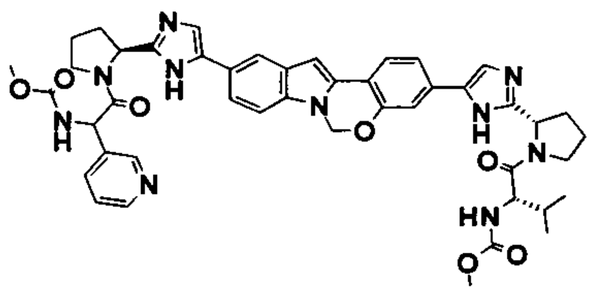
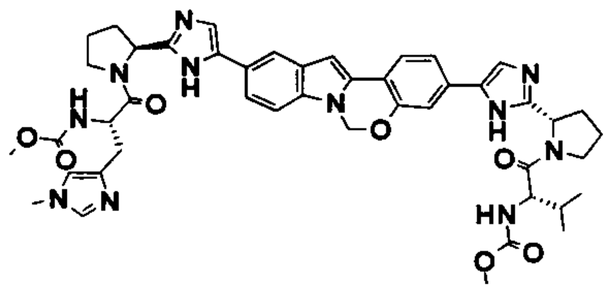
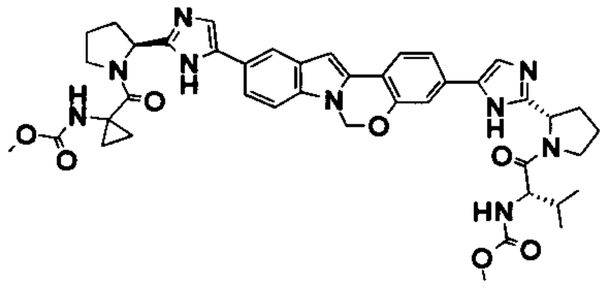
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1314		0.001	0.3	1.1	0.001	31	910.042	911.0	Mixture of isomers
1315		0.009	7.7	3	0.001	6	924.069	925.1	Mixture of isomers
1316		0.002	0.3	1	0.001	30	924.069	925.1	Mixture of isomers
1317		0.020	< 100	9.94	0.002	100.2	932.218	933.2	Mixture of isomers
1318		0.010	59.96	3.6	0.020	19.9	924.069	925.1	Mixture of isomers

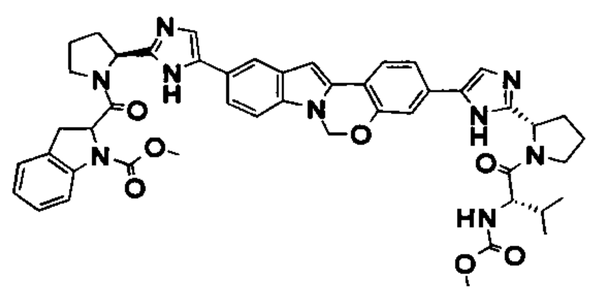
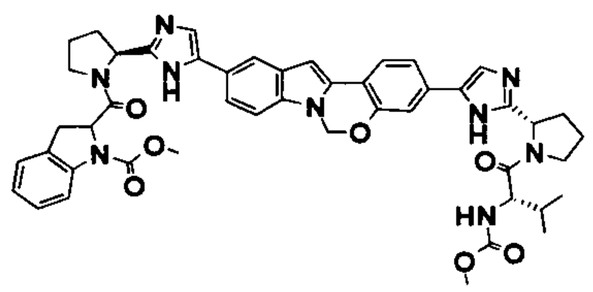
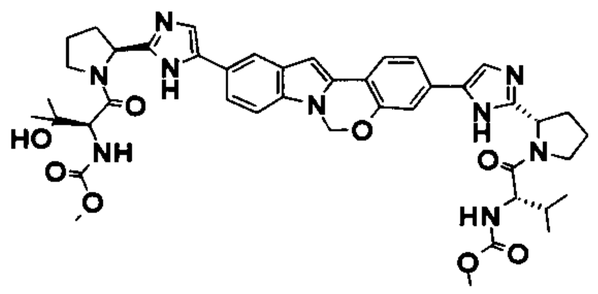
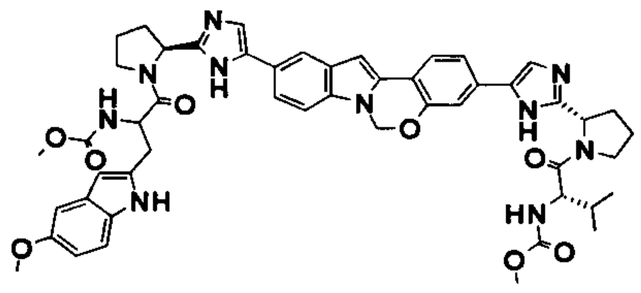
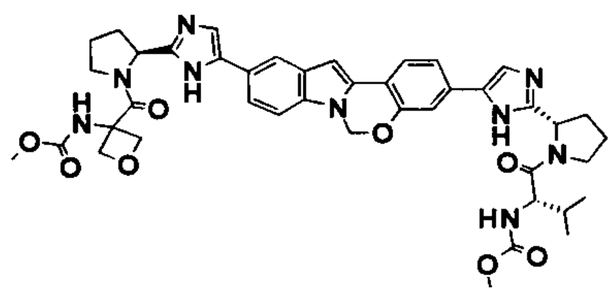
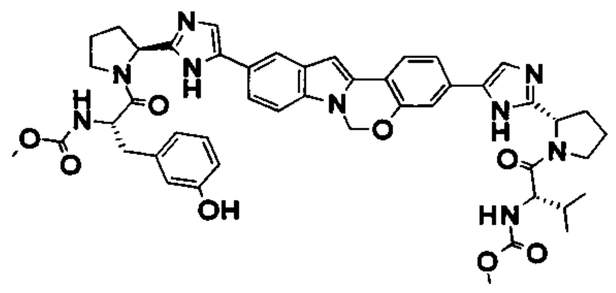
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1319		0.010	2	1.1	0.020	26.1	924.069	925.1	Mixture of isomers
1320		0.018	105	10		12	890.136	891.1	Mixture of isomers
1321		0.014	208	10		72.7	892.152	893.2	Mixture of isomers
1322		0.019	1	3.6	0.003	89	1000.48	1001.5	Mixture of isomers
1323		0.005	0.47	9.6	0.004	9.7	970.457	971.5	Mixture of isomers

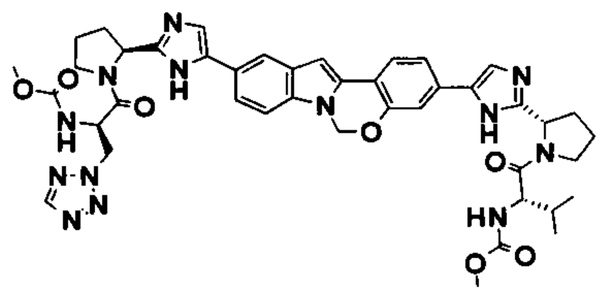
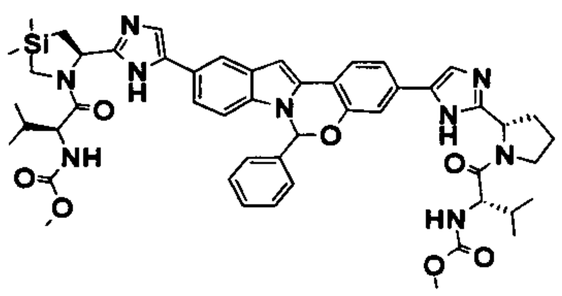
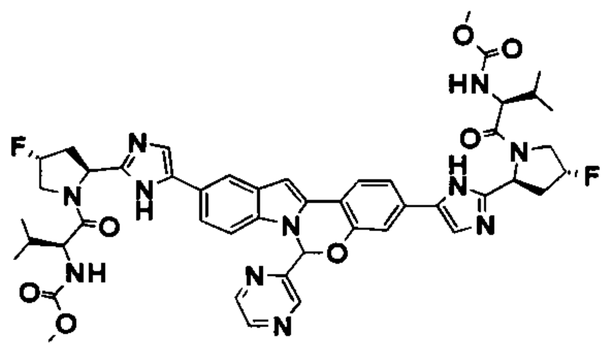
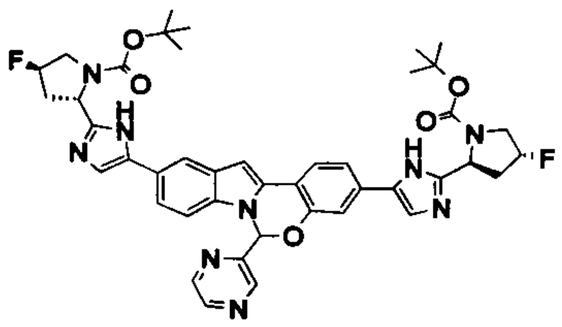
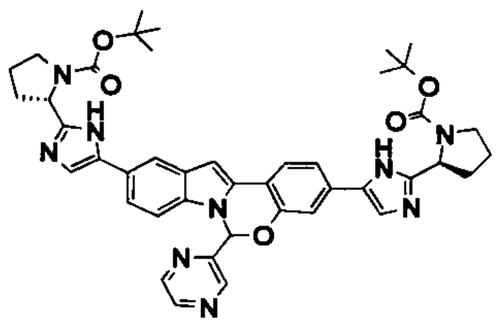
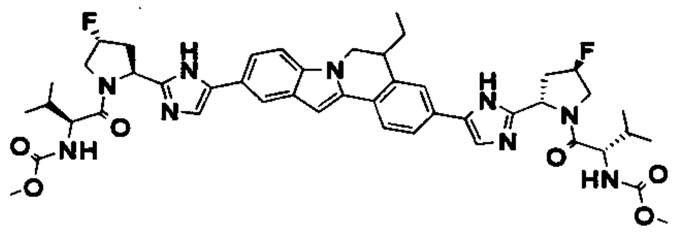
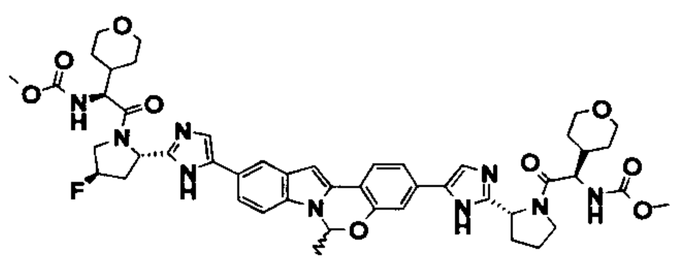
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1324		0.009	0.43	10.2	0.007	26.3	1016.1	1017.1	Mixture of isomers
1325		0.003	0.19	1.1	0.003	8.1	1021.12	1022.1	Mixture of isomers
1326		0.006	0.38	9.11	0.004	25.14	1019.15	1020.2	Mixture of isomers
1327		0.007	2.51	9.11	0.002	17.64	1042.14	1043.1	Mixture of isomers
1328		0.007	0.36	88.43	0.006	180.29	1046.13	1047.1	Mixture of isomers

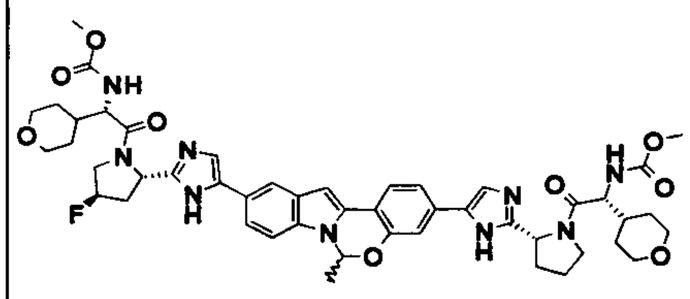
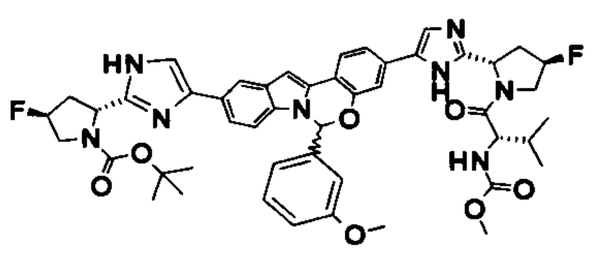
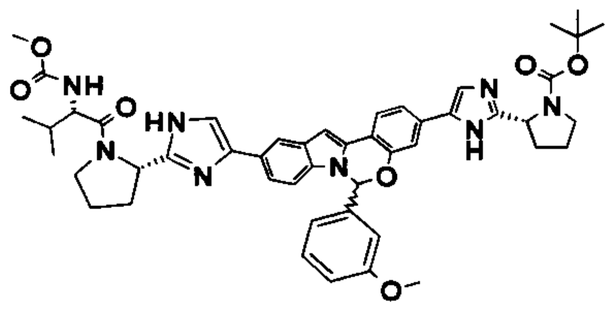
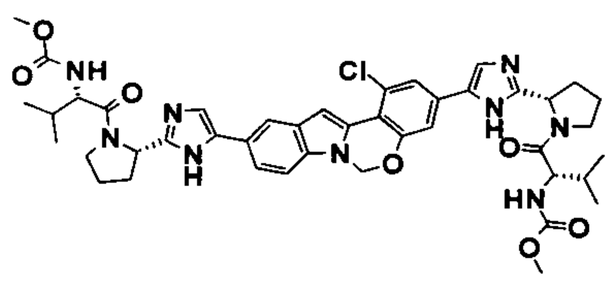
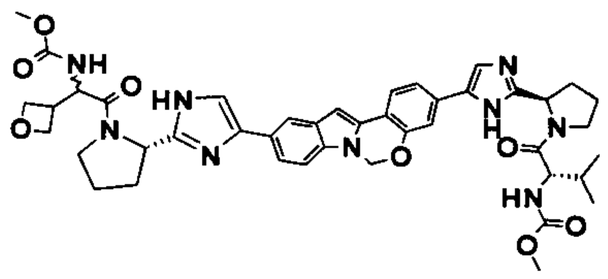
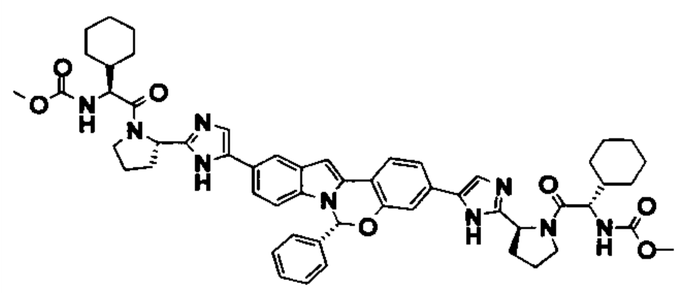
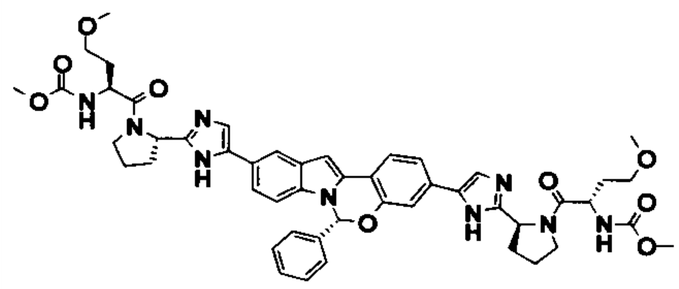
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1329		0.003	0.09	70.44	0.002	> 5000	970.457	971.5	Mixture of isomers
1330		0.006	0.19	1	0.004	18.3	1068.2	1069.2	Mixture of isomers
1331		0.005		0.8	0.004	10.04	1021.12	1022.1	Mixture of isomers
1332		0.037	0.3	7	0.002	51.1	976.505	977.5	Mixture of isomers
1333							942.06	943.1	Mixture of isomers
1334							1010.52	1011.5	Mixture of isomers

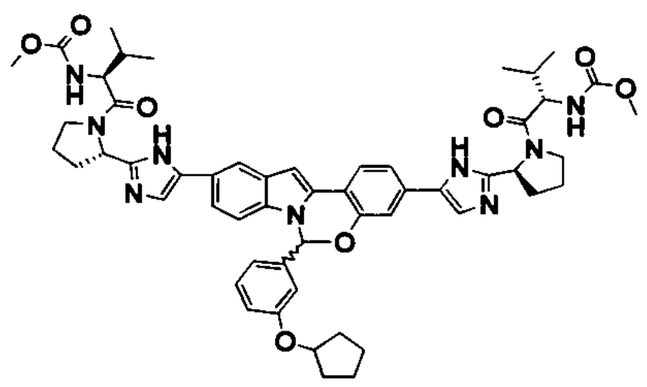
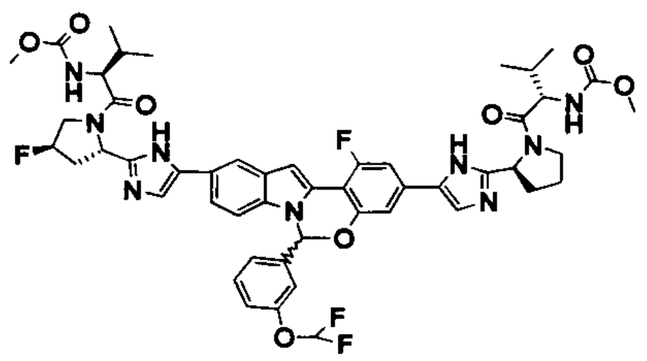
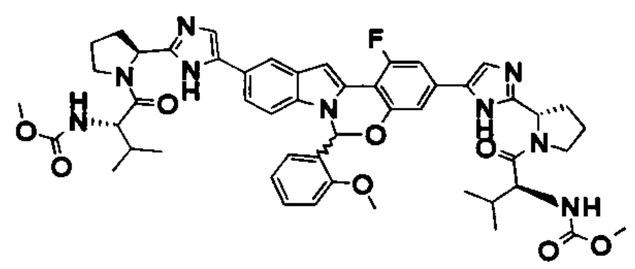
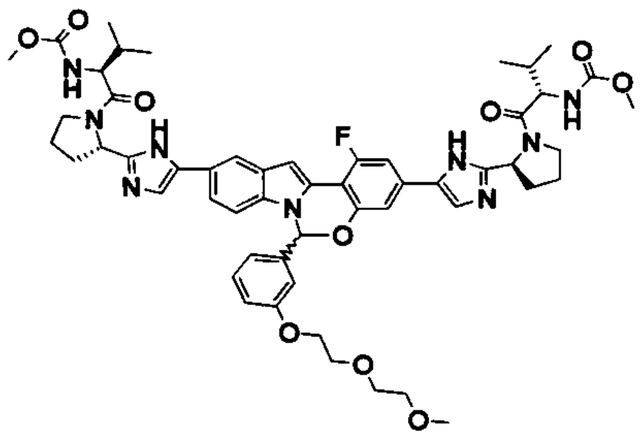
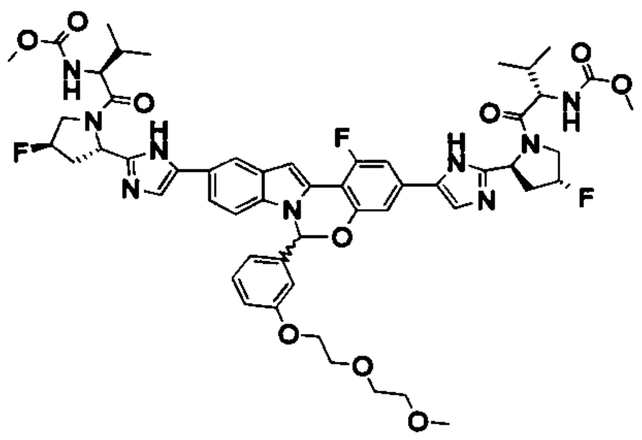
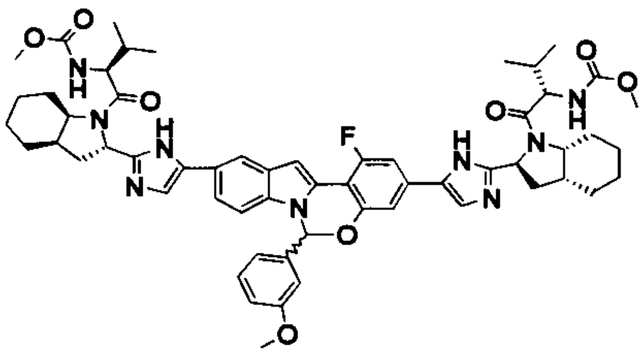
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1335		0.017	> 100	18.1	0.008	1.248	976.077	977.1	Mixture of isomers
1336		0.032	15.67	5.4	0.008	2.38	1051.15	1052.2	Mixture of isomers
1337		0.010	0.5	19	0.007	167	859.913	860.9	Single isomer
1338		0.009	53	1.7	0.008	26	821.941	822.9	Single isomer
1339		0.040	52.8	4.88	0.017	110	843.951	845.0	Single isomer

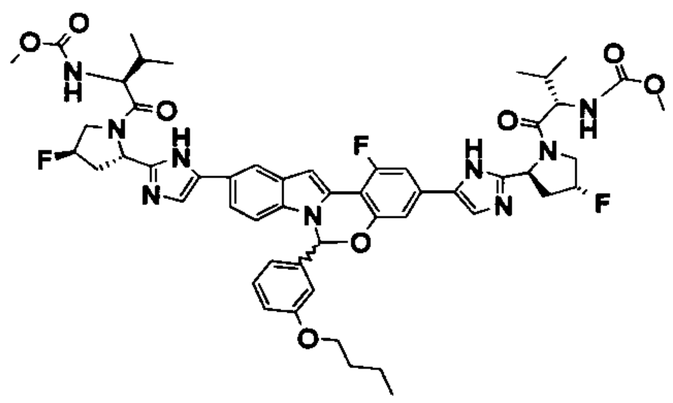
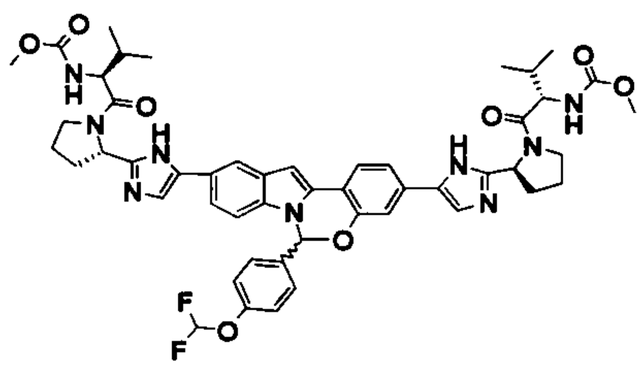
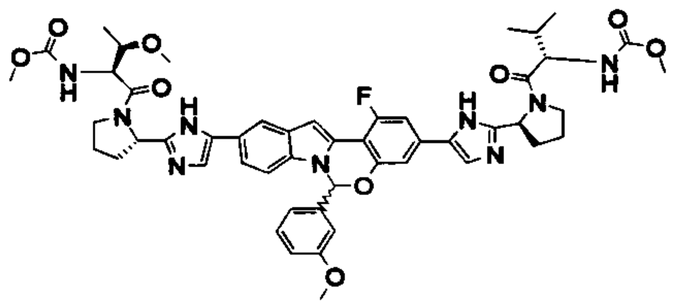
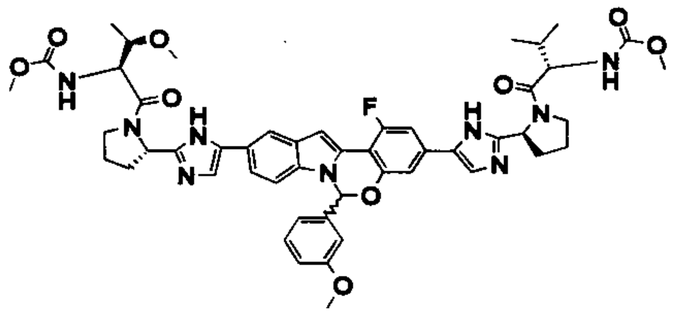
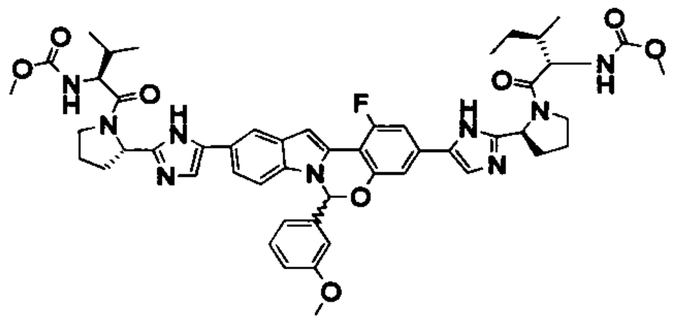
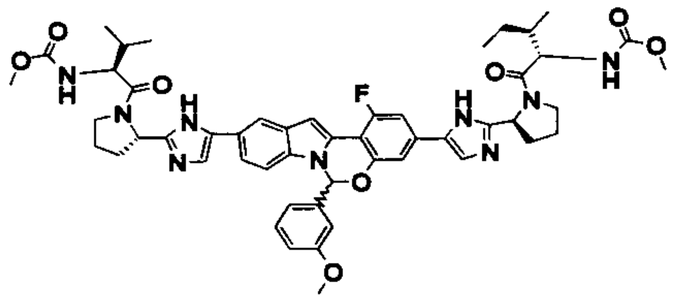
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1340		0.022	64.7	13.98	0.017	110	819.925	820.9	Single isomer
1341							1064.19	1065.2	Mixture of isomers
1342		0.036	42.2	29.15	0.023	110	819.925	820.9	Single isomer
1343		0.026	40.3	6.48	0.015	36	840.947	841.9	Mixture of isomers
1344		0.012	109.9	19.1	0.009	110	857.978	859.0	Single isomer
1345		0.054	109.9	109.9	0.018	110	789.899	790.9	Single isomer

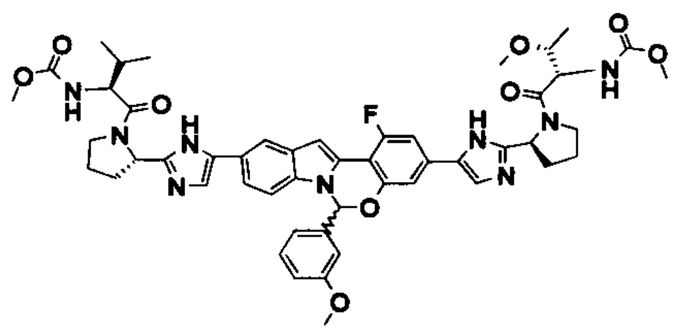
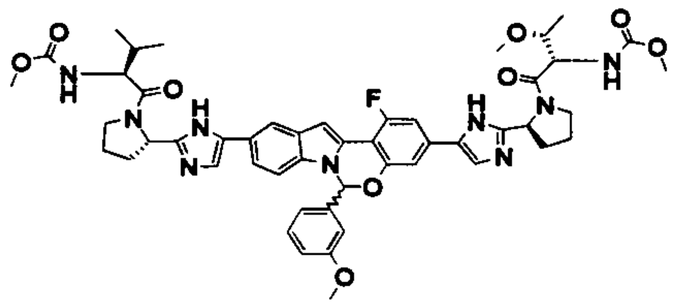
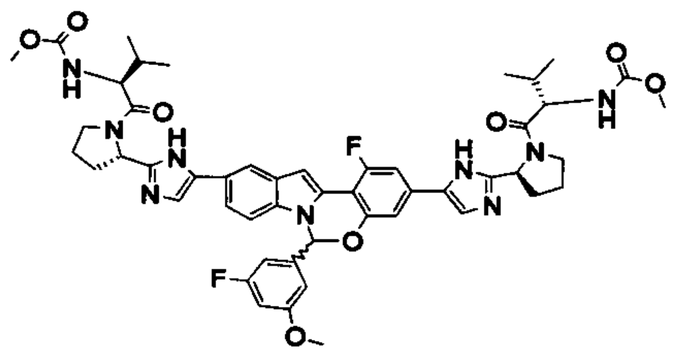
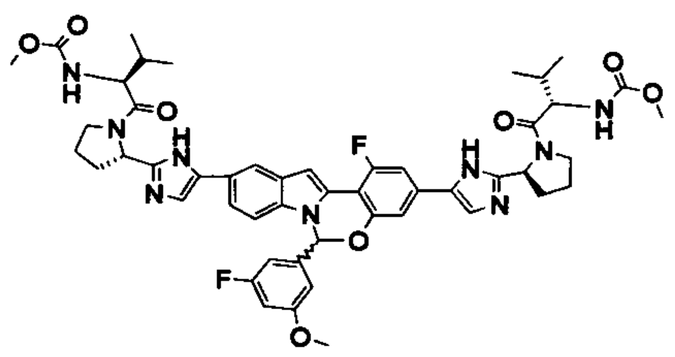
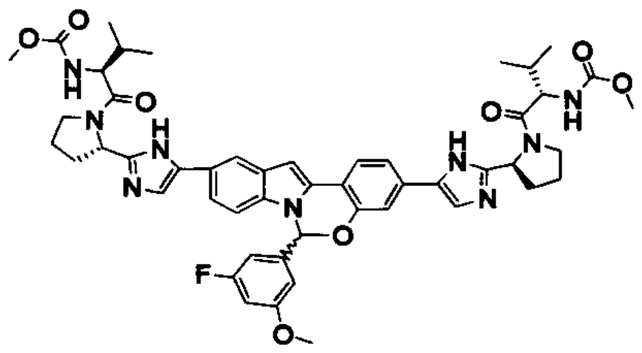
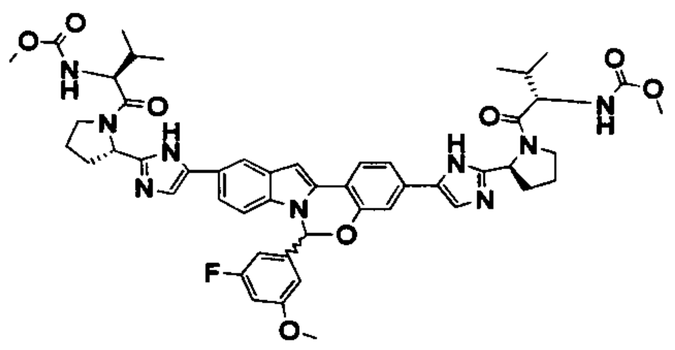
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1346		> 2	109.9	48.617	0.126	110	851.971	853.0	Mixture of isomers
1347		> 1	> 100	> 100	0.238	> 100	851.971	853.0	Mixture of isomers
1348		0.008	> 100	6.1	0.010	55.2	821.941	822.9	Single isomer
1349		0.691	> 100	90.1	0.107	> 100	923.05	924.1	Mixture of isomers
1350		0.051	> 100	> 100	0.015	> 100	805.898	806.9	Single isomer
1351		0.018	78.9	4.1	0.006	54.2	869.986	871.0	Single isomer

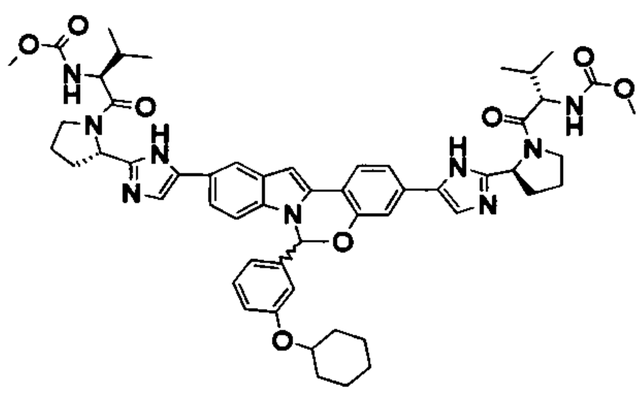
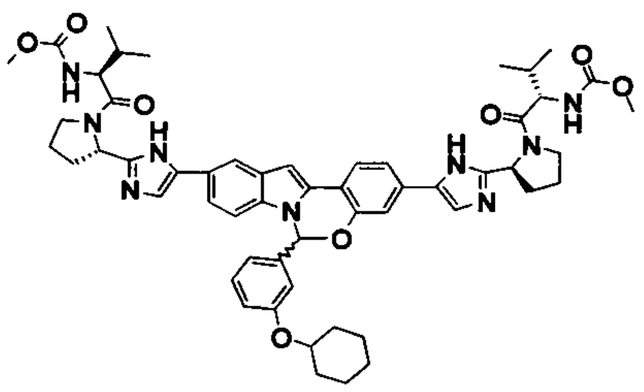
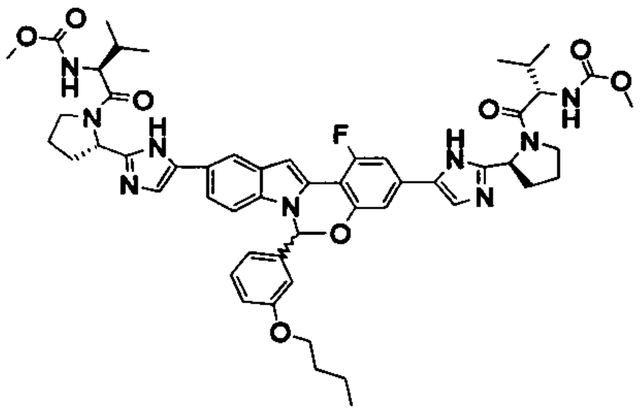
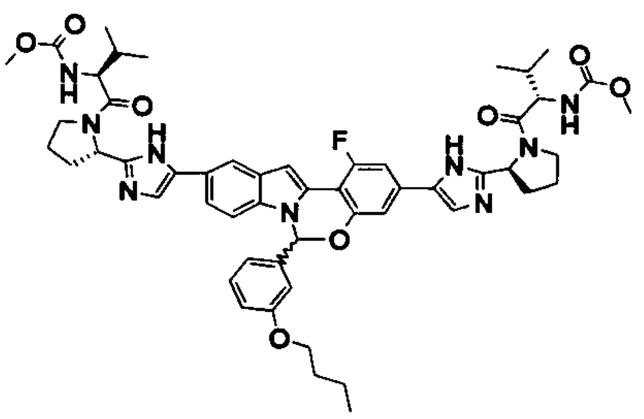
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1352		0.017	> 100	21.3	0.023	25.9	845.926	846.9	Single isomer
1353		0.004	13.96	1.16	0.006	53.67	926.17	927.2	Mixture of isomers
1354		0.051	> 200	31.6	0.010	> 200	919.997	921.0	Single isomer
1355		> 2	> 200	200	> 2	> 200	805.892	806.9	Single isomer
1356		> 2	> 200	> 200	> 2	> 200	769.911	770.9	Single isomer
1357		0.178	12.01	71.7	0.004	> 200	868.005	869.0	Mixture of isomers
1358		0.20	1.14	1.54	0.16	80.00	922.04	923.30	Mixture of isomers

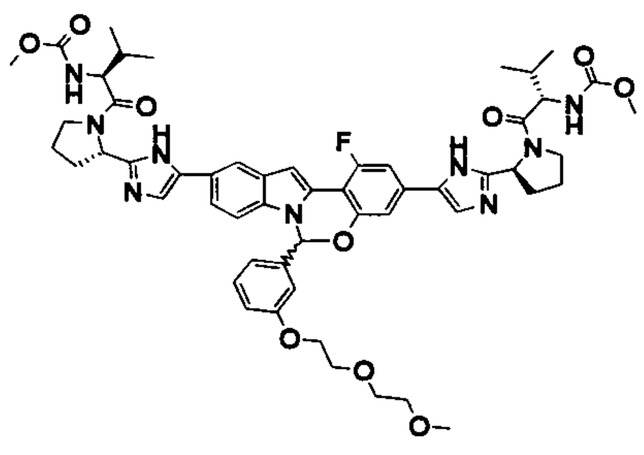
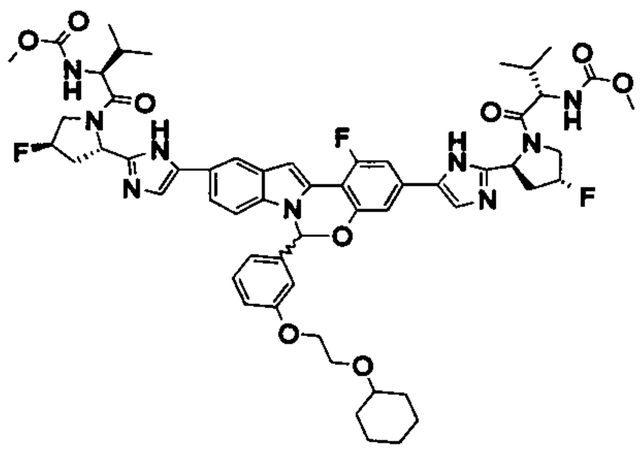
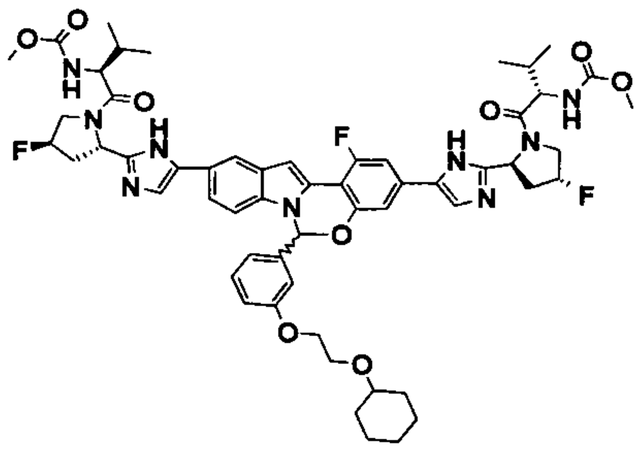
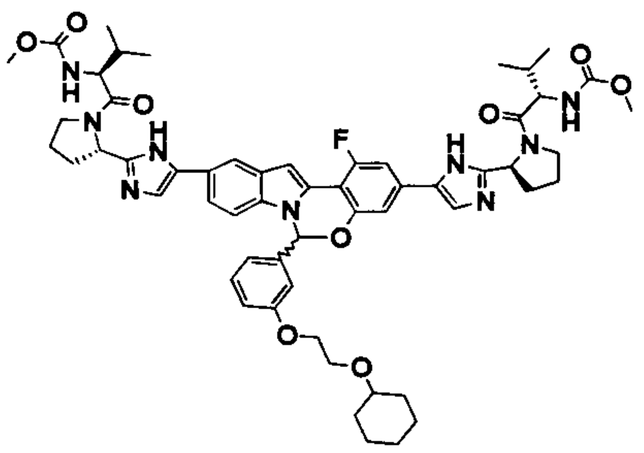
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1359		0.12	1.10	0.29	0.07	6.35	922.04	923.30	Mixture of isomers
1360		9.92	413.00	465.00	0.81	955.00	891.00	891.70	Mixture of isomers
1361		3.01	269.00	159.00	0.05	475.00	855.02	855.50	Mixture of isomers
1362		0.03	10.40		0.03	119.00	840.39	841.30	Single isomer
1363		0.22	231.00		0.09	245.00	819.93	820.30	Mixture of isomers
1364							962.17	963.30	Single isomer
1365							914.04	915.50	Single isomer

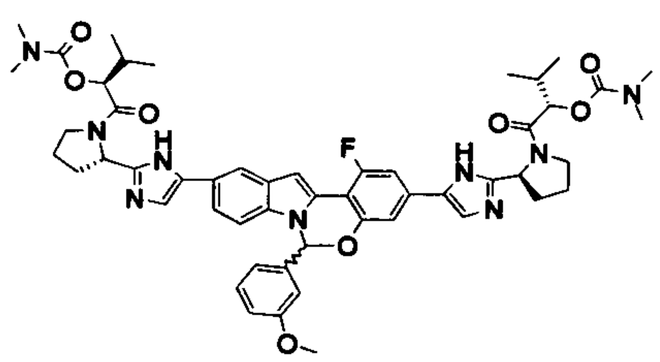
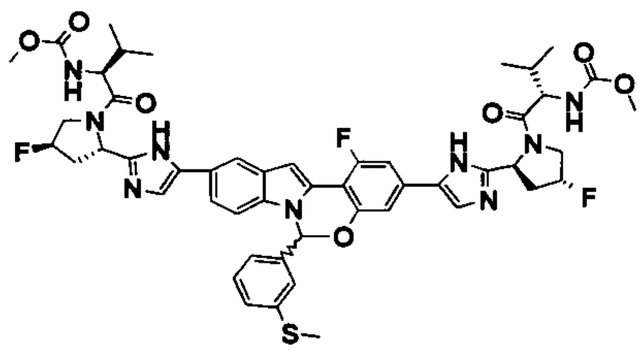
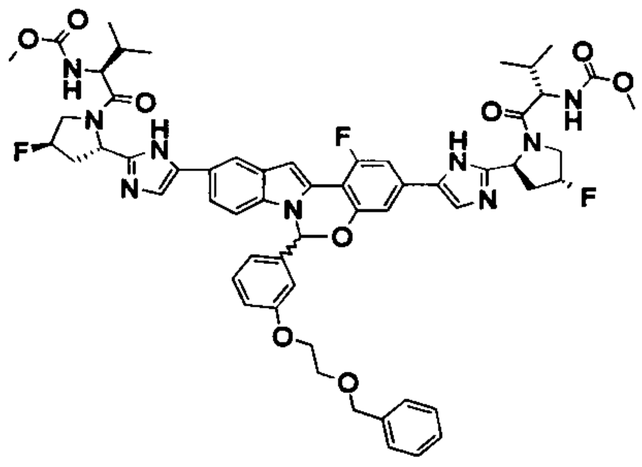
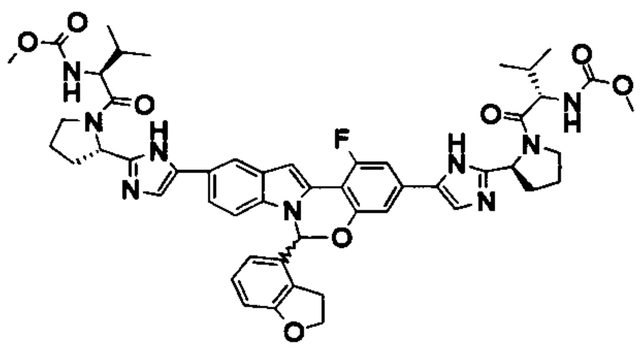
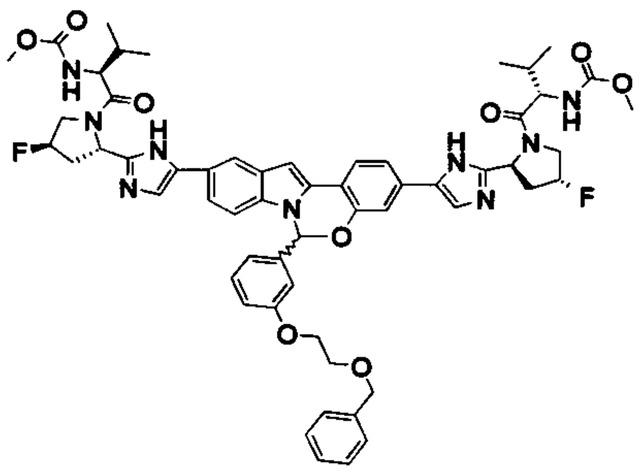
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1366		0.00981	0.567	1.38	0.00765	32.2	966.16	967.0	Single isomer
1367		0.00734	23.7	0.397	0.00568	4.85	984.03	985.0	Single isomer
1368		0.00574	15.3	0.297	0.0105	10.8	930.06	931.0	Single isomer
1369		0.0449	0.0706	7.05	0.0124	63.3	1018.16	1019.0	Single isomer
1370		0.133	49.2	0.52	0.0896	64.3	1054.15	1055.0	Single isomer
1371		0.0282	16.4	0.358	0.00711	7	1038.24	1039.0	Mixture of isomers

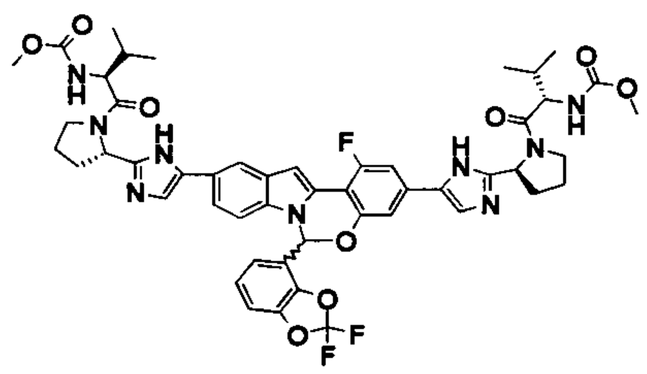
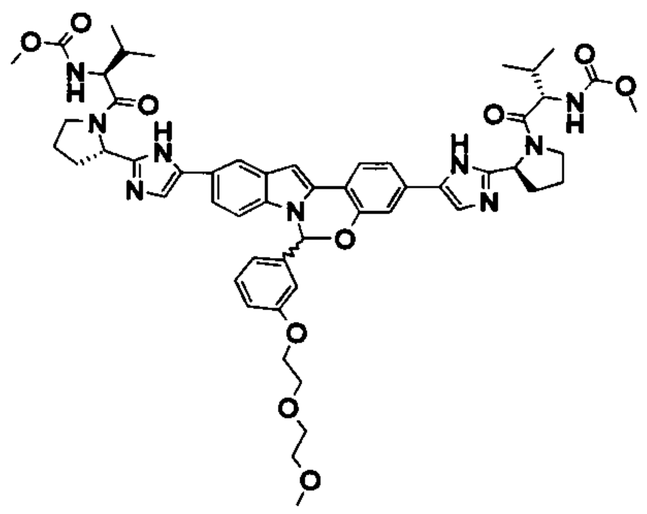
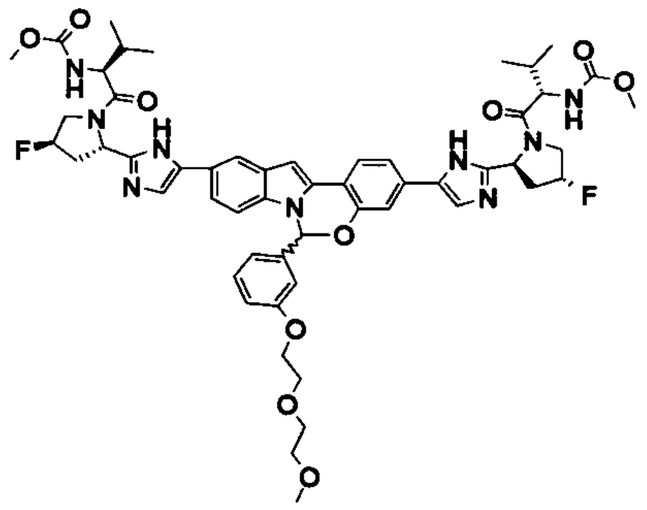
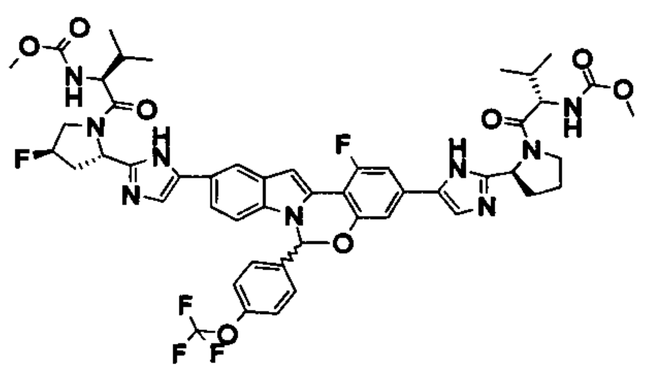
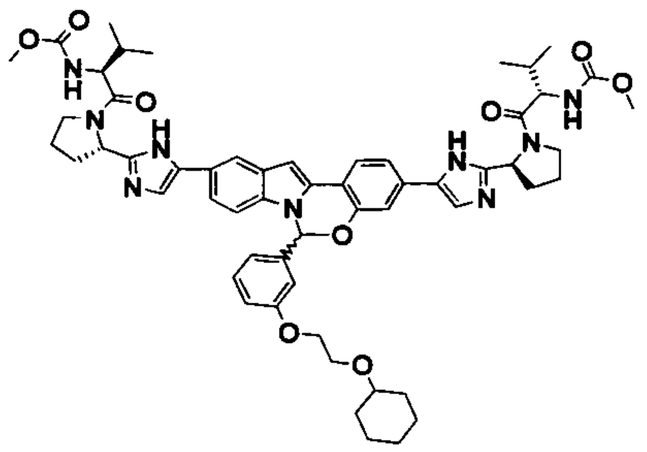
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1372		0.0146	2.35	0.162	0.00674	0.888	1008.12	1009.0	Mixture of isomers
1373		0.0041	24.9	0.14	0.00852	2.65	948.05	949.0	Mixture of isomers
1374		0.00352	1.12	0.0433	0.00799	0.587	946.06	947.0	Mixture of isomers
1375		0.00699	60.9	0.324		10.2	946.06	947.0	Mixture of isomers
1376		0.00595	1.8	0.0607	0.00453	1.55	944.09	945.0	Mixture of isomers
1377		0.00739	0.222	0.00448	0.00577	0.48	944.09	945.0	Mixture of isomers

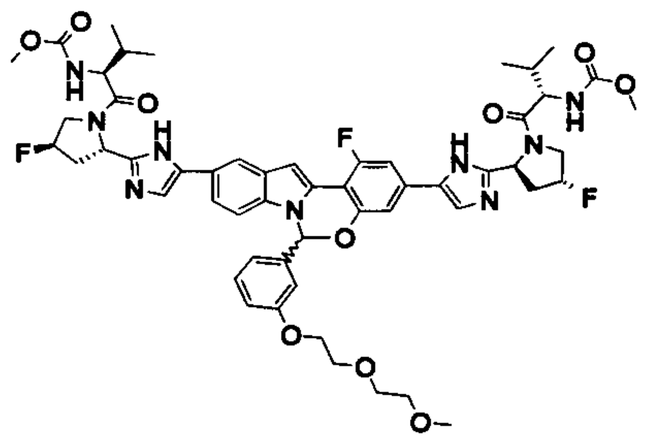
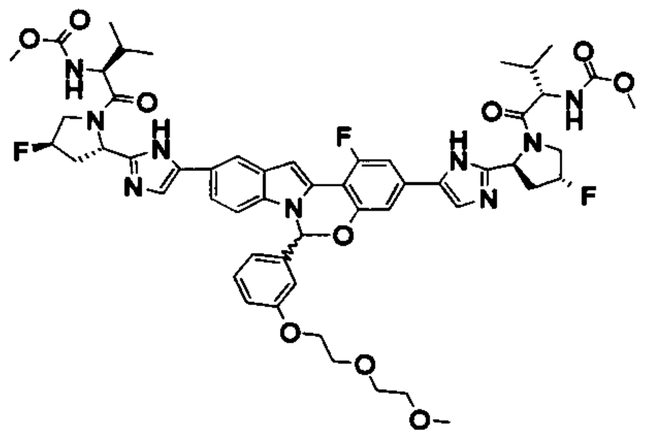
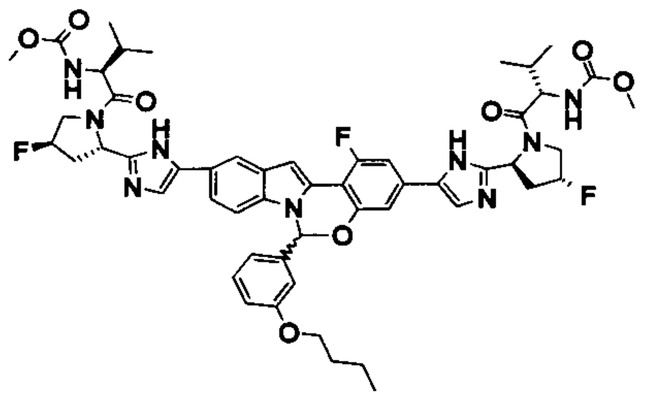
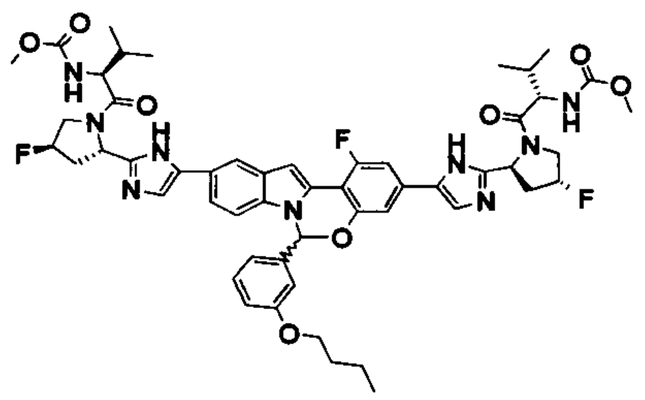
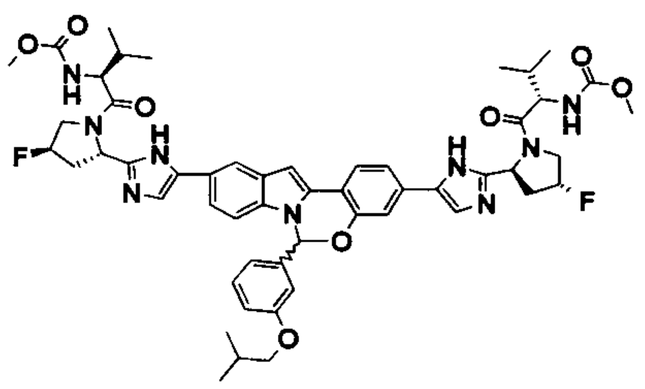
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1378		0.00577	2.87	0.0649	0.00497	3.3	946.06	947.0	Mixture of isomers
1379		0.00754	25.3	0.211	0.00462	8.25	946.06	947.0	Mixture of isomers
1380		0.00556	0.798	0.0467	0.00628	0.874	948.05	949.0	Mixture of isomers
1381		0.0283	44.6	0.519	0.00798	11	948.05	949.0	Mixture of isomers
1382		0.00634	2.27	0.106	0.00699	0.147	930.06	931.0	Mixture of isomers
1383		0.0205	56.4	0.419	0.0139	61.8	930.06	931.0	Mixture of isomers

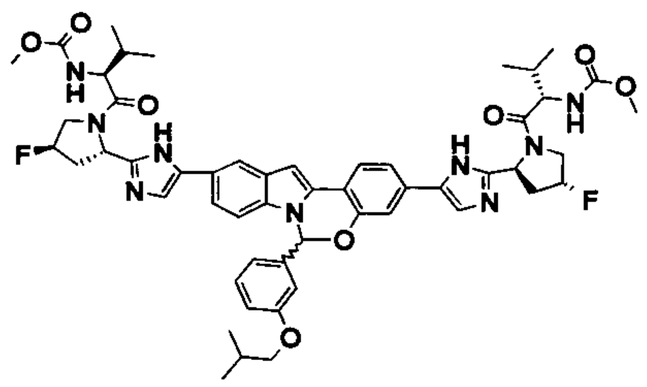
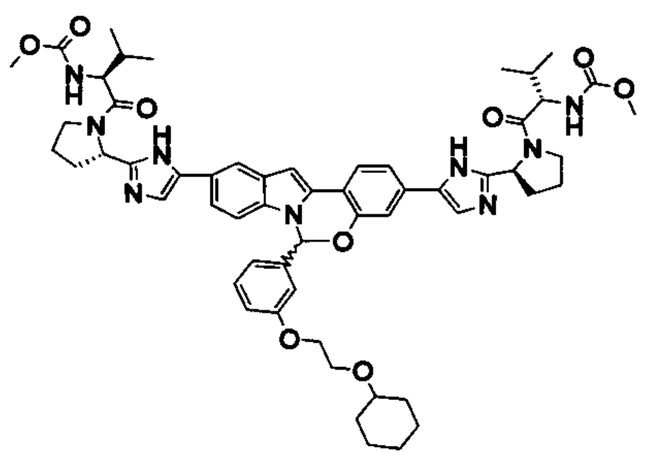
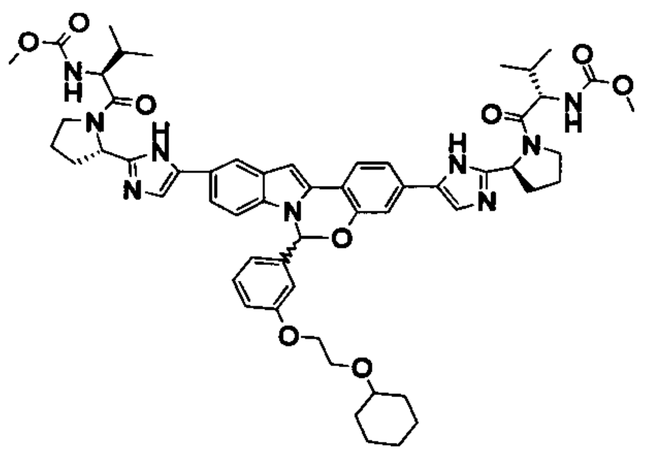
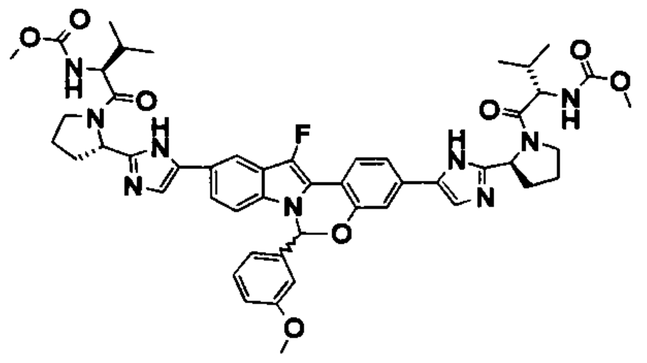
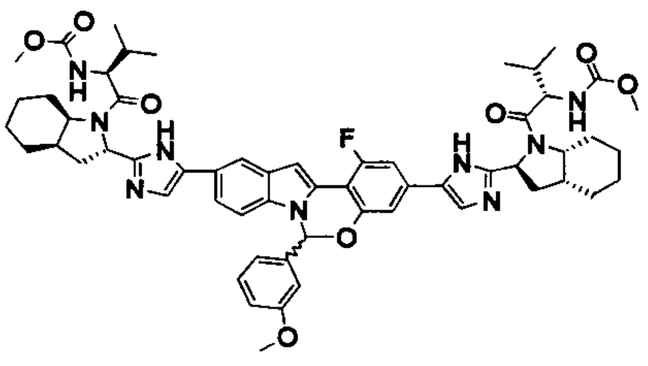
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1384		0.0112	2.85	0.0125	0.00672	6.99	980.19	981.0	Mixture of isomers
1385		0.0137	4.95	0.21	0.00649	7.2	980.19	981.0	Mixture of isomers
1386		0.00878	2.21	0.341	0.00578	19.1	972.14	973.0	Mixture of isomers
1387		0.0175	18.3	0.371	0.0104	7.62	972.14	973.0	Mixture of isomers
1388		0.0117	10	0.294	0.0107	20.3	1018.16	1019.0	Mixture of isomers

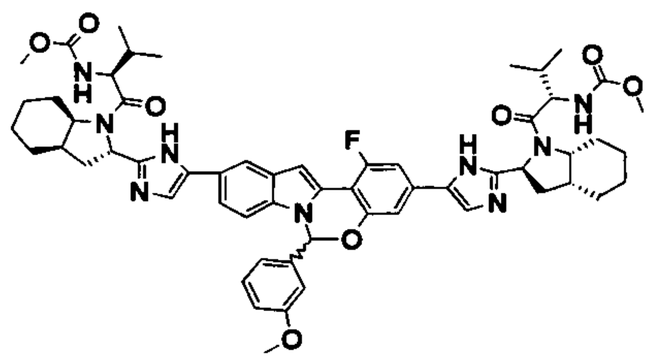
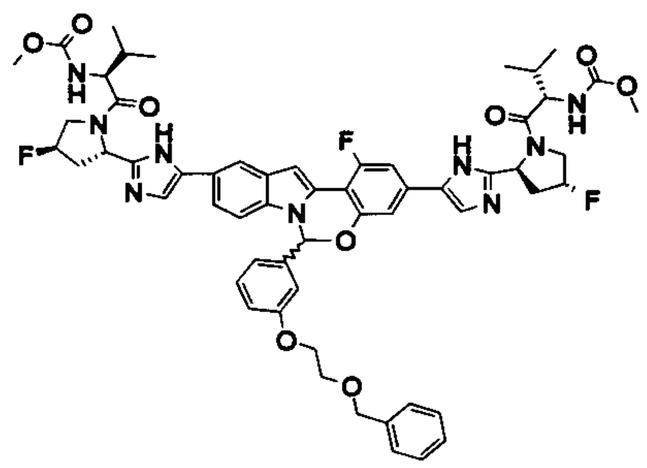
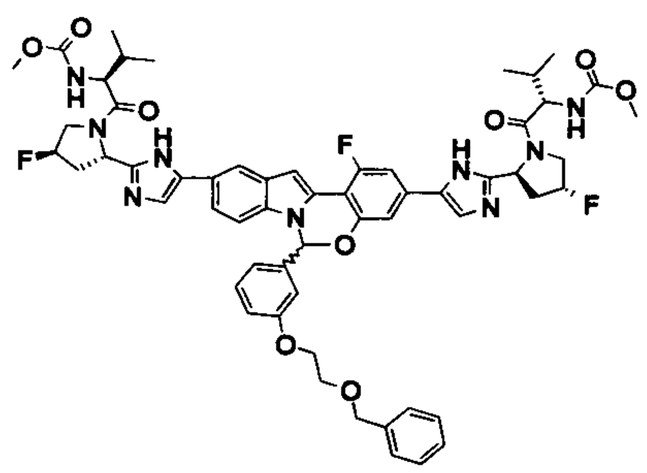
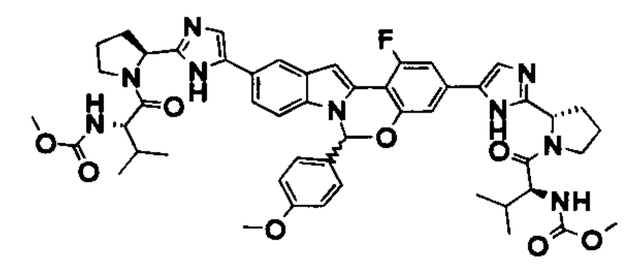
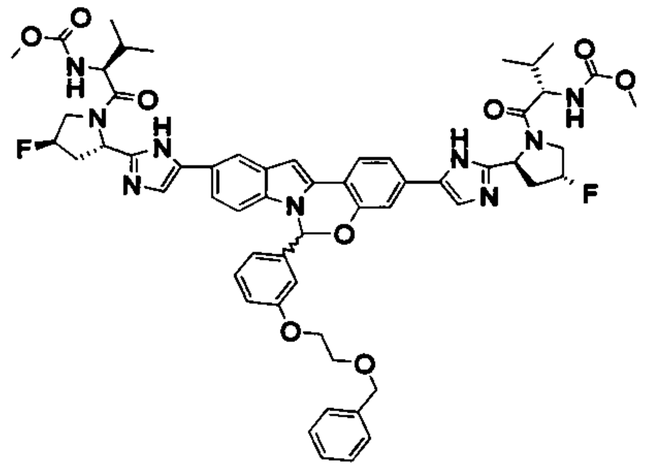
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1389		0.114	0.502	3.47	0.0139	66.6	1018.16	1019.0	Mixture of isomers
1390		0.00529	0.0155	1.85	0.00728	59.1	1078.21	1079.2	Mixture of isomers
1391		0.0236	19.2	0.217	0.00556	16.3	1078.21	1079.2	Mixture of isomers
1392		0.00813	0.894	0.0845	0.00329	5.01	1042.23	1043.0	Mixture of isomers
1393		56.8	252	457	3.62	934	1042.23	1043.0	Mixture of isomers

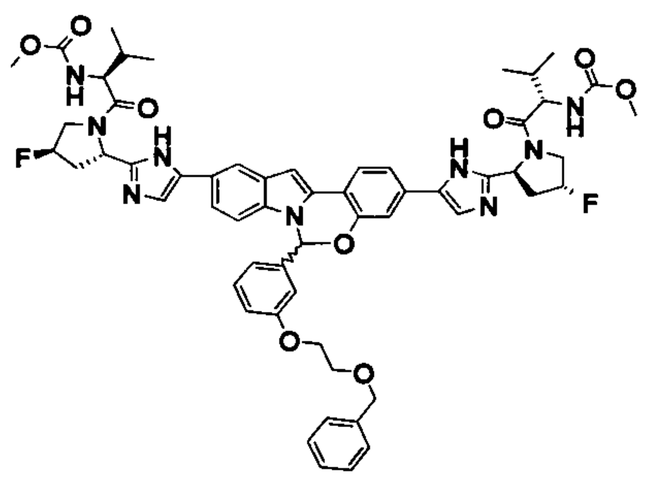
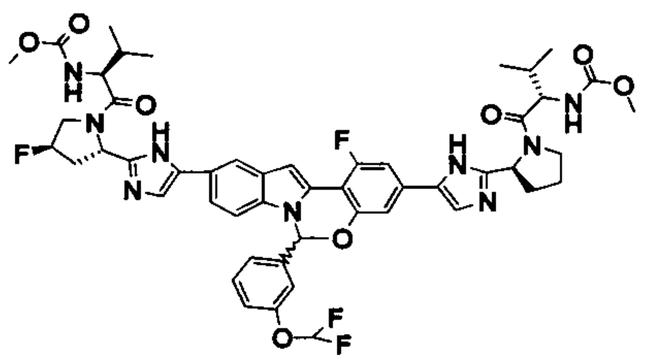
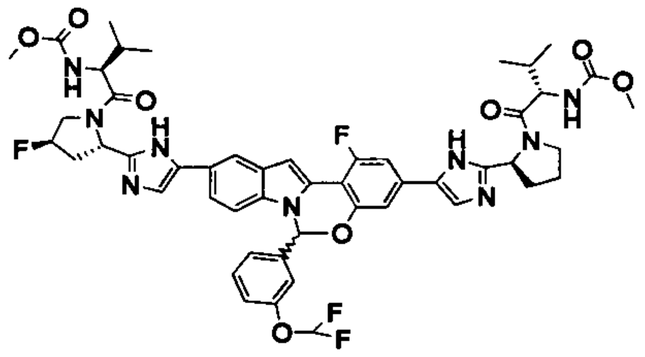
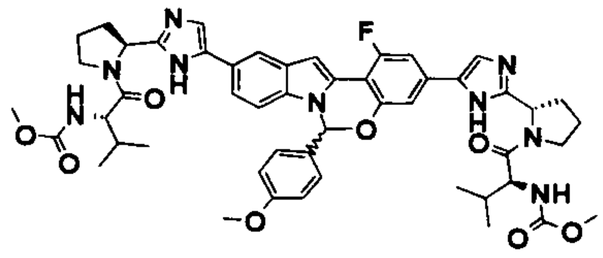
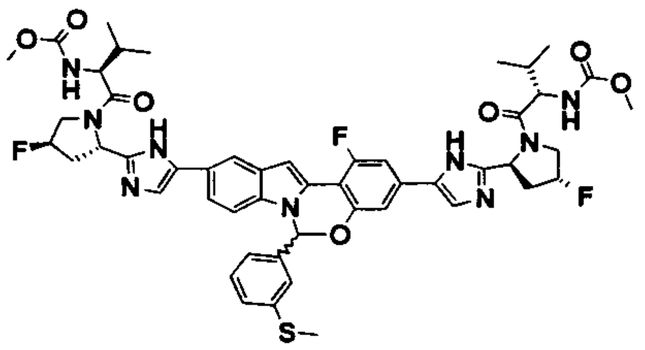
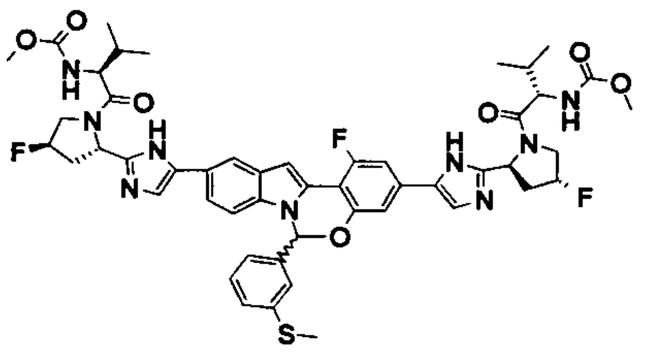
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1394							958.11	959.0	Mixture of isomers
1395							982.10	983.0	Mixture of isomers
1396							1086.19	1087.2	Mixture of isomers
1397							942.07	943.0	Mixture of isomers
1398							1068.20	1069.2	Mixture of isomers

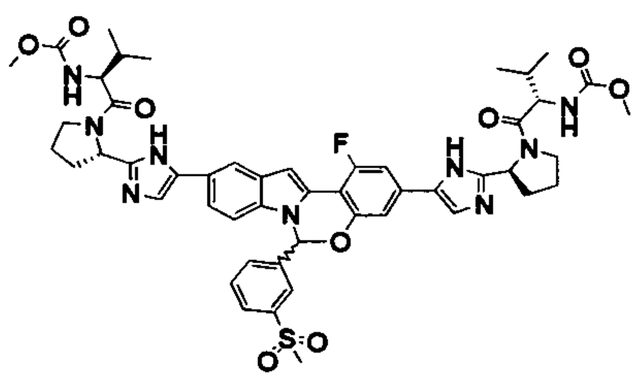
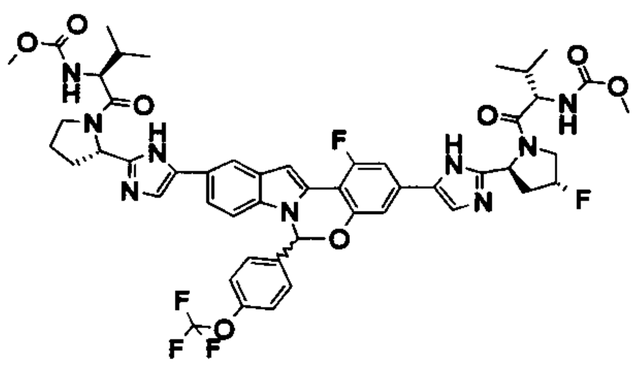
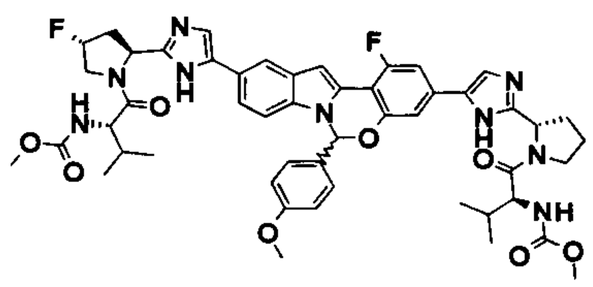
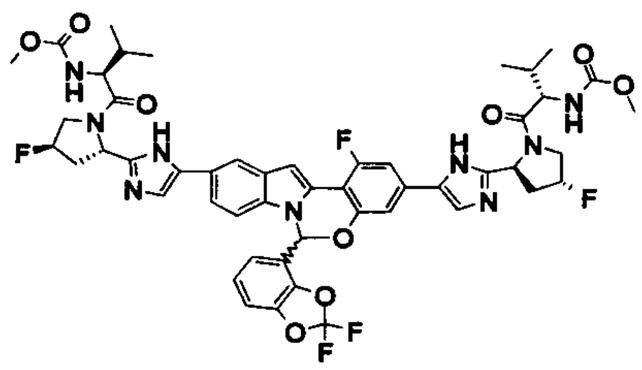
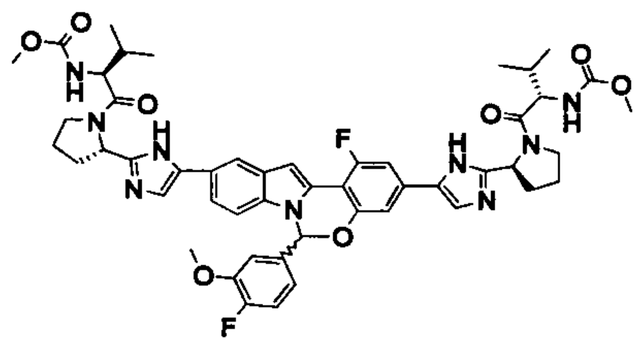
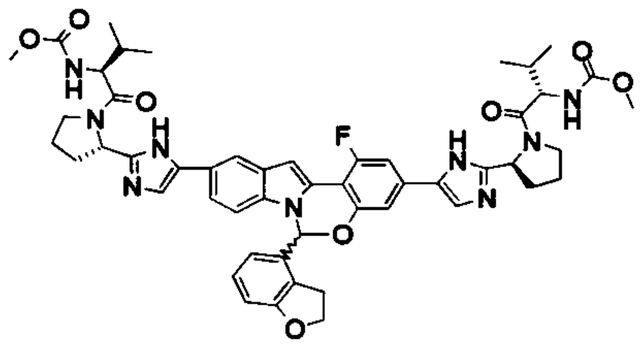
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1399							980.02	981.0	Mixture of isomers
1400							1000.17	1001.0	Mixture of isomers
1401							1036.16	1037.2	Mixture of isomers
1402							1002.02	1003.0	Mixture of isomers
1403							1024.24	1025.4	Mixture of isomers

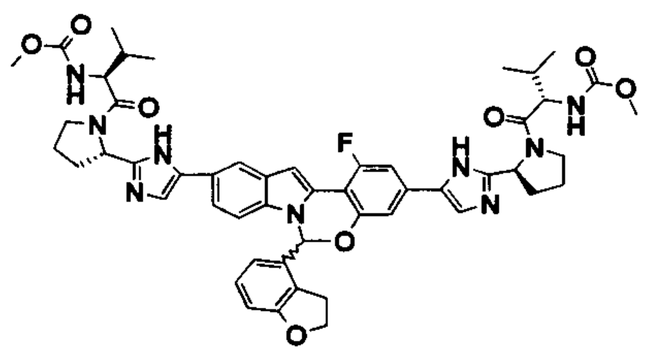
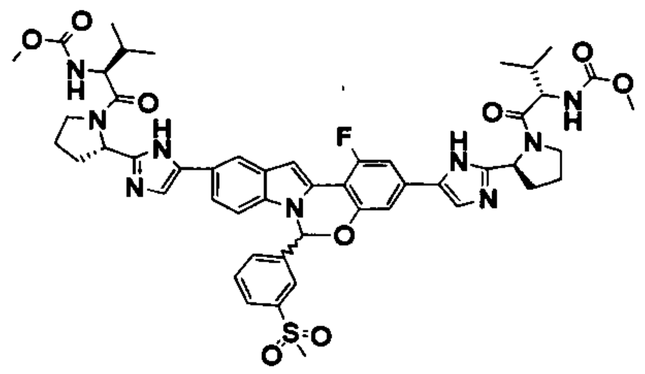
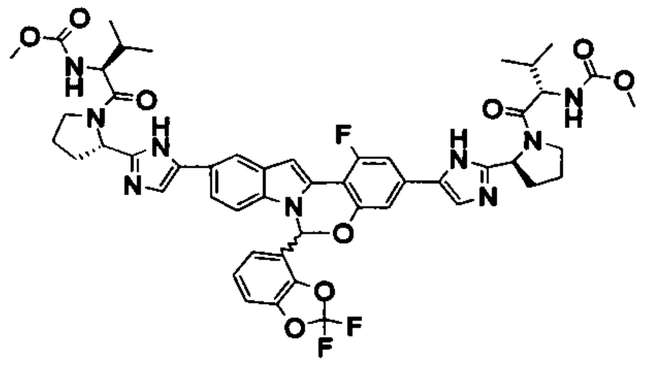
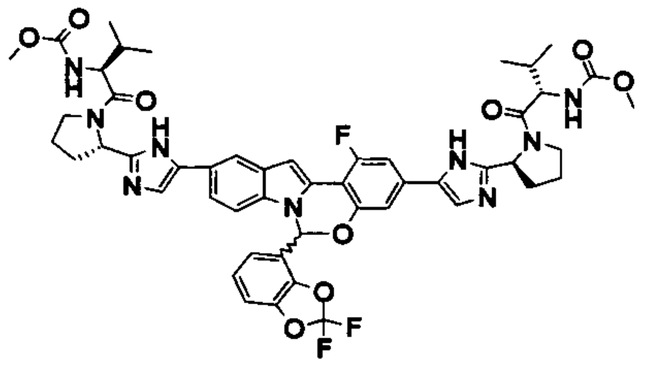
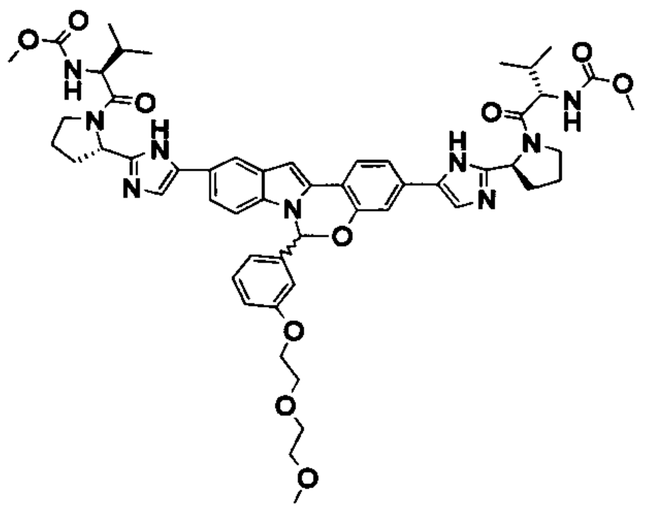
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1404							1054.15	1055.0	Mixture of isomers
1405							1054.15	1055.0	Mixture of isomers
1406							1008.12	1009.0	Mixture of isomers
1407							1008.12	1009.0	Mixture of isomers
1408							990.13	991.2	Mixture of isomers

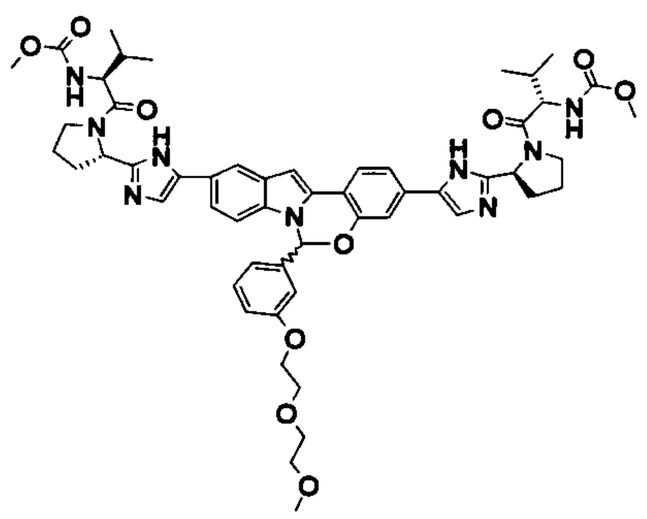
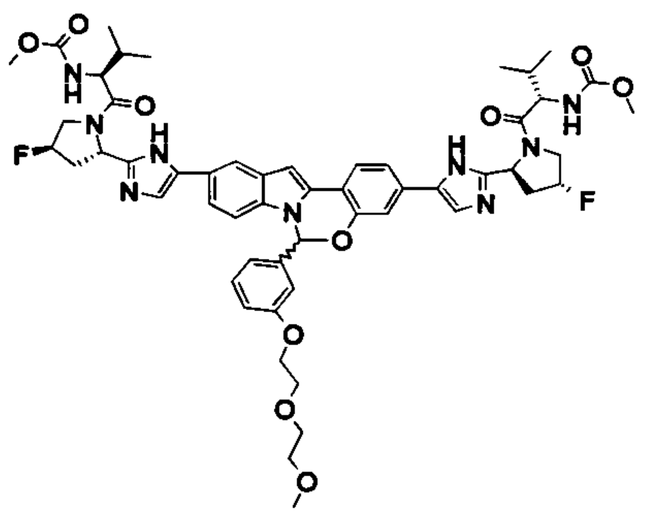
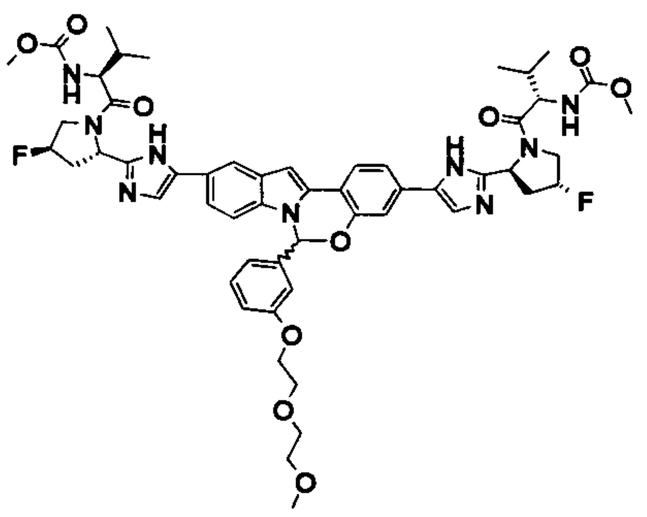
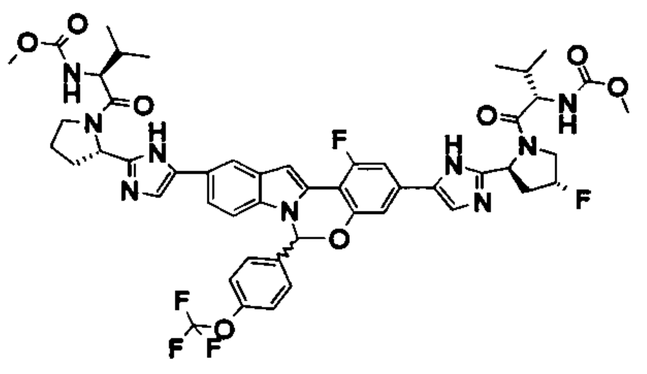
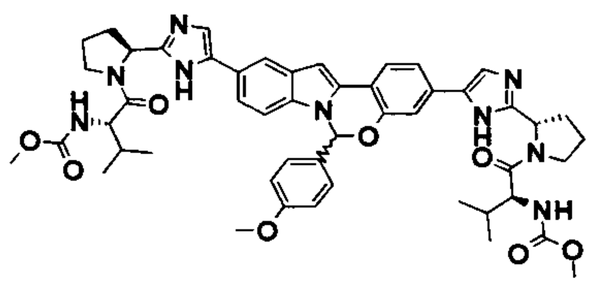
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1409							990.13	991.0	Mixture of isomers
1410							1024.24	1025.4	Mixture of isomers
1411							1024.24	1025.3	Mixture of isomers
1412							930.06	931.0	Mixture of isomers
1413							1038.24	1039.3	Mixture of isomers

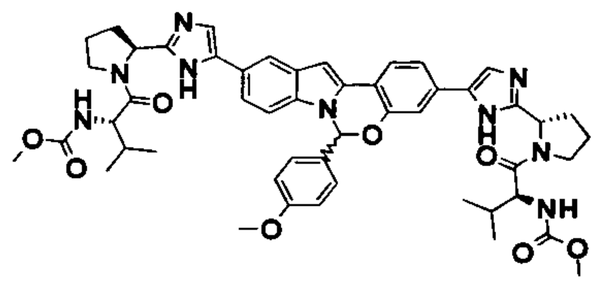
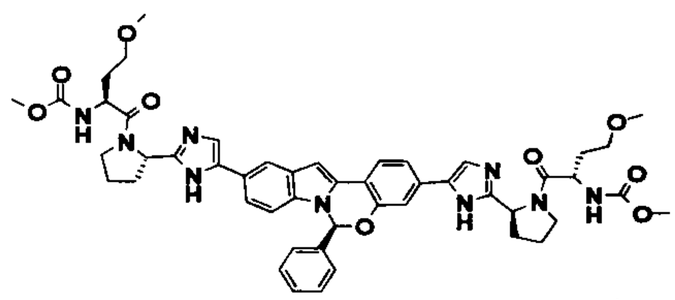
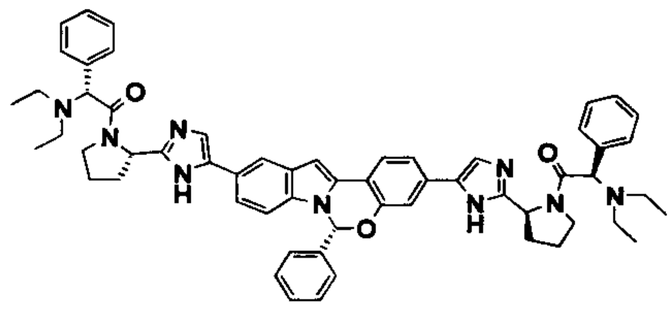
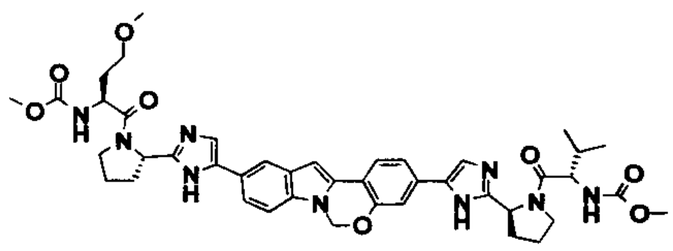
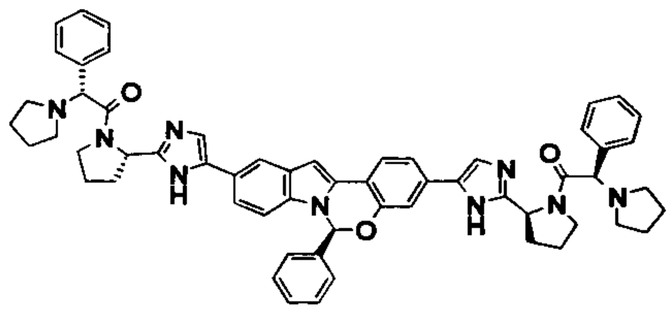
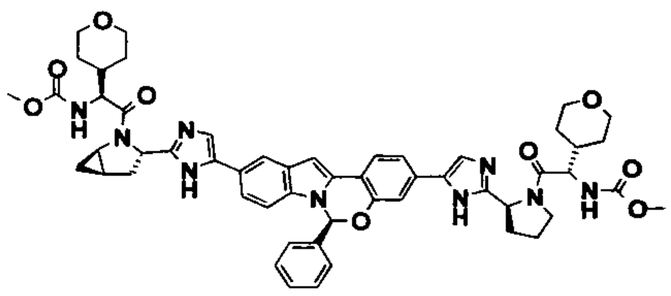
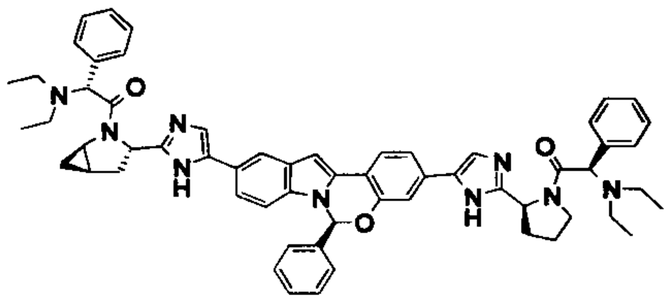
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1414							1038.24	1039.3	Mixture of isomers
1415							1086.19	1087.2	Mixture of isomers
1416							1086.19	1087.2	Mixture of isomers
1417							930.06	931.0	Mixture of isomers
1418							1068.20	1069.3	Mixture of isomers

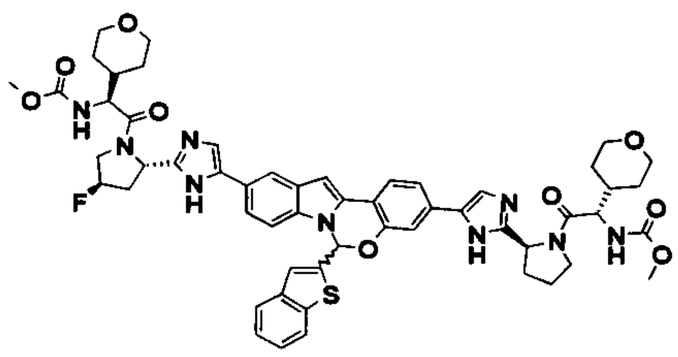
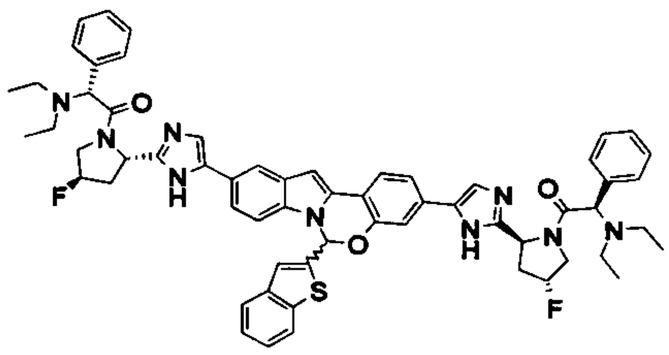
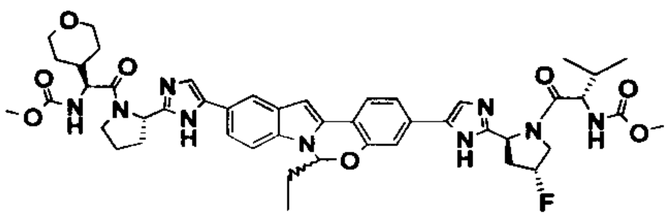
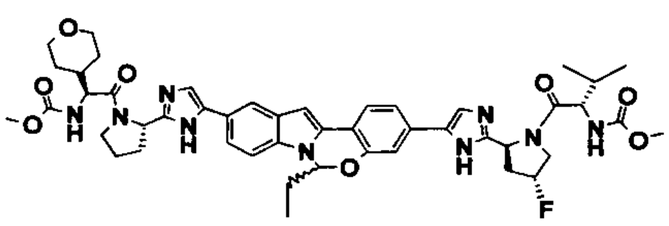
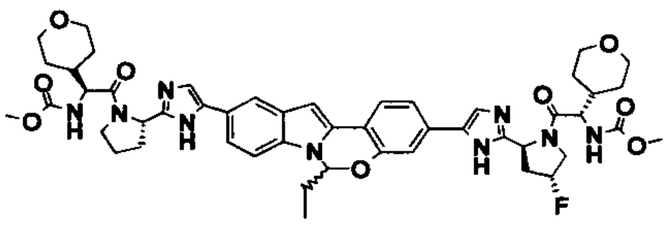
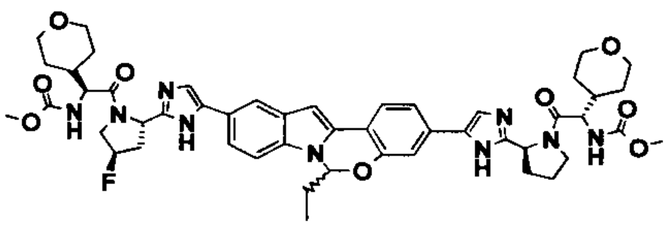
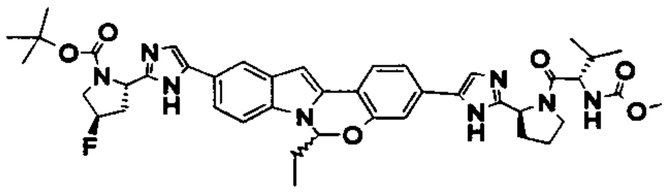
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1419							1068.20	1069.3	Mixture of isomers
1420							984.03	985.0	Mixture of isomers
1421							984.03	985.0	Mixture of isomers
1422							930.06	931.2	Mixture of isomers
1423							982.10	983.2	Mixture of isomers
1424							982.10	983.2	Mixture of isomers

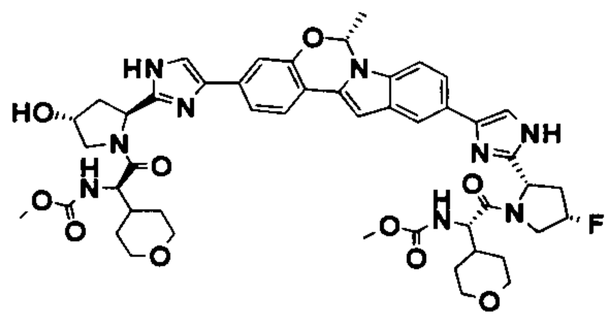
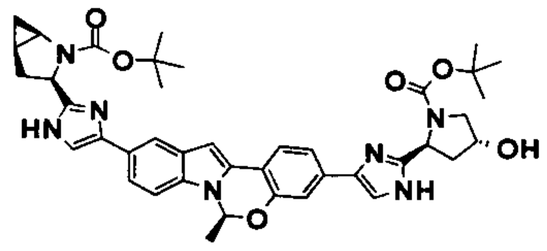
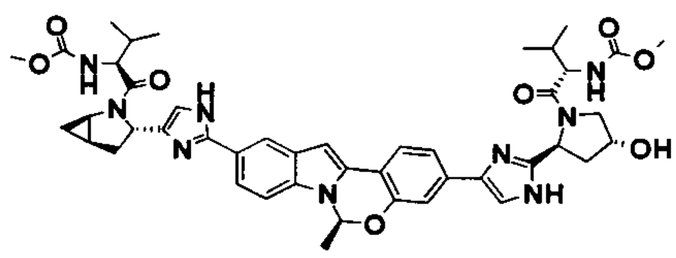
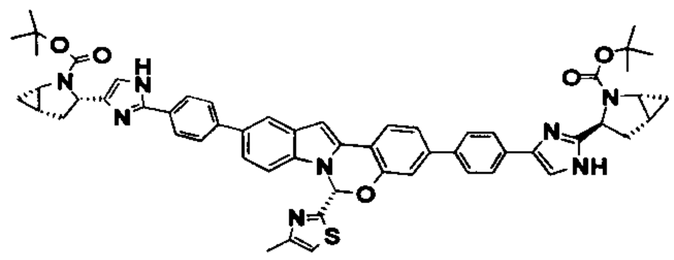
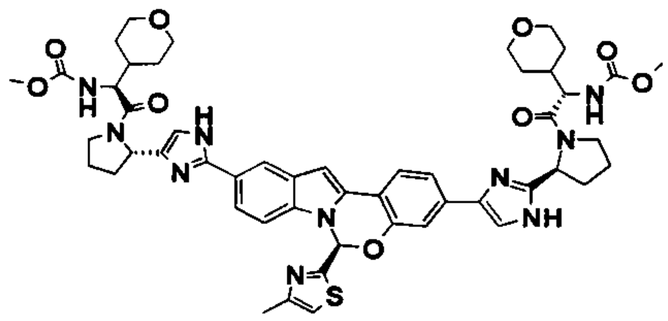
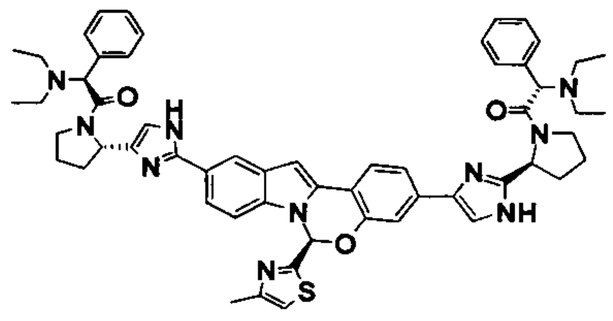
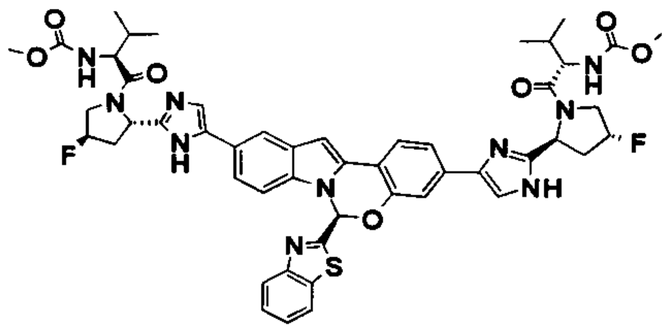
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1425							978.12	979.3	Mixture of isomers
1426							1002.02	1003.0	Mixture of isomers
1427							948.05	949.2	Mixture of isomers
1428							1016.00	1017.0	Mixture of isomers
1429							948.05	949.0	Mixture of isomers
1430							942.07	943.0	Mixture of isomers

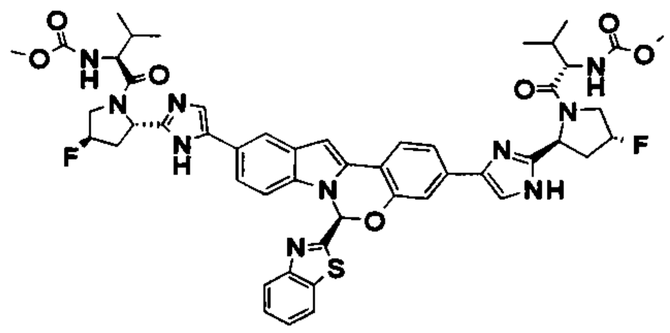
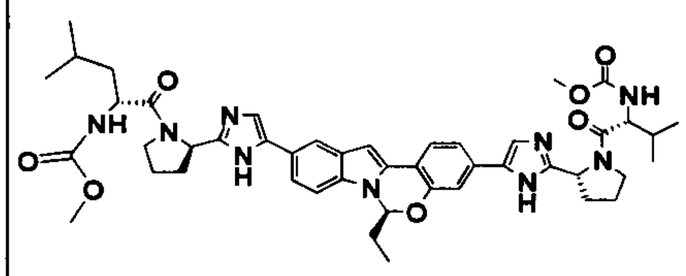
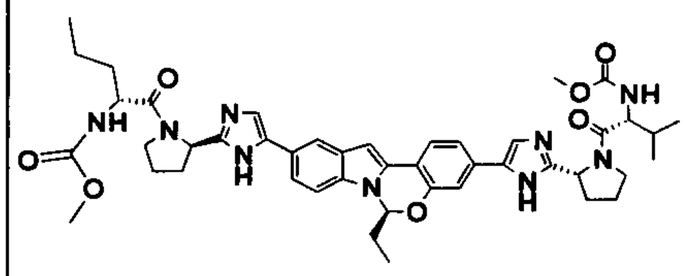
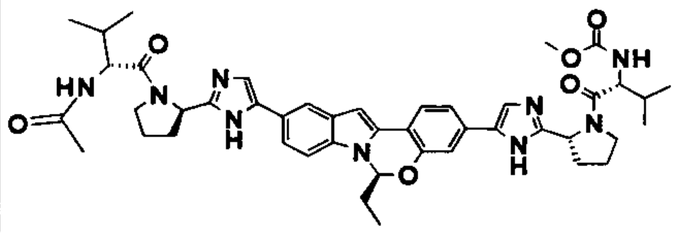
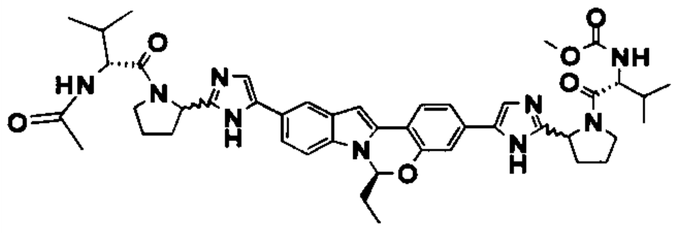
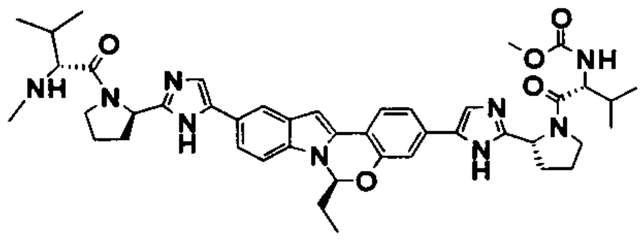
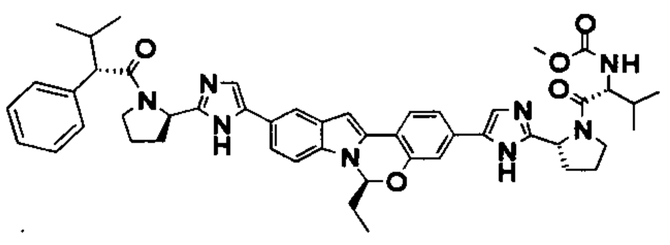
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1431							942.07	943.0	Mixture of isomers
1432							978.12	979.2	Mixture of isomers
1433							980.02	981.0	Mixture of isomers
1434							980.02	981.0	Mixture of isomers
1435							1000.17	1001.0	Mixture of isomers

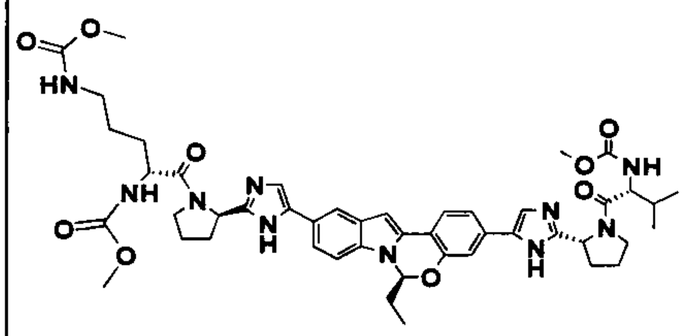
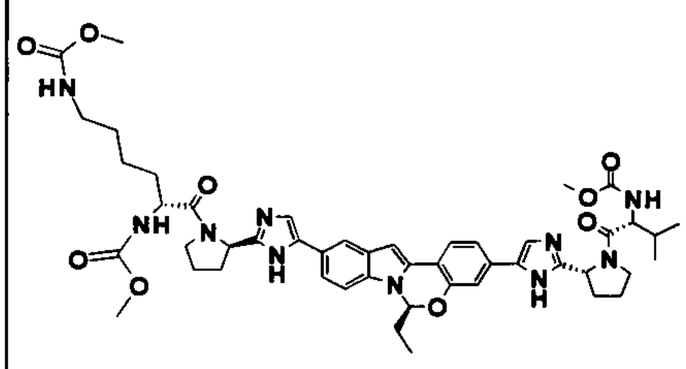
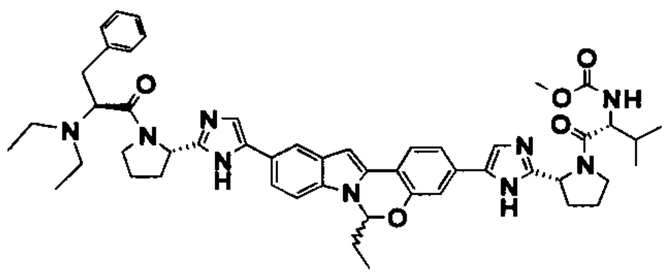
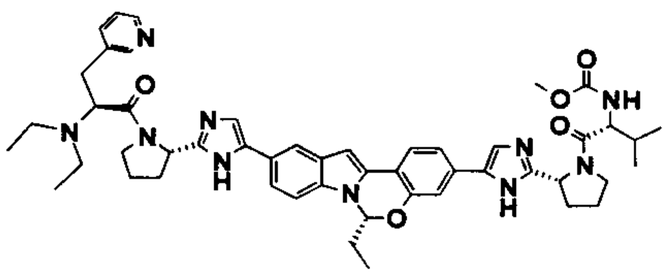
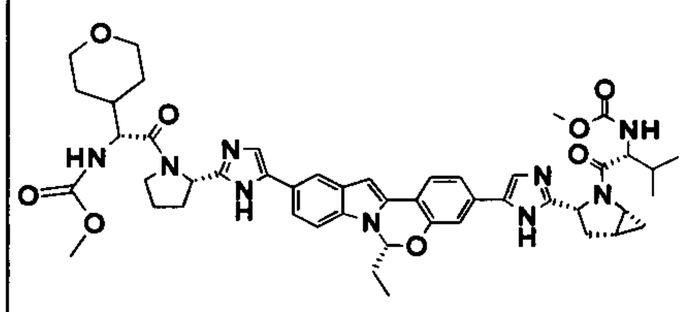
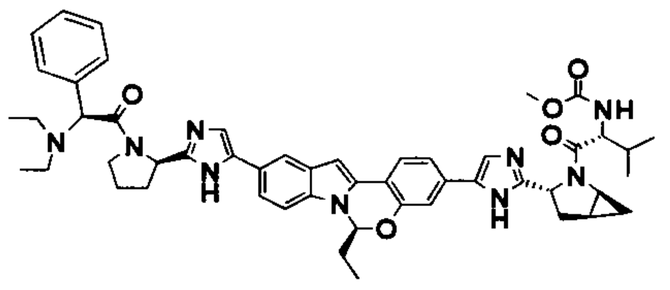
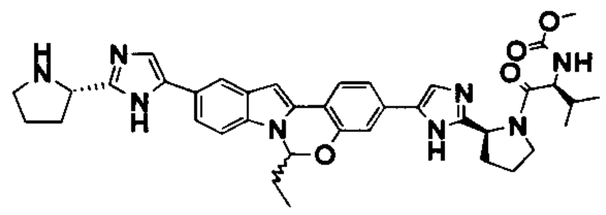
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1436							1000.17	1001.0	Mixture of isomers
1437							1036.16	1037.2	Mixture of isomers
1438							1036.16	1037.2	Mixture of isomers
1439							1002.02	1003.0	Mixture of isomers
1440							912.07	913.0	Mixture of isomers

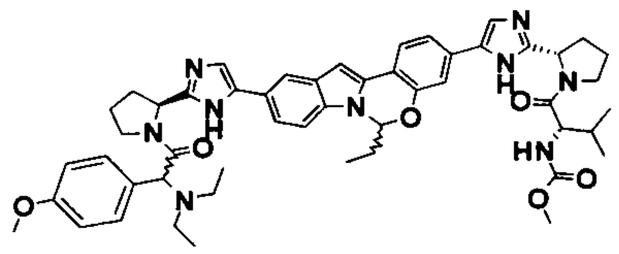
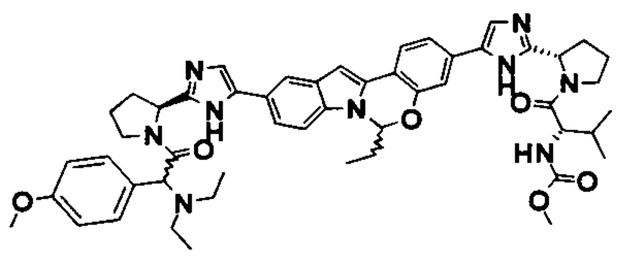
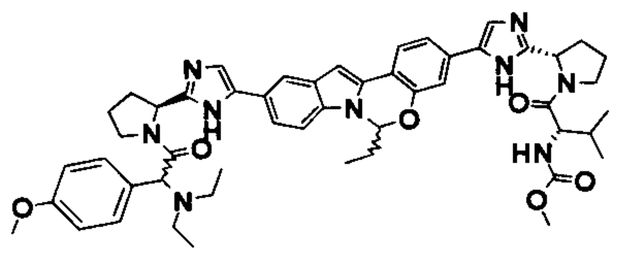
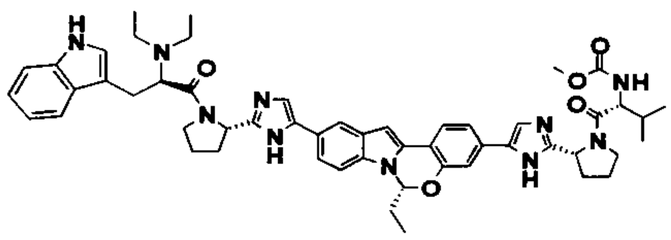
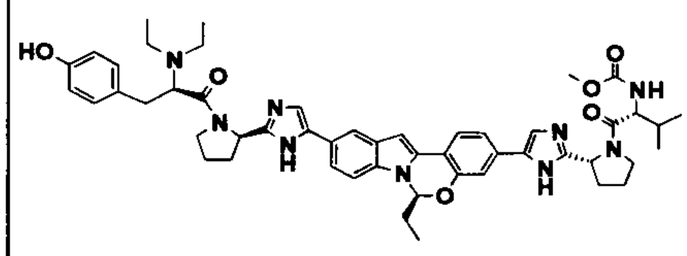
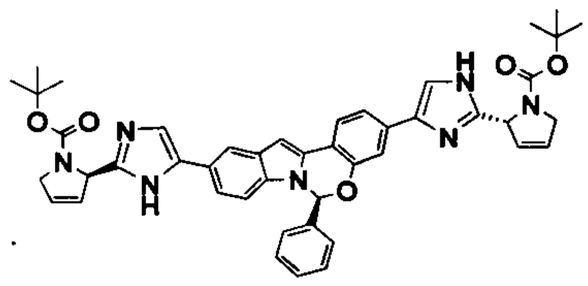
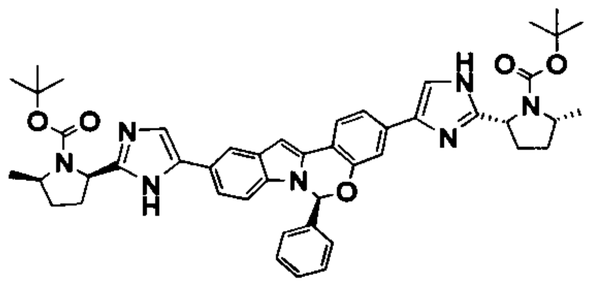
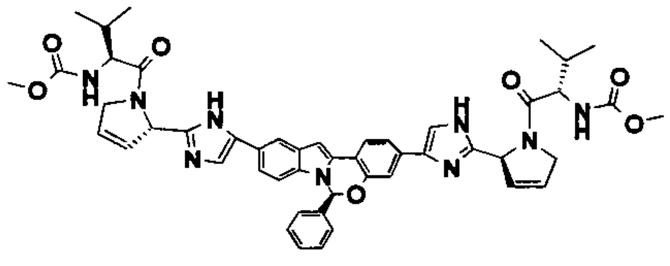
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1441							912.07	913.0	Mixture of isomers
1442		0.03	25.59	0.53		32.02	914.04	915.50	Single isomer
1443		0.10	100.00	0.33	0.04	0.20	946.22	946.50	Single isomer
1444							821.94	822.40	Single isomer
1445							942.19	943.30	Single isomer
1446							978.13	979.30	Single isomer
1447							958.23	959.30	Single isomer

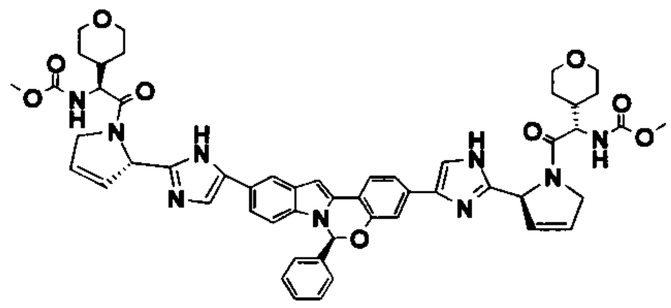
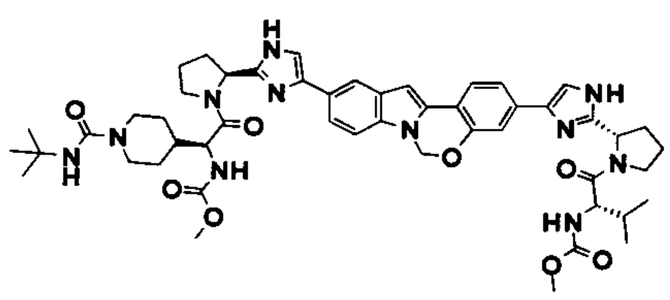
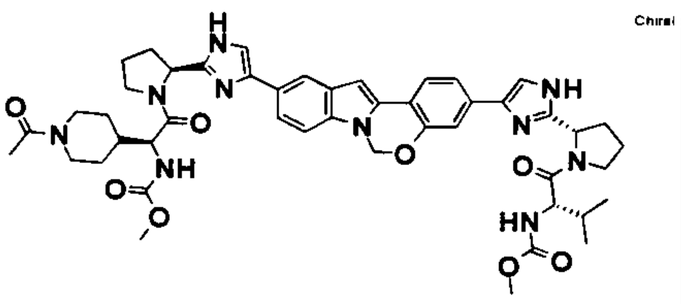
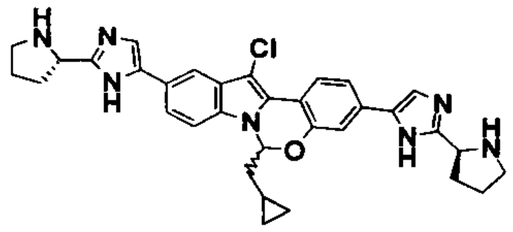
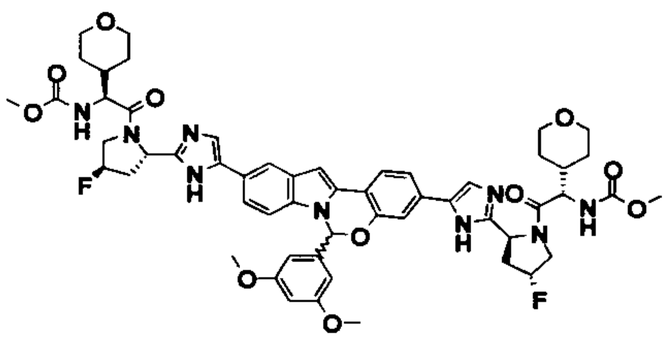
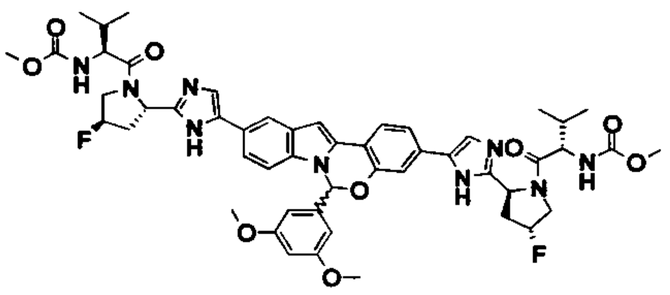
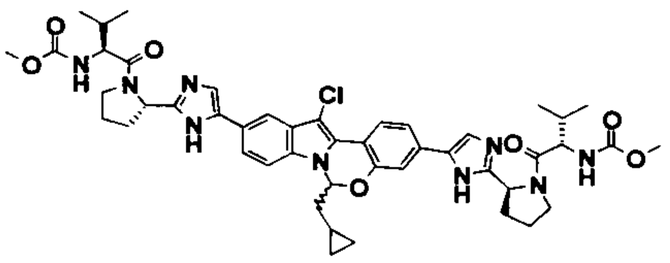
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1448							1040.19	1041.40	Mixture of isomers
1449							1038.29	1040.30	Mixture of isomers
1450		0.02	1.36	3.03		26.54	894.02	895.70	Mixture of isomers
1451		0.05	1.10	4.56	0.04	9.70	894.02	895.40	Mixture of isomers
1452							936.06	936.40	Mixture of isomers
1453							936.06	936.40	Mixture of isomers
1454							794.93	795.30	Mixture of isomers

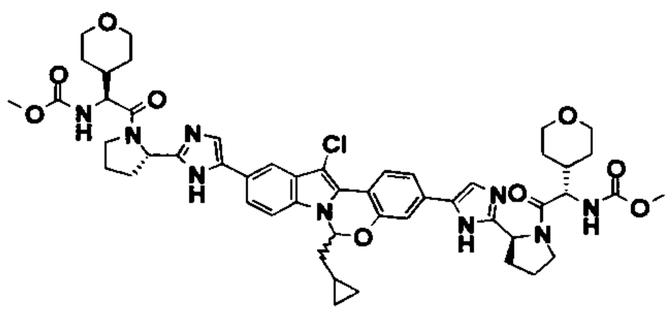
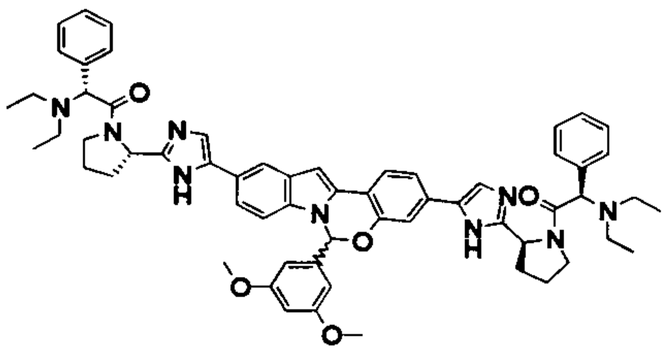
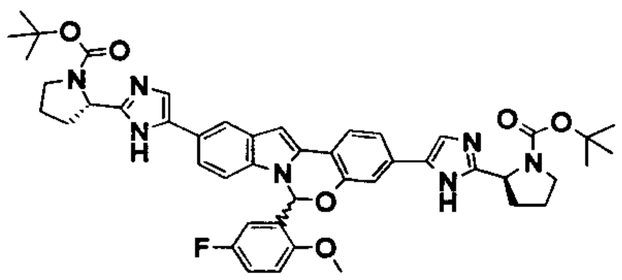
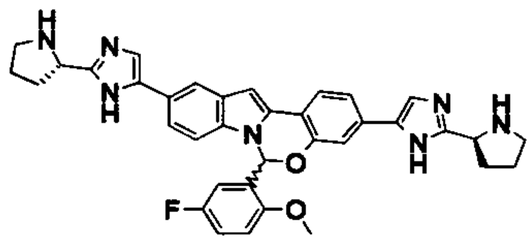
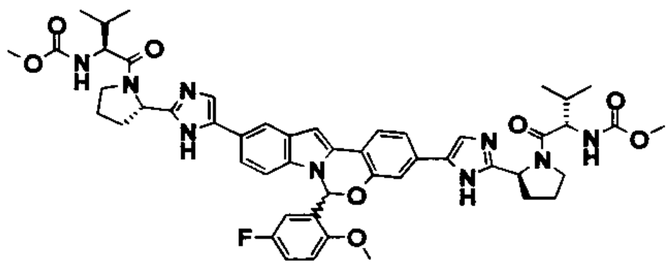
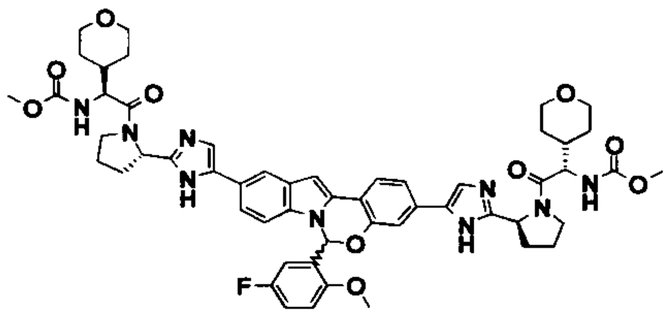
Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1455		2.22	1.32	76.29		162.61	938.03	938.30	Mixture of isomers
1456		496.26	999.00	999.00		999.00	733.88	734.20	Mixture of isomers
1457		0.06	4.20	37.15	0.03	260.00	847.98	849.20	Mixture of isomers
1458							965.20	965.40	Mixture of isomers
1459							987.16	988.20	Mixture of isomers
1460							967.26	967.30	Mixture of isomers
1461							975.10	975.20	Mixture of isomers

Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1462							975.10	975.20	Mixture of isomers
1463		0.02	18.45	11.59		60.56	848.02	849.07	Mixture of isomers
1464		0.03	94.59	25.51		50.60	834.00	835.05	Mixture of isomers
1465		0.05	26.35	91.54		142.92	818.00	819.05	Mixture of isomers
1466		0.77	277.13	123.04		220.76	818.00	819.05	Mixture of isomers
1467		0.10	261.86	103.84		486.23	789.99	791.04	Mixture of isomers
1468		0.21	227.84	121.41		138.16	837.04	838.09	Mixture of isomers

Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1469		0.05	30.90	6.04	0.03	7.10	907.05	908.10	Mixture of isomers
1470		0.06	17.50	8.05	0.03	19.15	921.08	922.13	Mixture of isomers
1471		3.33	414.70	116.89	0.02	378.28	880.11	881.16	Mixture of isomers
1472		1.29	455.20	93.80	0.03	233.68	881.10	882.15	Mixture of isomers
1473							888.05	889.10	Mixture of isomers
1474							878.10	879.15	Mixture of isomers
1475							676.83	677.88	Mixture of isomers

Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1476							896.11	897.16	Mixture of isomers
1477							896.11	897.16	Mixture of isomers
1478							896.11	897.16	Mixture of isomers
1479							919.15	920.20	Mixture of isomers
1480							896.11	897.16	Mixture of isomers
1481		244.15	984.80	999.00	125.00	549.30	763.90	764.95	Single isomer
1482		342.79	999.00	924.54	251.00	999.00	795.99	797.04	Single isomer
1483							878.01	879.06	Single isomer

Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1484							962.08	963.13	Single isomer
1485		0.05	13.40	2.73		23.00	945.50	946.50	Single isomer
1486		0.40	32.00	1.72		117.30	888.40	889.30	Single isomer
1487							580.14	581.19	Mixture of isomers
1488		0.06	0.15	0.03		1.90	1062.15	1063.20	Mixture of isomers
1489		0.03	0.08	0.99		52.10	978.08	979.13	Mixture of isomers
1490		0.02	30.00	3.68		20.00	894.48	895.53	Mixture of isomers

Cmpd #	Structure	EC50 1a	EC50 1aY93H	EC50 1aL31V	EC50 1b	EC50 2b	Calc.M.S.	Obs .M.S. $[M+H]^+$	Isomer Designation
1491		0.02		0.03		1.00	978.56	979.61	Mixture of isomers
1492		0.13	13.60	0.10	0.03	0.19	1006.27	1007.32	Mixture of isomers
1493		216.06	999.00				815.95	817.00	Mixture of isomers
1494							615.72	616.77	Mixture of isomers
1495		0.02	48.10	1.03	0.01	1.23	930.06	931.11	Mixture of isomers
1496							1014.13	1015.18	Mixture of isomers

DEMANDE OU BREVET VOLUMINEUX

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

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 504

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

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

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 504

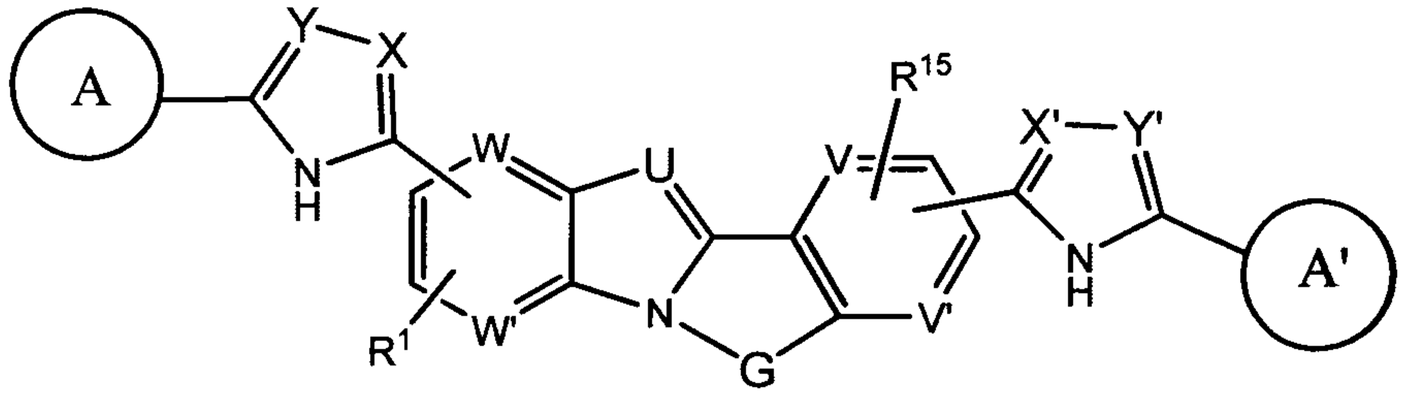
NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

1. A compound having the formula:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

A and A' are each independently a 5 or 6-membered monocyclic heterocycloalkyl, wherein said 5 or 6-membered monocyclic heterocycloalkyl group can be optionally fused to an aryl group; and wherein said 5 or 6-membered monocyclic heterocycloalkyl group can be optionally and independently substituted on one or more ring carbon atoms with R^{13}, such that any two R^{13} groups on the same ring, together with the carbon atoms to which they are attached, can join to form a fused, bridged or spirocyclic 3 to 6-membered cycloalkyl group or a fused, bridged or spirocyclic 4 to 6-membered heterocycloalkyl group, wherein said 5 or 6-membered monocyclic heterocycloalkyl contains from 1 to 2 ring heteroatoms, each independently selected from $N(R^4)$, S, O and $Si(R^{16})_2$;

G is selected from $–C(R^3)_2-O-$, $–C(R^3)_2-N(R^5)-$, $-C(O)-O-$, $-C(O)-N(R^5)-$, $-C(O)–C(R^3)_2-$, $-C(R^3)_2-C(O)-$, $-C(=NR^5)-N(R^5)-$, $–C(R^3)_2-SO_2-$, $-SO_2-C(R^3)_2-$, $-SO_2N(R^5)-$, $–C(R^3)_2–C(R^3)_2-$, $–C(R^{14})=C(R^{14})-$ and $–C(R^{14})=N-$;

U is selected from N and $C(R^2)$;

V and V' are each independently selected from N and $C(R^{15})$;

W and W' are each independently selected from N and $C(R^1)$;

X and X' are each independently selected from N and $C(R^{10})$;

Y and Y' are each independently selected from N and $C(R^{10})$;

R^1 is selected from H, C_1-C_6 alkyl, 3 to 6-membered cycloalkyl, halo, -OH, $-O-(C_1$-C_6 alkyl), C_1-C_6 haloalkyl and $–O-(C_1$-C_6 haloalkyl);

each occurrence of R^2 is independently selected from H, C_1-C_6 alkyl, 3 to 6 membered cycloalkyl, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl –O-(C_1-C_6 haloalkyl); halo, -OH, aryl, and heteroaryl;

each occurrence of R^3 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-(3 to 6 membered cycloalkyl), 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl, 9 or 10-membered bicyclic heteroaryl and benzyl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group, said 9 or 10-membered bicyclic heteroaryl group or the phenyl moiety of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), -O(C_1-C_6 haloalkyl), halo, –(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl) and –CN and wherein two R^3 groups attached to the same carbon atom, together with the common carbon atom to which they are attached, can join to form a carbonyl group, a 3 to 6-membered spirocyclic cycloalkyl group or a 3 to 6-membered spirocyclic heterocycloalkyl group;

each occurrence of R^4 is independently selected from -$[C(R^7)_2]_qN(R^6)_2$, -$C(O)R^{11}$, -C(O)-$[C(R^7)_2]_qN(R^6)_2$, -C(O)-$[C(R^7)_2]_q$-R^{11}, -C(O)-$[C(R^7)_2]_qN(R^6)C(O)$-R^{11}, -$C(O)[C(R^7)_2]_qN(R^6)SO_2$-$R^{11}$, -C(O)-$[C(R^7)_2]_qN(R^6)C(O)O$-$R^{11}$, -C(O)-$[C(R^7)_2]_qC(O)O$-$R^{11}$ and -alkylene-$N(R^6)$-$[C(R^7)_2]_q$-$N(R^6)$-C(O)O-R^{11};

each occurrence of R^5 is independently selected from H, C_1-C_6 alkyl, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl and benzyl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group or the phenyl moiety of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), halo, –(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl) and –CN;

each occurrence of R^6 is independently selected from H, C_1-C_6 alkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl and 5 or 6-membered monocyclic heteroaryl, wherein said 3 to 6-membered cycloalkyl group, said 4 to 6-membered heterocycloalkyl group, said aryl group and said 5 or 6-membered monocyclic heteroaryl group can be optionally and independently substituted with up to two R^8

groups, and wherein two R^6 groups that are attached to the same nitrogen atom, together with the common nitrogen atom to which they are attached, can join to form a 4 to 6-membered heterocycloalkyl group;

each occurrence of R^7 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -alkylene-O-(C_1-C_6 alkyl), 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl and 5 or 6-membered monocyclic heteroaryl, wherein said 3 to 6-membered cycloalkyl group, said 4 to 6-membered heterocycloalkyl group, said aryl group and said 5 or 6-membered monocyclic heteroaryl group can be optionally substituted with up to three R^8 groups;

each occurrence of R^8 is independently selected from H, C_1-C_6 alkyl, halo, -C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -OH, -C(O)NH-(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -O-(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$ and -NHC(O)-(C_1-C_6 alkyl);

each occurrence of R^9 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl and 5 or 6-membered monocyclic heteroaryl;

each occurrence of R^{10} is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo, -OH, -O-(C_1-C_6 alkyl) and –CN;

each occurrence of R^{11} is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, 3 to 6-membered cycloalkyl and 4 to 6-membered heterocycloalkyl;

each occurrence of R^{12} is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl and 5 or 6-membered monocyclic heteroaryl;

each occurrence of R^{13} is independently selected from H, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, -CN, -OR^9, -N(R^9)$_2$, -C(O)R^{12}, -C(O)OR^9, -C(O)N(R^9)$_2$, -NHC(O)R^{12}, -NHC(O)NHR^9, -NHC(O)OR^9, -OC(O)R^{12}, -SR^9 and –S(O)$_2R^{12}$, wherein two R^{12} groups together with the carbon atom(s) to which they are attached, can optionally join to form a 3 to 6-membered cycloalkyl group or 4 to 6-membered heterocycloalkyl group;

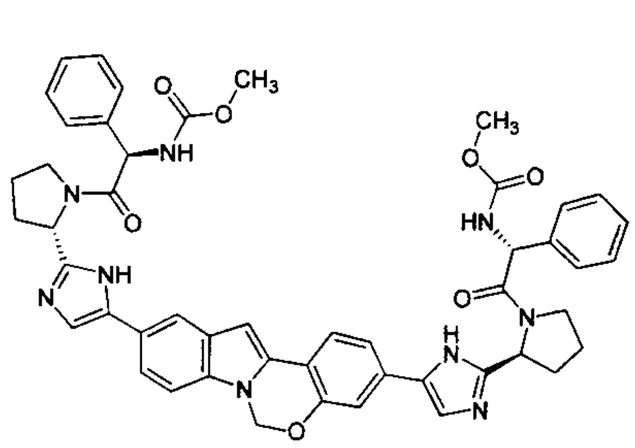
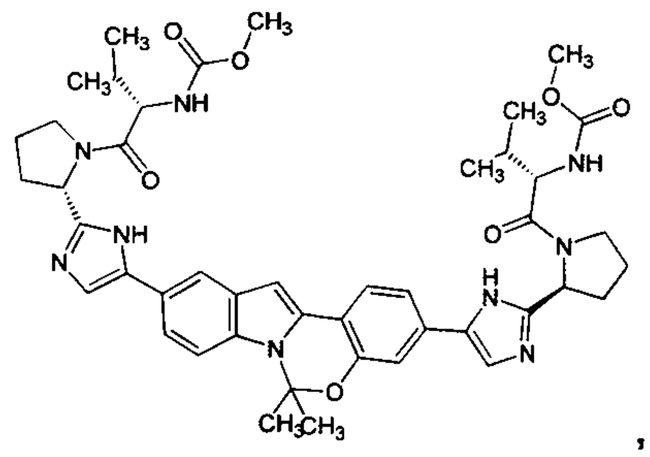
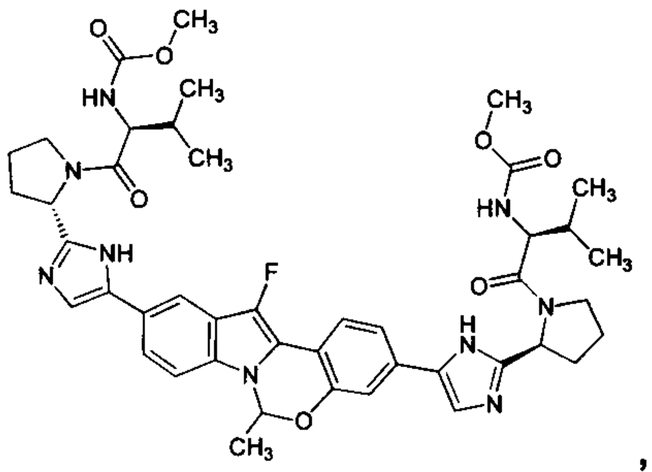
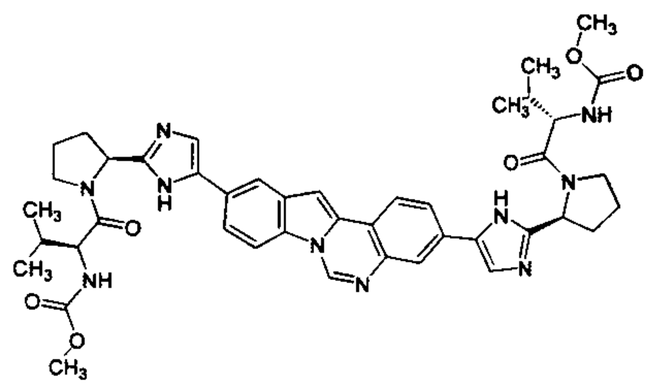
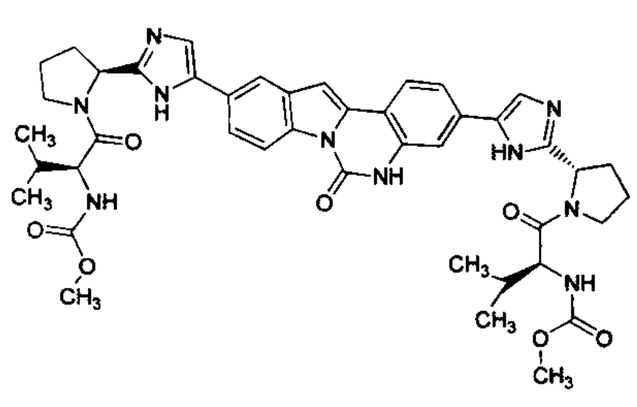
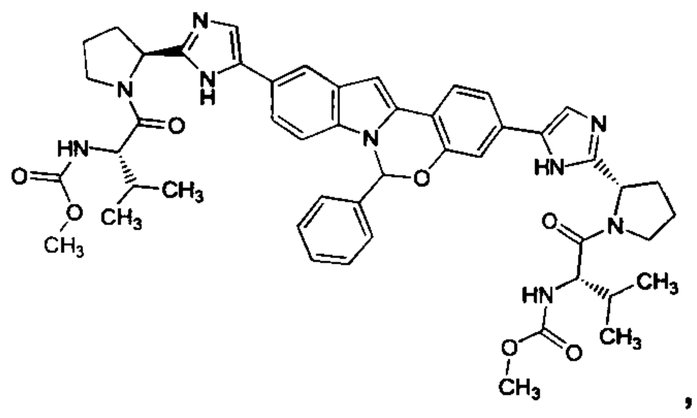
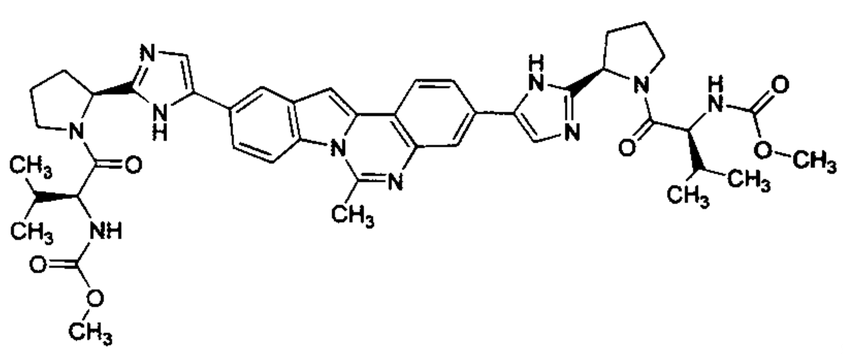
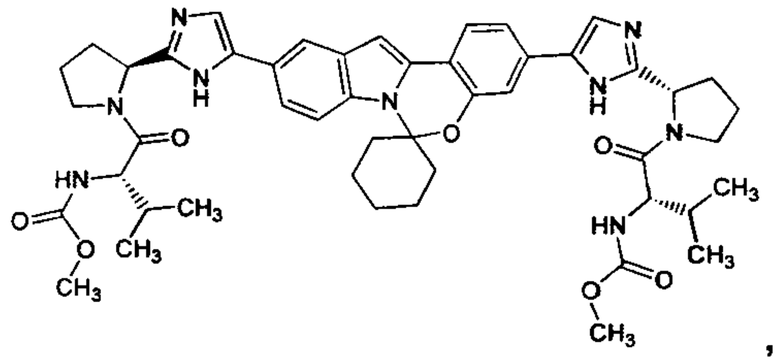
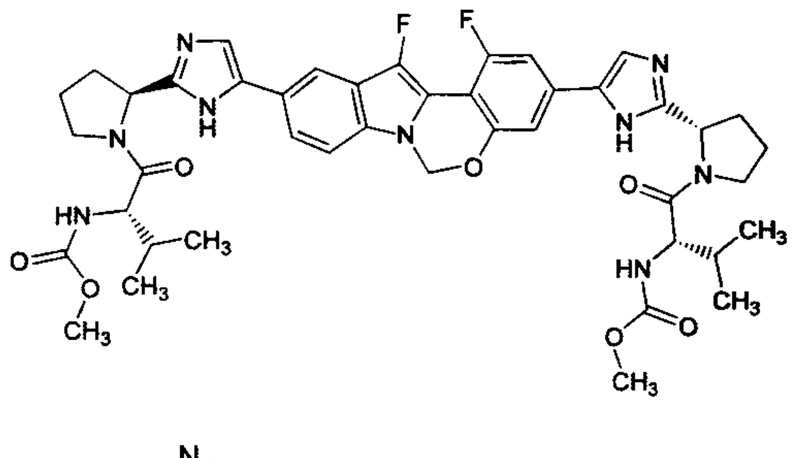
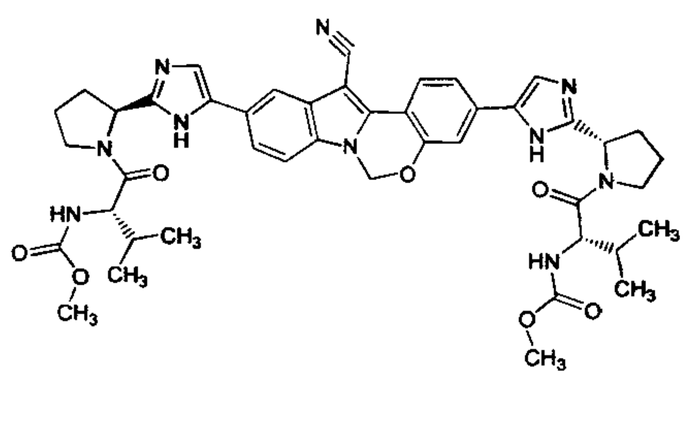
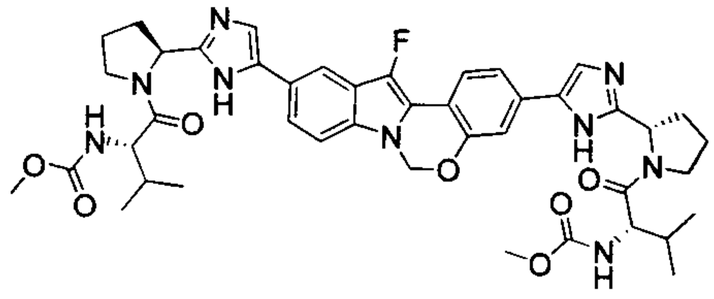
each occurrence of R^{14} is independently selected from H, halo, C_1-C_6 alkyl, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), 3 to 6-membered cycloalkyl, C_1-C_6 haloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl and benzyl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group or the phenyl moiety of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), –(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl) and -O-(C_1-C_6 haloalkyl);

each occurrence of R^{15} is independently selected from H, C_1-C_6 alkyl, 3 to 6-membered cycloalkyl, halo, -OH, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkyl and –O-(C_1-C_6 haloalkyl);

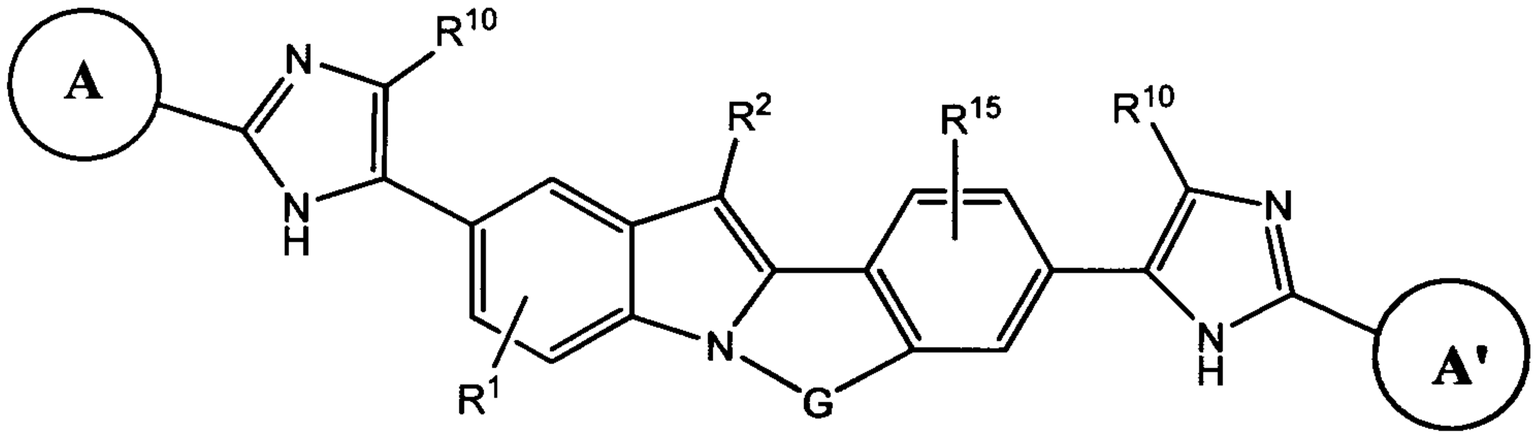
each occurrence of R^{16} is independently selected from H, halo, C_1-C_6 alkyl and 3 to 6-membered cycloalkyl, wherein two R^{16} groups that are attached to a common silicon atom can join to form a –$(CH_2)_4$- or a –$(CH_2)_5$- group; and

each occurrence of q is independently an integer ranging from 0 to 4,

provided that the compound of formula (I) is other than:


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or

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2. The compound of claim 1 having the formula:



(Ia)

and pharmaceutically acceptable salts thereof, wherein:

A and A' are each independently a 5-membered monocyclic heterocycloalkyl, wherein said 5-membered monocyclic heterocycloalkyl group can be optionally and independently substituted on one or more ring carbon atoms with R^{13}, such that any two R^{13} groups on the same ring, together with the carbon atoms to which they are attached, can join to form a fused, bridged or spirocyclic 3 to 6-membered cycloalkyl group or a fused, bridged or spirocyclic 4 to 6-membered heterocycloalkyl group, wherein said 5-membered monocyclic heterocycloalkyl contains from 1 to 2 ring heteroatoms, each independently selected from $N(R^4)$ and $Si(R^{16})_2$;

G is selected from–$C(R^3)_2$-O-, or –$C(R^3)_2$–$C(R^3)_2$-

R^1 represents an optional ring substituent on the phenyl ring to which R^1 is attached, wherein said substituent is selected from C_1-C_6 alkyl, -OC_1-C_6 alkyl and halo;

each occurrence of R^2 is independently selected from H, halo C_1-C_6 alkyl, 3 to 6 membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl, benzyl, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkylene –O-(C_1-C_6 haloalkyl); -(C_1-C_6 alkylene)C(=O)NH-alkyl, -(C_1-C_6 alkylene)aryl, and -(C_1-C_6 alkylene)heteroaryl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group or the phenyl group of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-(C_1-C_6 haloalkyl);

each occurrence of R^3 is independently selected from H, C_1-C_6 haloalkyl, C_1-C_6 alkyl, 3 to 6 membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl, 9 or 10-membered bicyclic heteroaryl, benzyl, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkylene –O-(C_1-C_6 haloalkyl); -(C_1-C_6 alkylene)C(=O)NH-alkyl, -(C_1-C_6 alkylene)aryl, and -(C_1-C_6 alkylene)heteroaryl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group, said 9 or 10-membered bicyclic heteroaryl group or the phenyl group of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-(C_1-C_6 haloalkyl);

each occurrence of R^4 is independently -C(O)-[$C(R^7)_2$]N(R^6)C(O)O-R^{11};

each occurrence of R^6 is independently selected from H and C_1-C_6 alkyl;

each occurrence of R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3 to 6-membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl and 5 or 6-membered monocyclic heteroaryl, wherein said 3 to 6-membered cycloalkyl group, said 4 to 6-membered heterocycloalkyl group, said aryl group and said 5 or 6-membered monocyclic heteroaryl group can be optionally and independently substituted with up to three R^8 groups;

each occurrence of R^8 is independently selected from H, C_1-C_6 alkyl, halo, -C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -OH, -C(O)NH-(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -O-(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$ and -NHC(O)-(C_1-C_6 alkyl);

each occurrence of R^{10} is independently selected from H and halo;

each occurrence of R^{11} is independently C_1-C_6 alkyl;

each occurrence of R^{13} is independently selected from H and halo, wherein two R^{13} groups, together with the carbon atom(s) to which they are attached, can optionally join to form a 3 to 6-membered cycloalkyl group or 4 to 6-membered heterocycloalkyl group;

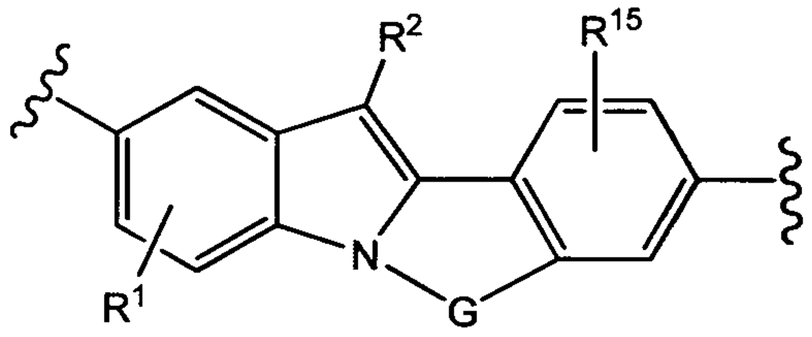
each occurrence of R^{14} is independently selected from H, halo C_1-C_6 alkyl, 3 to 6 membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl, benzyl, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkylene –O-(C_1-C_6

haloalkyl); -(C_1-C_6 alkylene)C(=O)NH-alkyl, -(C_1-C_6 alkylene)aryl, and -(C_1-C_6 alkylene)heteroaryl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group or the phenyl group of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-(C_1-C_6 haloalkyl);

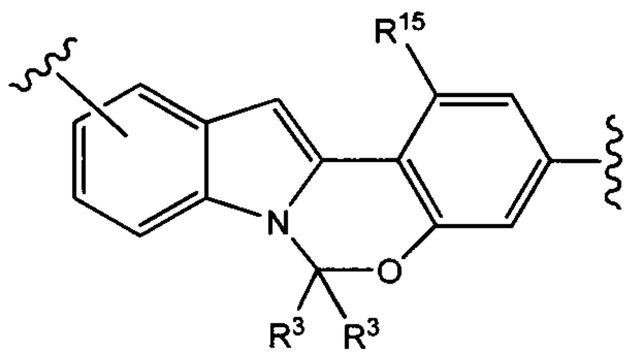
each occurrence of R^{15} is independently selected from H, halo C_1-C_6 alkyl, 3 to 6 membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl, benzyl, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkylene –O-(C_1-C_6 haloalkyl); -(C_1-C_6 alkylene)C(=O)NH-alkyl, -(C_1-C_6 alkylene)aryl, and -(C_1-C_6 alkylene)heteroaryl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group or the phenyl group of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-(C_1-C_6 haloalkyl); and

each occurrence of R^{16} is independently selected from C_1-C_6 alkyl.

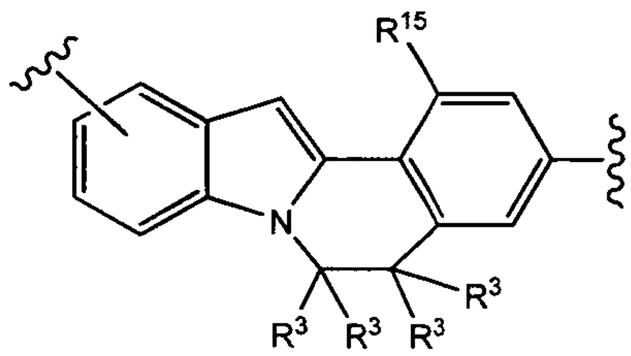
3. The compound of claim 1 or 2 wherein the group:



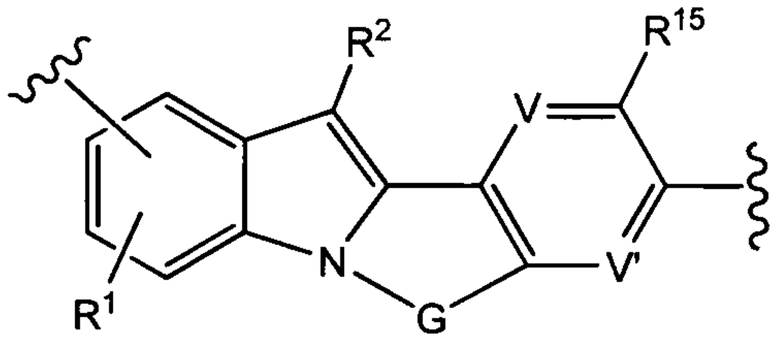
has the structure:



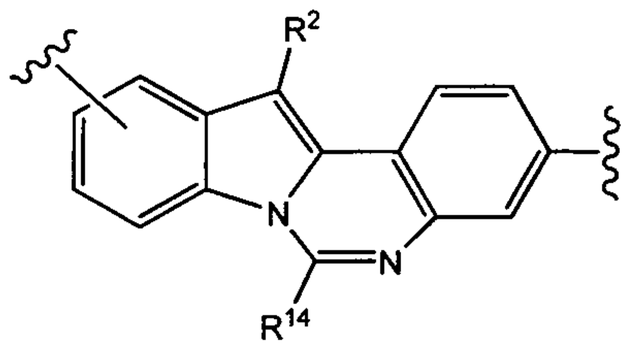
and

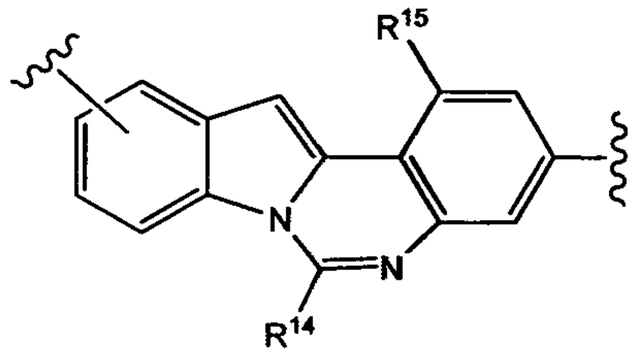


4. The compound of claim 1 or 2, wherein the group:

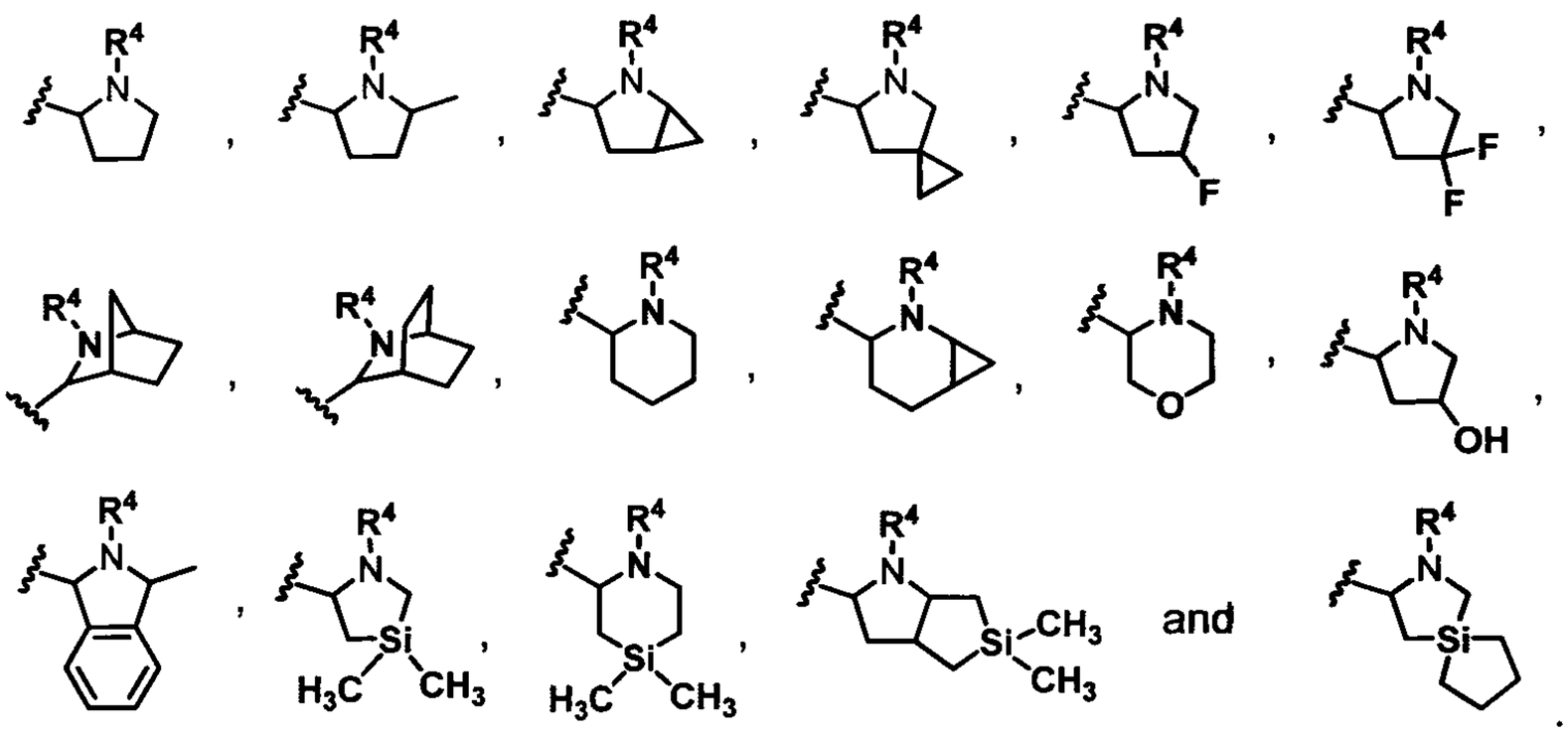


has the structure:

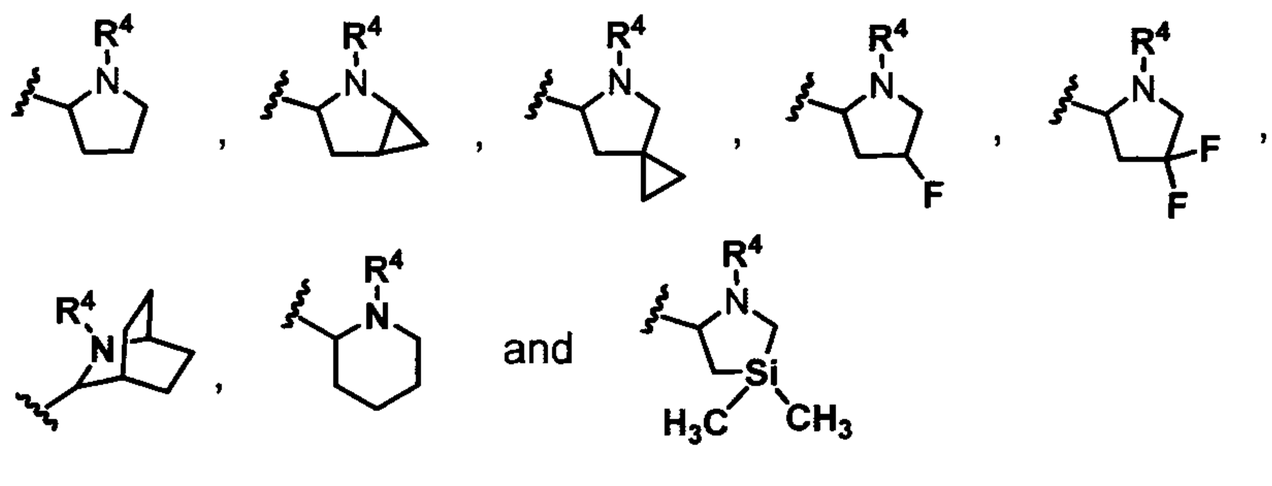




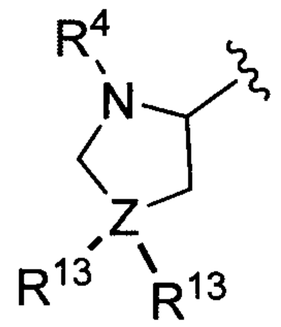
5. The compound of any one of claims 1 to 4, wherein A and A' are each independently selected from:



6. The compound of claim 5, wherein A and A' are each independently selected from:



7. The compound of any one of claims 1 to 6, wherein A and A' are each

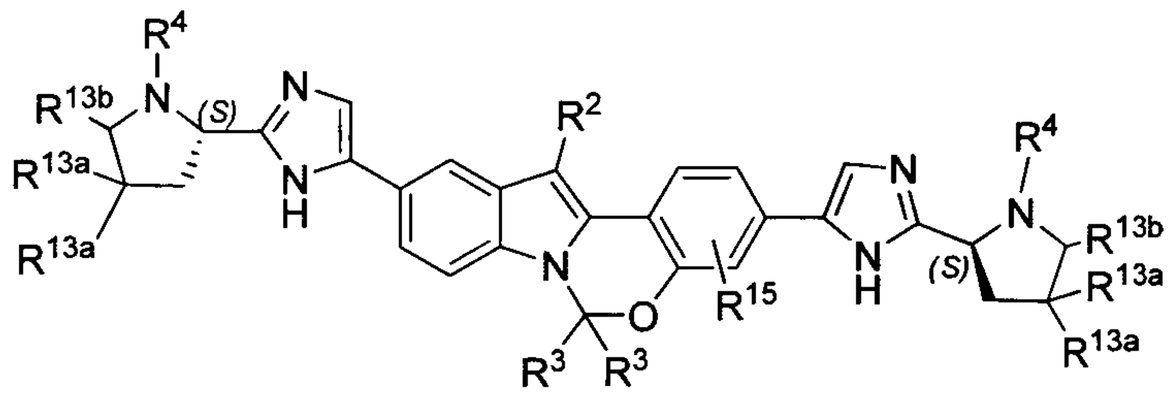


wherein each occurrence of Z is independently $-Si(R^{13})_2-$, $-C(R^{13})_2-$ or –S-, and each occurrence of R^{13} is independently H, Me, F or two R^{13} groups together with Z, can combine to form a spirocyclic 3 to 6-membered cycloalkyl group or a spirocyclic 3 to 6-membered silyl-containing heterocycloalkyl group.

8. The compound of any one of claims 1 to 6, wherein each occurrence of R^4 is independently $-C(O)C(R^7)_2NHC(O)O-R^{11}$ or $-C(O)C(R^7)_2N(R^6)_2$.

9. The compound of any one of claim 8, wherein each occurrence of R^4 is independently –C(O)CH(alkyl)-NHC(O)Oalkyl, C(O)CH(cycloalkyl)-NHC(O)Oalkyl, C(O)CH(heterocycloalkyl)-NHC(O)Oalkyl, C(O)CH(aryl)-NHC(O)Oalkyl or $C(O)CH(aryl)-N(alkyl)_2$.

10. The compound of claim 1 having the formula:



(Ib)

or a pharmaceutically acceptable salt thereof, wherein:

R^2 is H or F;

each occurrence of R^3 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3 to 6 membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl, 9 or 10-membered bicyclic heteroaryl, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkylene –O-(C_1-C_6 haloalkyl); -(C_1-C_6 alkylene)C(=O)NH-alkyl, -(C_1-C_6 alkylene)aryl, and -(C_1-C_6 alkylene)heteroaryl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group, said 9 or 10-membered bicyclic heteroaryl group or the phenyl group of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-(C_1-C_6 haloalkyl);

each occurrence of R^4 is independently selected from –C(O)O-(C_1-C_6 alkyl), –C(O)-CH(R^7)N(R^6)$_2$ and –C(O)-CH(R^7)C(O)O-R^{11};

each occurrence of R^6 is independently H or C_1-C_6 alkyl;

each occurrence of R^7 is independently selected from C_1-C_6 alkyl, phenyl, 4 to 6-membered heterocycloalkyl and 3 to 6 membered cycloalkyl;

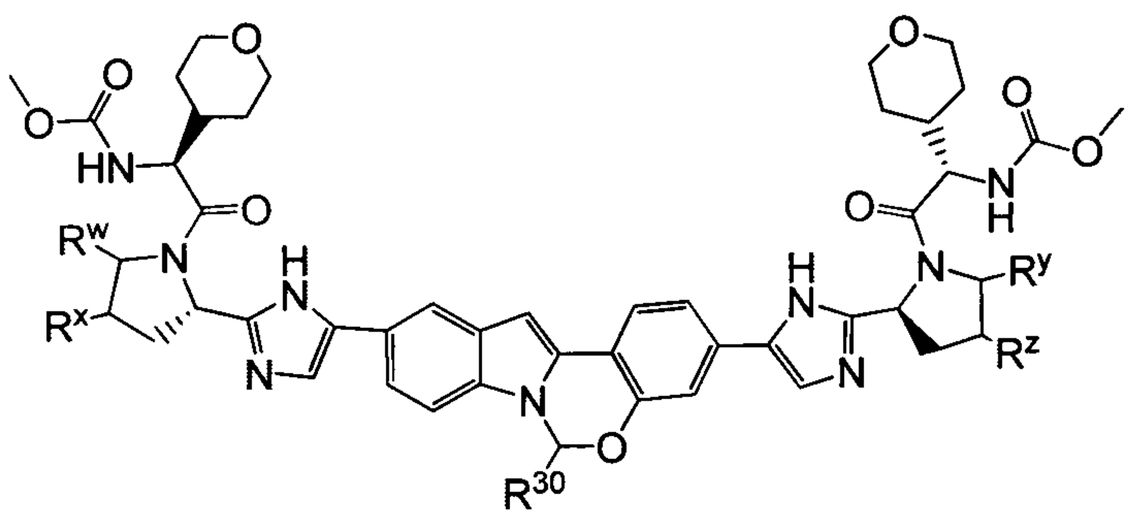
each occurrence of R^{11} is independently C_1-C_6 alkyl;

each occurrence of R^{13a} is independently H, Me or F; or two R^{13a} groups that are attached to the same carbon atom, together with the common carbon atom to which they are attached, combine to form a spirocyclic 3 to 6 membered cycloalkyl group;

each occurrence of R^{13b} is independently H, or one or both R^{13b} groups and an $R13^a$ group that are attached to same ring, together with the ring carbon atoms to which they are attached, can combine to form a fused 3 to 6 membered cycloalkyl group; and

R^{15} represents up to 2 substituents, each independently selected from H, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3 to 6 membered cycloalkyl, 4 to 6-membered heterocycloalkyl, aryl, 5 or 6-membered monocyclic heteroaryl, benzyl, -O-(C_1-C_6 alkyl), C_1-C_6 haloalkylene –O-(C_1-C_6 haloalkyl) -(C_1-C_6 alkylene)C(=O)NH-alkyl, -(C_1-C_6 alkylene)aryl, and -(C_1-C_6 alkylene)heteroaryl, wherein said aryl group, said 5 or 6-membered monocyclic heteroaryl group or the phenyl group of said benzyl group can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-(C_1-C_6 haloalkyl).

11. The compound of claim 1 having the formula:



(Id)

or a pharmaceutically acceptable salt thereof,

wherein:

R^{30} is C_1-C_6 alkyl, aryl, 5 or 6-membered monocyclic heteroaryl or 9-membered bicyclic heteroaryl;

R^w is H, or R^w and R^x, together with the ring carbon atoms to which they are attached, combine to form a fused 3 to 6-membered cycloalkyl group;

R^x is H or F, or R^w and R^x, together with the ring carbon atoms to which they are attached, combine to form a fused 3 to 6-membered cycloalkyl group;

R^y is H, or R^y and R^z, together with the ring carbon atoms to which they are attached, combine to form a fused 3 to 6-membered cycloalkyl group; and

R^z is H or F, or R^y and R^z, together with the ring carbon atoms to which they are attached, combine to form a fused 3 to 6-membered cycloalkyl group.

12. A compound of Table 1 or Table 2 of the above specification or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising an effective amount of the compound of any of claims 1 to 12 and a pharmaceutically acceptable carrier.

14. The pharmaceutical composition according to claim 13 further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

15. The pharmaceutical composition according to claim 14, further comprising a third therapeutic agent selected from the group consisting of HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

16. The use of the compound according to any of claims 1 to 12 for inhibiting HCV replication or for treating infection by HCV in a patient in need thereof.

17. A method of treating a patient infected with HCV comprising the step of administering an amount of (i) the compound according to any of claims 1 to 10 or (ii) the composition according to any of claims 13 to 15 effective to treat infection by HCV in said patient.

18. The method according to claim 17, further comprising the step of administering pegylated-interferon alpha and an HCV protease to said patient.

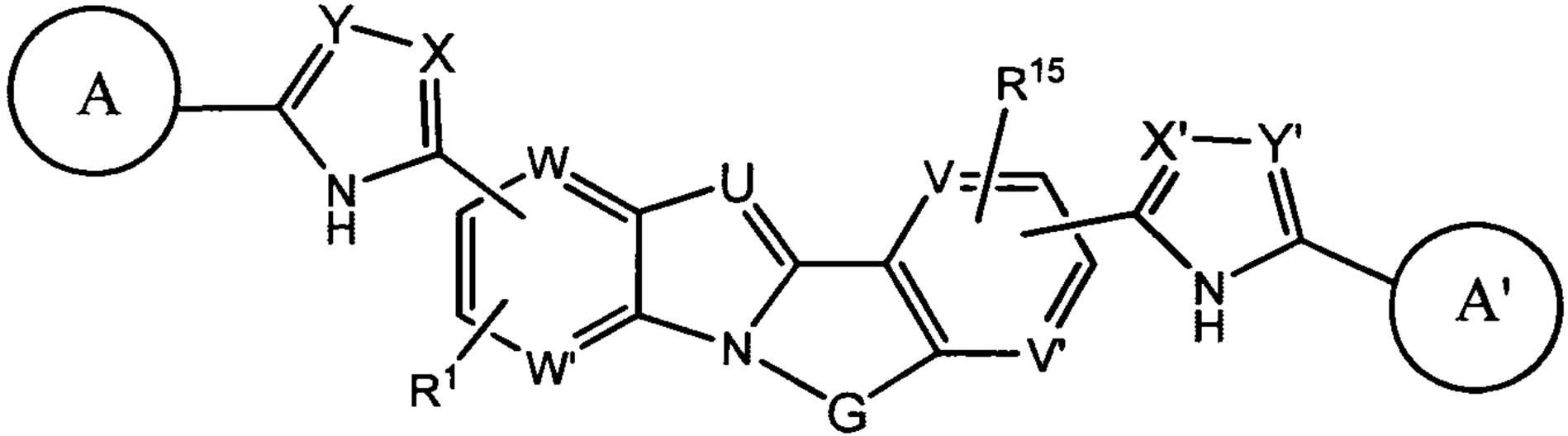
19. The method according to claim 17 or 18, further comprising the step of administering ribavirin to said patient.

20. The method according to claim 17 or 18, further comprising the step of administering from one to three additional therapeutic agents to said patient,

wherein the additional therapeutic agents are each independently selected from HCV protease inhibitors, HCV NS5A inhibitors and HCV NS5B polymerase inhibitors.

21. The method according to claim 20, wherein the one to three additional therapeutic agents comprises MK-5172.

22. The method according to claim 21 or 22, wherein the one to three additional therapeutic agents comprises PSI-7977.



(I)