

INTERNAL CYCLIC SULPHIAMIDINE AMIDE-ARYL AMIDE COMPOUND AND USE THEREOF FOR TREATING HEPATITIS B

FIELD OF THE INVENTION

The present invention belongs to the field of medicine, and in particular, the present invention relates to a class of cyclic sulfonimidamide-arylamide compounds and the use as a medicine for treating hepatitis B thereof.

BACKGROUND OF THE INVENTION

Hepatitis B virus (HBV) is an enveloped virus of hepatotropic virus DNA family (Hepadnaviridae) with partially double-stranded DNA (dsDNA). The genome thereof contains 4 overlapped reading frames: precore / core gene, polymerase gene, UM and S genes (which encode three envelope proteins), and X gene. In the early stage of infection, the partially double-stranded DNA genome (open-loop DNA, rcDNA) in the host cell nucleus is transformed into covalently closed circular DNA (cccDNA) and transcribed into virus mRNA. Once encapsulated, the pre-genome RNA (pgRNA) (which encodes the core protein and Pol) serves as a template for reverse transcription, which regenerates this partial dsDNA genome (rcDNA) in the nucleocapsid.

HBV causes epidemics in certain areas of Asia and Africa, and is endemic in China. HBV has infected about 2 billion people worldwide, of which about 350 million people have developed into chronic infectious diseases. The virus causes hepatitis B disease and chronic infectious diseases are associated with a highly increased risk of development of cirrhosis and liver cancer.

The spread of hepatitis B virus is caused by exposure to infectious blood or body fluid, and the virus is detected in the saliva, tears, and urine of chronic carriers with high DNA titers in the serum.

Although there is currently an effective and well tolerated vaccine, the option of direct treatment is still limited to interferon and the following antiviral drugs: tenofovir, lamivudine, adefovir, entecavir and telbivudine.

Additionally, heteroaryldihydropyrimidines (HAPs) are identified as a class of HBV inhibitors in tissue cultivation and animal models (Weber et al., Antiviral Res. 54: 69-78).

WO2013/006394 (published on January 10, 2013) and WO 2013/096744 (published on June 27, 2013) also disclosed sulfamoyl-arylamides having anti-HBV activity.

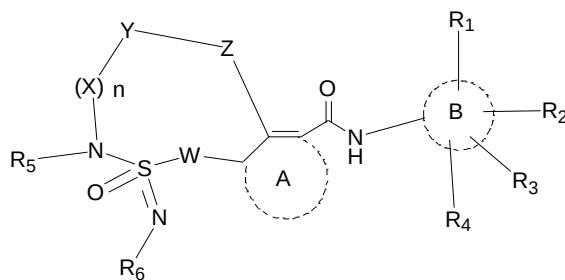
However, problems encountered in these direct HBV antiviral drugs are toxicity, mutagenicity, lack of selectivity, poor efficacy, poor bioavailability, and difficulty in synthesis.

Therefore, in order to overcome the above defects, it is necessary to develop HBV inhibitors with advantages such as high potency and lower toxicity.

SUMMARY OF INVENTION

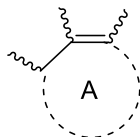
An object of the present invention is to provide a class of structurally novel compounds useful as HBV inhibitors.

In the first aspect of the invention, a compound of the formula L, or a stereoisomer thereof, or a tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof is provided,

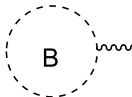


L

wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;



is a substituted or unsubstituted five or six membered ring, wherein the five or six membered ring optionally contains one or more heteroatoms selected from the group consisting of O, S, N and P; the substituted means that the hydrogen atoms on the group are substituted by one or more substituents selected from the group consisting of C1-C3 alkyl (especially methyl), C3-C4 cycloalkyl, cyano, or halogen;



is a substituted or unsubstituted five- or six-membered aromatic ring, or a substituted or unsubstituted five- or six-membered heteroaromatic ring;

X is $\text{-CR}^a\text{R}^b\text{-}$;

Y is substituted or unsubstituted C1-C7 alkylene, or substituted or unsubstituted C2-C7 alkenylene, wherein the substituent is selected from the group consisting of C1-C4 alkyl, hydroxyl;

Z is selected from the group consisting of O, S, N or P, or Z is a C-C single bond (i.e., Z is none);

W is NRc or none;

R^1 , R^2 , R^3 and R^4 are each independently selected from the group consisting of H, halogen, cyano, substituted or unsubstituted C3-C4 cycloalkyl, substituted or unsubstituted C1-C4 alkyl, substituted or unsubstituted C1-C4 alkoxy; wherein the substituted means that hydrogen atoms on the group are replaced by one or more substituents selected from the group consisting of halogen, C1-C4 alkyl (such as difluoromethyl, difluoroethyl, monofluoromethyl, trifluoromethyl, trifluoromethoxy);

R^5 , R^6 are each independently selected from the group consisting of H, halogen,

-CN, hydroxyl, amino, carboxyl, -(C=O)-substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₂-C₆ alkenyl, substituted or unsubstituted C₂-C₆ alkynyl, substituted or unsubstituted C₁-C₈ alkylamino, substituted or unsubstituted C₁-C₈ alkoxy, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted 3-10 membered heterocycloalkyl having 1-3 heteroatoms selected from the group consisting of N, S and O, substituted or unsubstituted C₆-C₁₀ aryl, and substituted or unsubstituted 5-10 membered heteroaryl having 1-3 heteroatoms selected from the group consisting of N, S and O;

R^a and R^b are each independently H, halogen, -CN, hydroxyl, amino, carboxyl, -(C=O)-substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₂-C₆ alkenyl, substituted or unsubstituted C₂-C₆ alkynyl, substituted or unsubstituted C₁-C₈ alkylamino, substituted or unsubstituted C₁-C₈ alkoxy, substituted or unsubstituted C₁-C₆ alkoxy-alkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted 3-10 membered heterocycloalkyl having 1-3 heteroatoms selected from the group consisting of N, S and O, substituted or unsubstituted C₆-C₁₀ aryl, and substituted or unsubstituted 5-10 membered heteroaryl having 1-3 heteroatoms selected from the group consisting of N, S and O;

R_c is H, halogen, -CN, hydroxyl, amino, carboxyl, -(C=O)-substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₂-C₆ alkenyl, substituted or unsubstituted C₂-C₆ alkynyl, substituted or unsubstituted C₁-C₈ alkylamine, substituted or unsubstituted C₁-C₈ alkoxy, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted 3-10 membered heterocycloalkyl having 1-3 heteroatoms selected from the group consisting of N, S and O, substituted or unsubstituted C₆-C₁₀ aryl, and substituted or unsubstituted 5-10 membered heteroaryl having 1-3 heteroatoms selected from the group consisting of N, S and O;

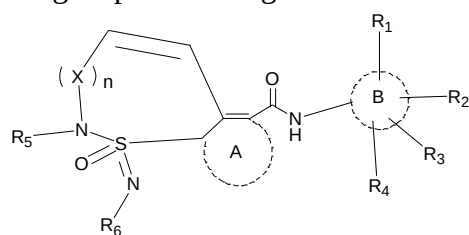
unless otherwise specified, "substituted" means that the group substituted by one or more (such as 2, 3, 4, etc.) substituents selected from the group consisting of halogen, C₁-C₆ alkyl, halogenated C₁-C₆ alkyl, C₁-C₆ alkoxy, halogenated C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, halogenated C₃-C₈ cycloalkyl, oxo, -CN, hydroxyl, amino, carboxyl, and the following groups unsubstituted or substituted by one or more substituents: C₆-C₁₀ aryl, halogenated C₆-C₁₀ aryl, 5-10 membered heteroaryl having 1-3 heteroatoms selected from the group consisting of N, S and O, halogenated 5-10 membered heteroaryl having 1-3 heteroatoms selected from N, S and O; and the substituent is selected from the group consisting of halogen and C₁-C₆ alkoxy.

In another preferred embodiment, the Y is selected from the group consisting of C₁-C₄ alkylene and substituted or unsubstituted C₂-C₄ alkenylene.

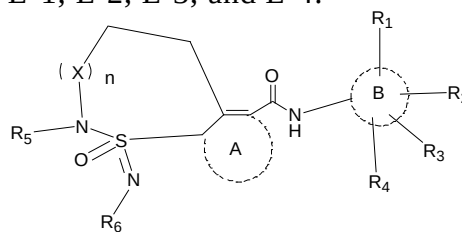
In another preferred embodiment, the R_a and R_b are each independently substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₁-C₈ alkoxy; wherein the substituent is selected from the group consisting of halogen, hydroxyl, and cyano.

In another preferred embodiment, the compound has a structure selected from

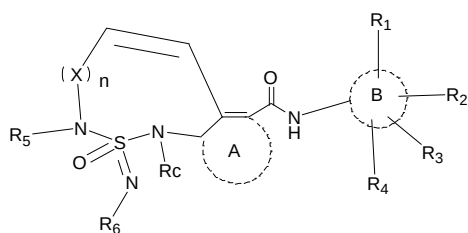
the group consisting of the following formulas L-1, L-2, L-3, and L-4:



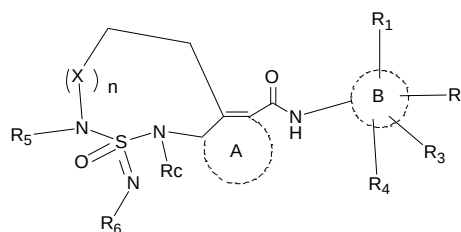
L-1



L-2



L-3



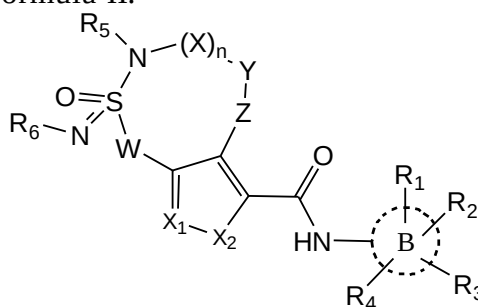
L-4

In each formula, n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

the definitions of ring A, ring B, X, R₁, R₂, R₃, R₄, R₅ and R₆ are as described in the first aspect of the present invention.

In another preferred embodiment, the R_a and R_b are each independently substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₁-C₈ alkoxy; wherein the substituent is selected from the group consisting of halogen, hydroxyl, and cyano.

In another preferred embodiment, the formula I compound has the structure shown by the following formula II:

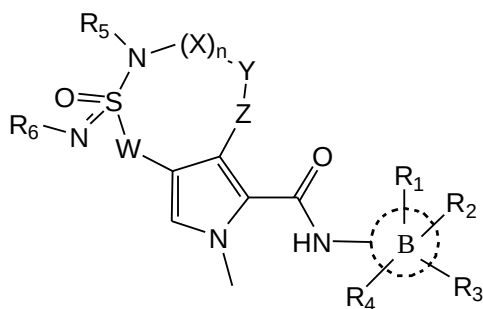


II

wherein X₁ is -CR= or -N=, X₂ is -NR-; and R is H or C₁-C₄ alkyl.

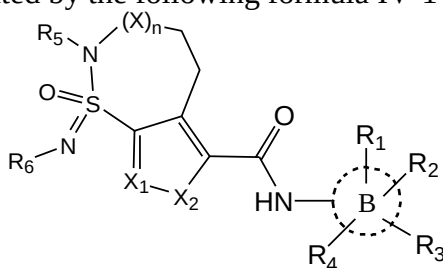
In another preferred embodiment, the X₂ is -NCH₃-.

In another preferred embodiment, the compound of formula I has the following structure:

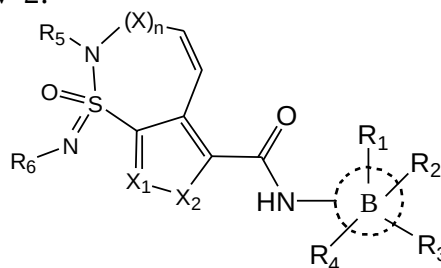


III

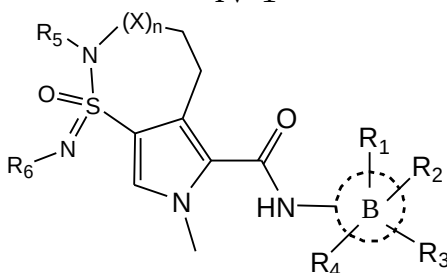
In another preferred embodiment, the compound of formula I has a structure represented by the following formula IV-1 or IV-2:



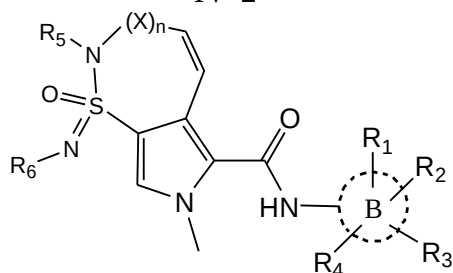
IV-1



IV-2



V-1



V-2

In a preferred embodiment, n is 1.

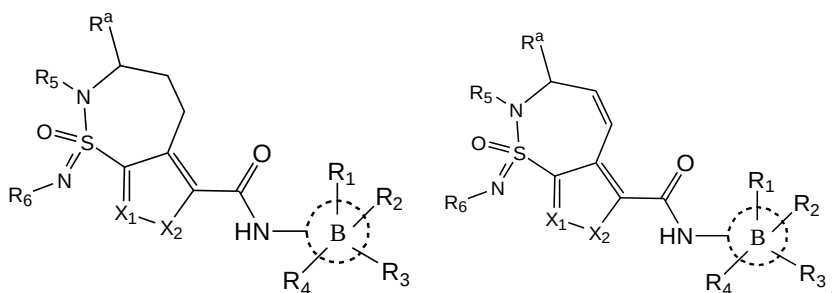
In a preferred embodiment, Ra is selected from the group consisting of substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₁-C₈ alkoxy, substituted or unsubstituted C₁-C₆ alkoxy-alkyl; substituted or unsubstituted C₃-C₆ cycloalkyl, C₁-C₄ alkyl substituted by substituted or unsubstituted C₃-C₆ cycloalkyl, halogenated phenyl, substituted or unsubstituted C₁-C₆ alkoxy-phenyl, and Rb is H.

In a preferred embodiment, Ra is selected from the group consisting of substituted or unsubstituted C₁-C₈ alkyl; wherein, substituted refers to one or more hydrogen atoms being replaced by substituents selected from the group consisting of C₁-C₄ alkoxy, hydroxyl, C₆-C₁₀ aryl unsubstituted or substituted by one or more substituents selected from the group consisting of halogen or C₁-C₆ alkoxy.

In a preferred embodiment, R^a is selected from the group consisting of substituted or unsubstituted C₃-C₆ cycloalkyl, C₁-C₄ alkyl substituted by substituted or unsubstituted C₃-C₆ cycloalkyl, halogenated phenyl.

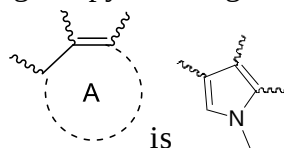
In a preferred embodiment, R^a is selected from the group consisting of cyclopropyl, methylene cyclopropyl, 4-fluorophenyl, 4-methoxyphenyl.

In a preferred embodiment, the compound has the following structure:



In a preferred embodiment, the B ring is a benzene ring or a pyridine ring.

In another preferred embodiment, the A ring is a pyrrole ring.



In another preferred embodiment, said

In another preferred embodiment, the R₁, R₂, R₃ and R₄ are each independently selected from the group consisting of H, halogen, and cyano.

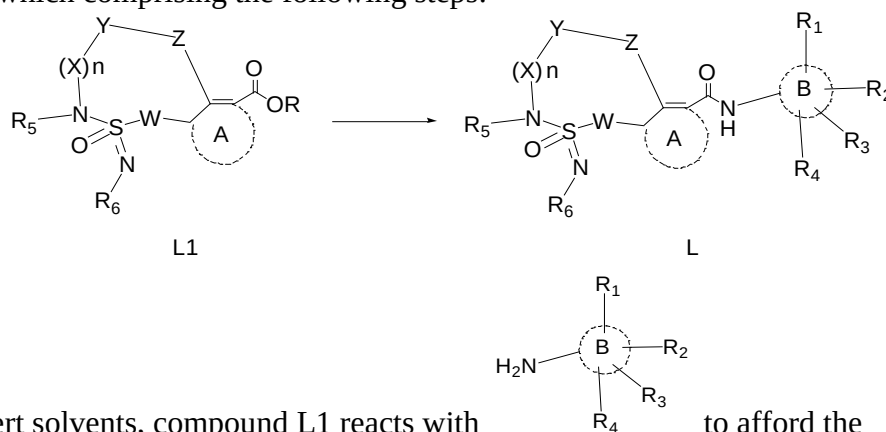
In another preferred embodiment, the R₅ is selected from the group consisting of H, substituted or unsubstituted C₁-C₈ alkyl, and substituted or unsubstituted C₃-C₁₀ cycloalkyl.

In another preferred embodiment, the R₆ is selected from the group consisting of H, substituted or unsubstituted C₁-C₈ alkyl, and substituted or unsubstituted C₃-C₁₀ cycloalkyl.

In another preferred embodiment, the compound is the compound 10a1-100c20 as described in Table 1, wherein Peak 1 and Peak 2 refer to the order of the enantiomers' peaks in reversed-phase HPLC, wherein Peak 1 is the first peak in the enantiomer, and Peak 2 is the latter peak of the enantiomer.

In another preferred embodiment, in the above table, HPLC is reversed-phase HPLC, where wherein, peak 1 refers to compound with high polarity, peak 2 refers to compound with low polarity.

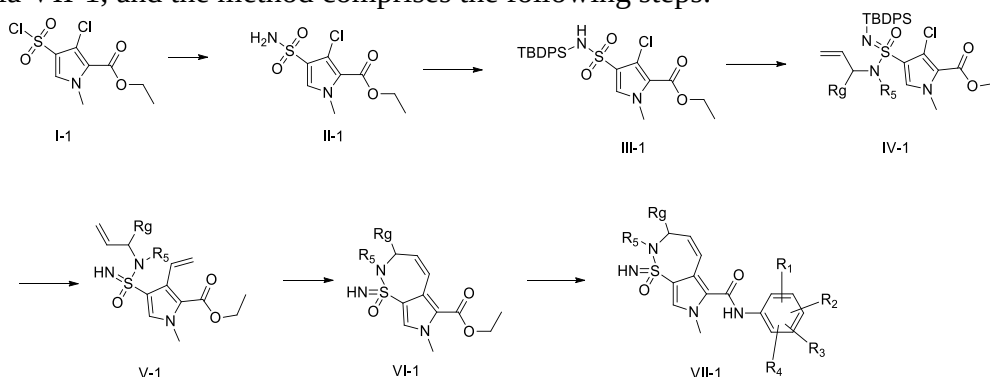
In the second aspect of the invention, a method for preparing compound of the formula I, or a stereoisomer thereof, or a tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof of the first aspect of the present invention is provided, which comprising the following steps:



In inert solvents, compound L1 reacts with

wherein, R is a leaving group, and the definitions of the remaining groups are as described in the first aspect of the present invention.

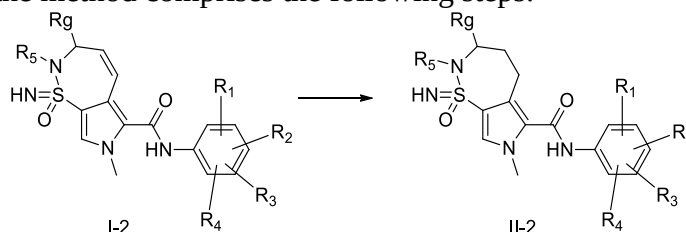
In another preferred embodiment, the compound of formula L is a compound of formula VII-1, and the method comprises the following steps:



wherein Rg is selected from the group consisting of H, halogen, -CN, hydroxyl, amino, carboxyl, -(C=O)-substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₂-C₆ alkenyl, substituted or unsubstituted C₂-C₆ alkynyl, substituted or unsubstituted C₁-C₈ alkylamino, substituted or unsubstituted C₁-C₈ alkoxy, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted 3-10 membered heterocycloalkyl having 1-3 heteroatoms selected from the group consisting of N, S and O, substituted or unsubstituted C₆-C₁₀ aryl, and substituted or unsubstituted 5-10 membered heteroaryl having 1-3 heteroatoms selected from the group consisting of N, S and O;

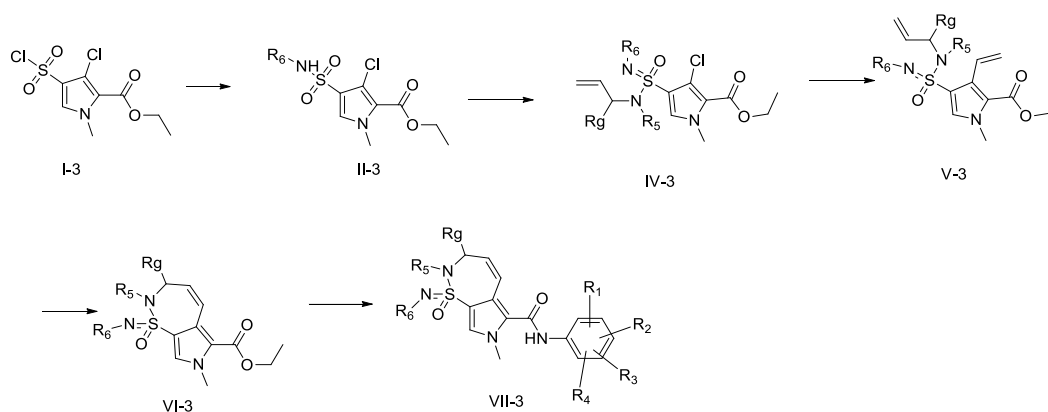
each group is defined as above.

In another preferred embodiment, the compound of formula L is a compound of formula II-2, and the method comprises the following steps:



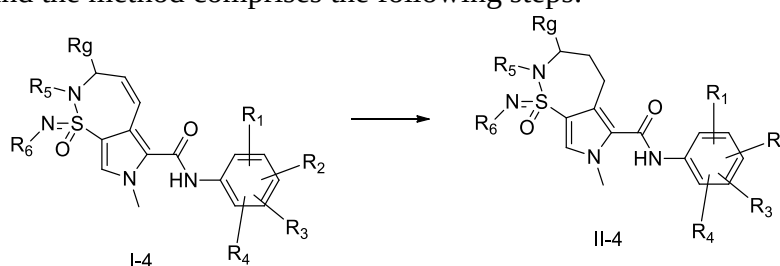
wherein, each group is defined as above.

In another preferred embodiment, the compound of formula L is a compound of formula VII-3, and the method comprises the following steps:



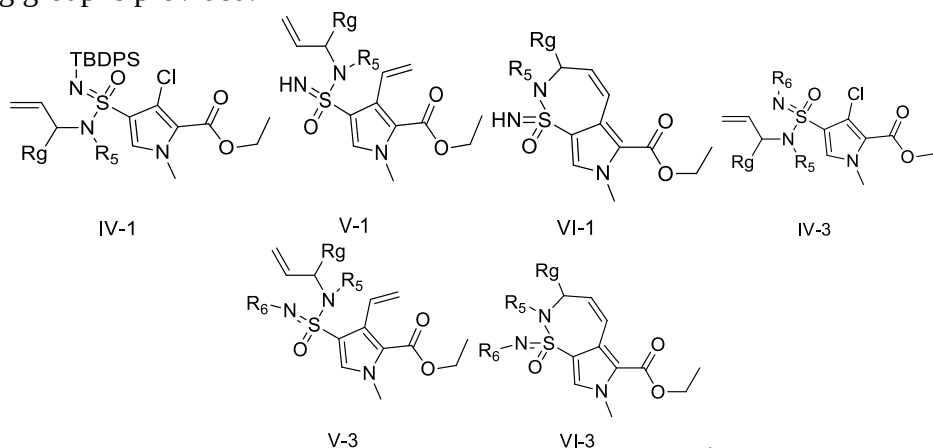
wherein, each group is defined as above.

In another preferred embodiment, the compound of formula L is a compound of formula II-4, and the method comprises the following steps:



wherein, each group is defined as above.

In the third aspect of the present invention, a compound selected from the following group is provided:



in each formula, Rg is selected from the group consisting of H, halogen, -CN, hydroxyl, amino, carboxyl, -(C=O)-substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₂-C₆ alkenyl, substituted or unsubstituted C₂-C₆ alkynyl, substituted or unsubstituted C₁-C₈ alkylamino, substituted or unsubstituted C₁-C₈ alkoxy, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted 3-10 membered heterocycloalkyl having 1-3 heteroatoms selected from the group consisting of N, S and O, substituted or unsubstituted C₆-C₁₀ aryl, and substituted or unsubstituted 5-10 membered heteroaryl having 1-3 heteroatoms selected from the group consisting of N, S and O;

each group is defined as described in the first aspect of the present invention.

In the fourth aspect of the invention, a pharmaceutical composition is provided, which comprising (1) a compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof according to the first aspect of the invention; and (2) pharmaceutically acceptable carriers.

In the fifth aspect of the invention, a use of compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof according to the first aspect of the invention, or a use of the pharmaceutical composition according to the fourth aspect of the invention is provided, which is used for the preparation of medicine for the prevention and / or treatment of Hepatitis B.

In the sixth aspect of the invention, an inhibitor of hepatitis B virus is provided, which comprises the compound of the formula I, or a stereoisomer thereof, or a tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof of the first aspect of the present invention.

In the seventh aspect of the invention, a method for the prevention and / or treatment of hepatitis B is provided, which comprises the steps: administering the compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof of the first aspect of the invention, or the pharmaceutical composition of the fourth aspect of the invention to a subject in need thereof.

In the eighth aspect of the invention, a method for inhibiting replication of hepatitis B virus is provided, which comprises the steps: contacting the compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof of the first aspect of the invention with hepatitis B virus, thus inhibiting the replication of hepatitis B.

It should be understood that, in the present invention, each of the technical features specifically described above and below (such as those in the Examples) can be combined with each other, thereby constituting new or preferred technical solutions which are not necessarily specified one by one herein.

EMBODIMENTS FOR CARRYING OUT THE INVENTION

After extensive and intensive research, the inventors have found a novel class of compounds having excellent therapeutic effects on hepatitis B. The inventors have completed the present invention on this basis.

TERMS

As used herein, the term “alkyl” includes straight or branched alkyl groups. For example, C₁-C₈ alkyl refers to straight or branched alkyls having 1-8 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, and the like.

As used herein, the term “alkenyl” includes straight or branched alkenyl groups. For example, C₂-C₆ alkenyl refers to straight or branched alkenyl groups having 2-6 carbon atoms, such as vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl,

2-butenyl, and the like.

As used herein, the term "alkynyl" includes straight or branched alkynyl groups. For example, "C₂-C₆ alkynyl" refers to a straight or branched alkynyl having 2-6 carbon atoms, such as ethynyl, propynyl, butynyl, and the like.

As used herein, the term "C₃-C₁₀ cycloalkyl" refers to cycloalkyl group having 3 to 10 carbon atoms. It may be a monocyclic ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. It may also be of bicyclic form, such as bridged or spiro ring form.

As used herein, the term "C₁-C₈ alkylamino" refers to an amine group substituted by C₁-C₈ alkyl, which may be monosubstituted or di-substituted; for example, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino, dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, di(tert-butyl)amino, and the like.

As used herein, the term "C₁-C₈ alkoxy" refers to straight or branched alkoxy groups having 1-8 carbon atoms; such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, and the like.

As used herein, the term "3-10 membered heterocycloalkyl having 1-3 heteroatoms selected from the group consisting of N, S and O" refers to a saturated or partially saturated cyclic group having 3-10 atoms, wherein 1-3 atoms are heteroatoms selected from the group consisting of N, S and O. It may be a monocyclic ring or bicyclic form, such as bridged or spiro ring form. Specific examples may be oxetane, azetidine, tetrahydro-2H-pyran, piperidine, tetrahydrofuran, morpholine and pyrrolidine, and the like.

As used herein, the term "C₆-C₁₀ aryl" refers to an aryl group having 6 to 10 carbon atoms, such as phenyl, naphthyl, and the like.

As used herein, the term "5-10 membered heteroaryl having 1-3 heteroatoms selected from the group consisting of N, S and O" refers to cyclic aromatic groups having 5-10 atoms, of which 1-3 is selected from the group consisting of N, S and O. It may be a monocyclic ring or fused ring form. Specific examples may be pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3)-triazolyl and (1,2,4)-triazolyl, tetrazyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, etc.

Unless otherwise specified as "substituted or unsubstituted", all the groups described in the present invention may be substituted with substituents selected from the group consisting of halogen, cyano, nitro, hydroxy, amino, C₁-C₆ alkyl-amino, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halogenated C₁-C₆ alkyl, halogenated C₂-C₆ alkenyl, halogenated C₂-C₆ alkynyl, halogenated C₁-C₆ alkoxy, allyl, benzyl, C₆-C₁₂ aryl, C₁-C₆ alkoxy-C₁-C₆ alkyl, C₁-C₆ alkoxy-carbonyl, phenoxycarbonyl, C₂-C₆ alkynyl-carbonyl, C₂-C₆ alkenyl-carbonyl, C₃-C₆ cycloalkyl-carbonyl, C₁-C₆ alkyl-sulfonyl, etc.

As used herein, "halogen" or "halogen atom" refers to F, Cl, Br, and I. More preferably, the halogen or halogen atom is selected from F, Cl or Br.

“Halogenated” means substitution by atom(s) selected from the group consisting of F, Cl, Br, and I.

Unless otherwise specified, the structural formula described herein are intended to include all isomeric forms (such as enantiomeric, diastereomeric, and geometric isomers (or conformational isomers)): for example, R, S configuration having asymmetrical centers, (Z), (E) isomers of double bonds, etc. Therefore, the single stereo chemical isomers or enantiomers, diastereomers or geometric isomers (or conformers) of the compounds of the invention, or mixtures thereof all fall within the scope of the invention.

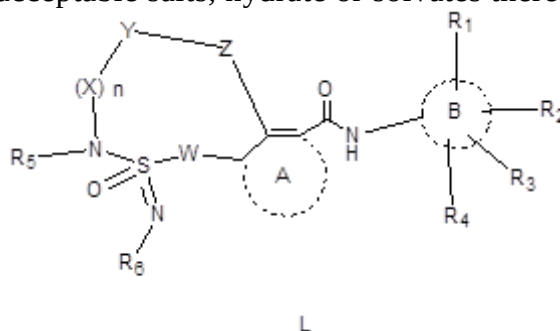
As used herein, the term "tautomer" means that structural isomers having different energies can exceed the low energy barrier and thereby transform between each other. For example, proton tautomers (proton shift) includes interconversion by proton transfer, such as 1H-carbazole and 2H-carbazole. Valence tautomers include interconversion through some bonding electron recombination.

As used herein, the term “solvate” refers to a complex of specific ratio formed by a compound of the invention coordinating to a solvent molecule.

As used herein, the term “hydrate” refers to a complex formed by the coordination of a compound of the invention with water.

ACTIVE INGREDIENTS

As used herein, “compound of the invention” refers to the compound according to formula L and various crystal forms of the compound of formula L, or the pharmaceutically acceptable salts, hydrate or solvates thereof.

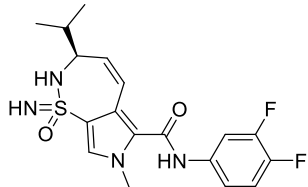
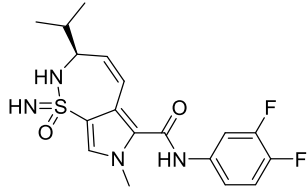
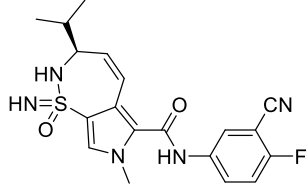
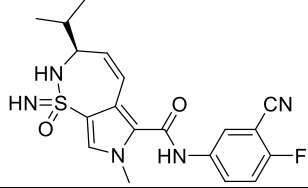
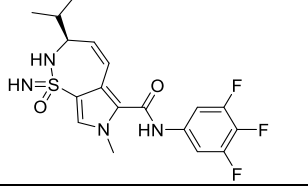
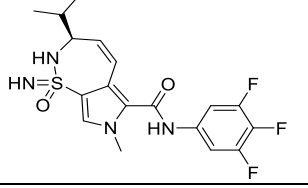
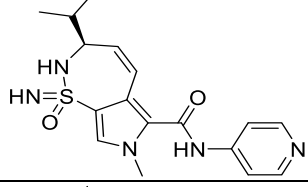
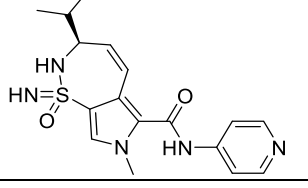


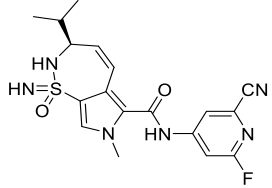
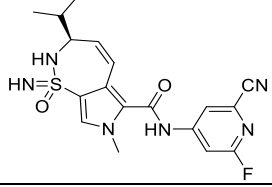
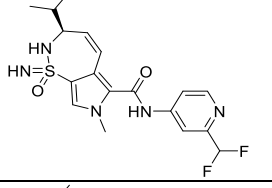
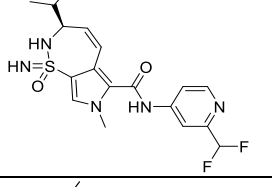
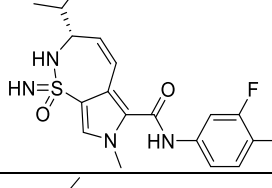
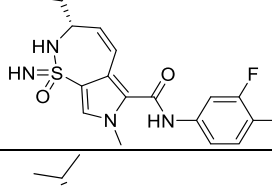
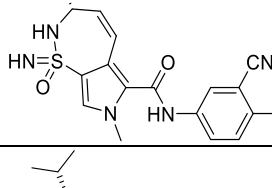
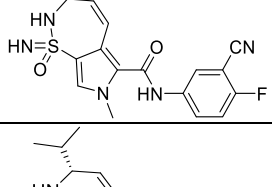
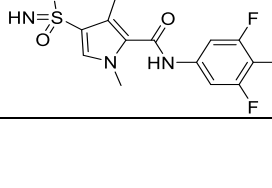
As used herein, the "pharmaceutically acceptable salts" refers to salts suitable for use in pharmaceutical which is formed by a compound of the present invention with an acid or base. The pharmaceutically acceptable salts include inorganic and organic salts. Preferred type of salts are salts formed by the compounds of the present invention and acid. Suitable salt-forming acids include, but are not limited to: inorganic acids such as hydrochloric acid, hydro bromic acid, hydrofluoric acid, sulfuric acid, nitric acid, phosphoric acid and the like; organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, picric acid, methane sulfonic acid, toluene sulfonic acid, benzene sulfonic acid and the like; and acidic amino acids such as aspartic acid, glutamic acid.

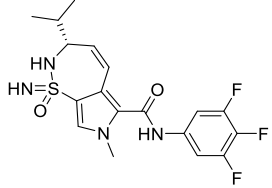
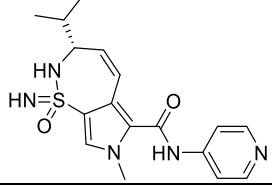
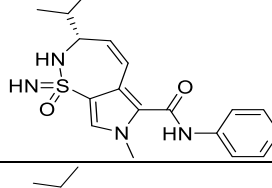
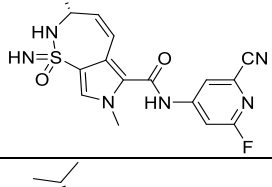
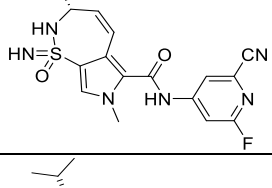
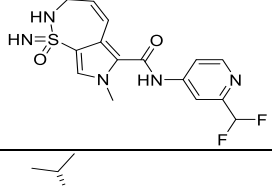
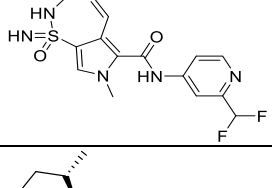
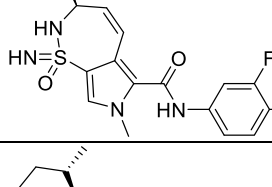
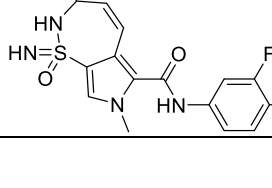
In another preferred embodiment, said ring A, ring B, R1, R2, R3, R4, R₅ and R₆ are each independently the corresponding group of each compound in Table 1.

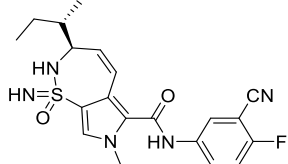
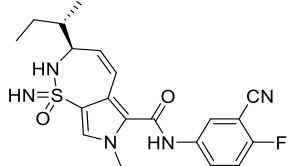
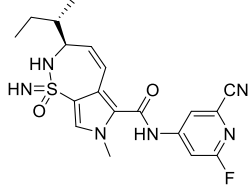
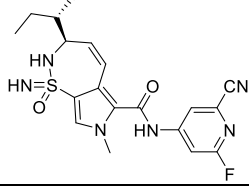
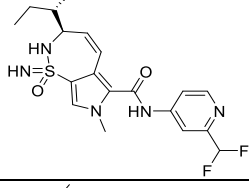
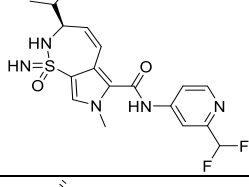
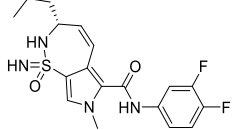
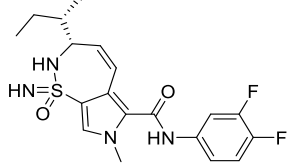
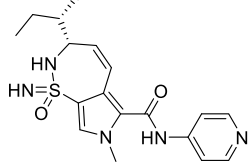
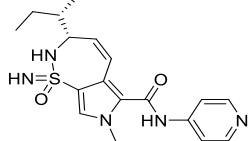
A preferred type of compounds thereof is as presented in table 1.

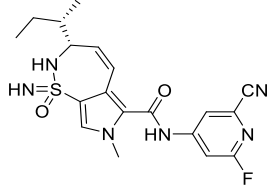
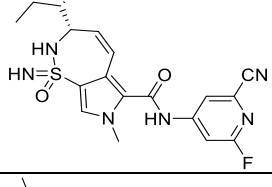
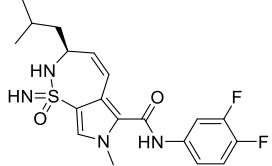
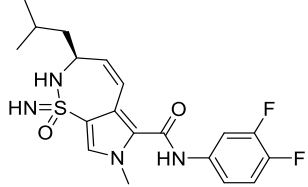
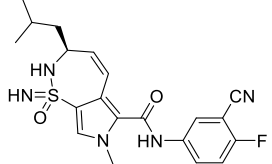
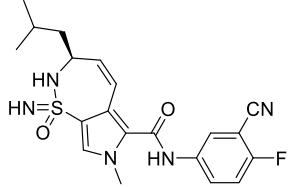
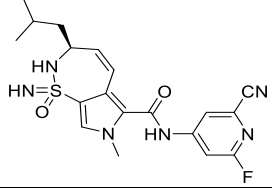
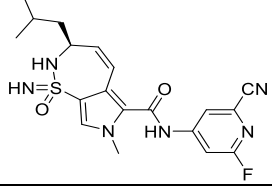
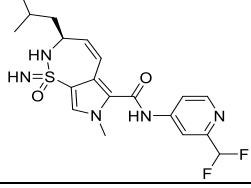
Table 1

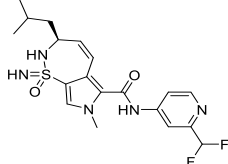
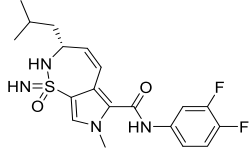
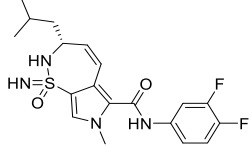
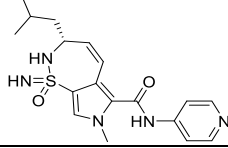
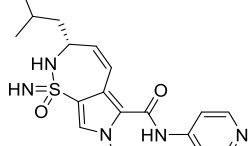
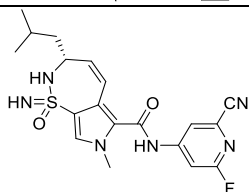
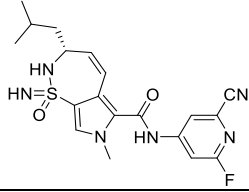
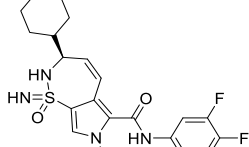
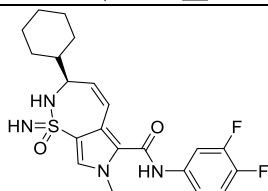
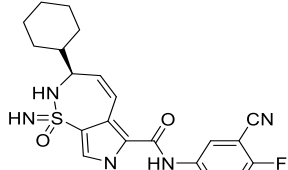
No.	Structure	ESI-MS, (M+H)	Remark
10a1		395	Peak1 (HPLC)
10a2		395	Peak2 (HPLC)
10b1		402	Peak1 (HPLC)
10b2		402	Peak2 (HPLC)
10c1		413	Peak1 (HPLC)
10c2		413	Peak2 (HPLC)
10d1		360	Peak1 (HPLC)
10d2		360	Peak2 (HPLC)

10e1		403	Peak1 (HPLC)
10e2		403	Peak2 (HPLC)
10f1		410	Peak1 (HPLC)
10f2		410	Peak2 (HPLC)
10g1		395	Peak1 (HPLC)
10g2		395	Peak2 (HPLC)
10h1		402	Peak1 (HPLC)
10h2		402	Peak2 (HPLC)
10i1		413	Peak1 (HPLC)

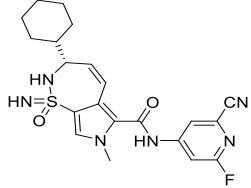
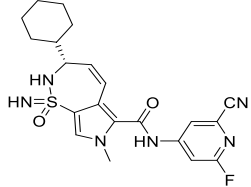
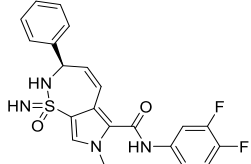
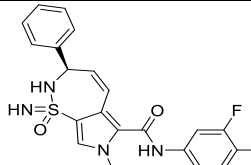
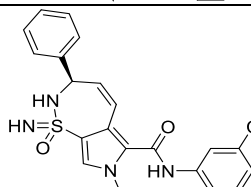
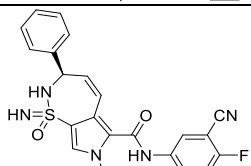
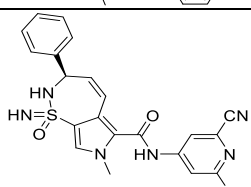
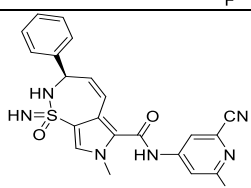
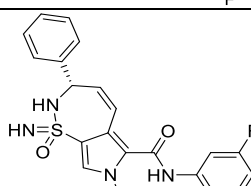
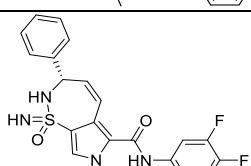
10i2		413	Peak2 (HPLC)
10j1		360	Peak1 (HPLC)
10j2		360	Peak2 (HPLC)
10k1		403	Peak1 (HPLC)
10k2		403	Peak2 (HPLC)
10m1		410	Peak1 (HPLC)
10m2		410	Peak2 (HPLC)
10n1		409	Peak1 (HPLC)
10n2		409	Peak2 (HPLC)

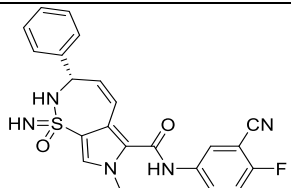
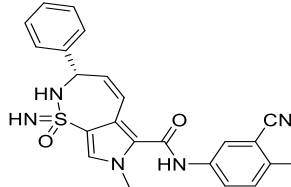
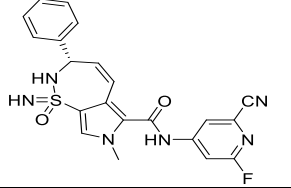
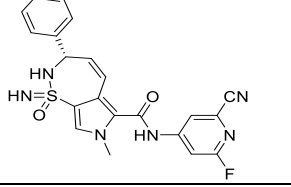
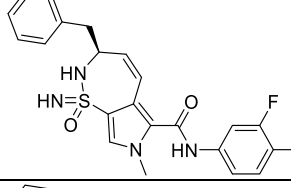
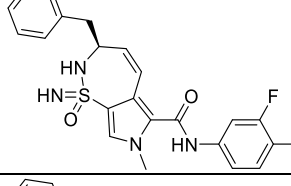
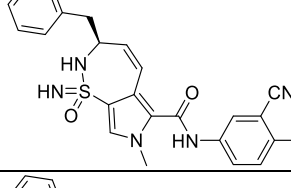
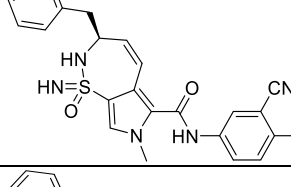
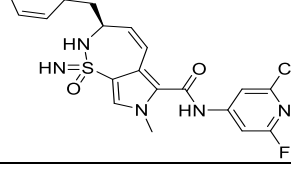
10o1		416	Peak1 (HPLC)
10o2		416	Peak2 (HPLC)
10p1		417	Peak1 (HPLC)
10p2		417	Peak2 (HPLC)
10q1		424	Peak1 (HPLC)
10q2		424	Peak2 (HPLC)
10r1		409	Peak1 (HPLC)
10r2		409	Peak2 (HPLC)
10s1		374	Peak1 (HPLC)
10s2		374	Peak2 (HPLC)

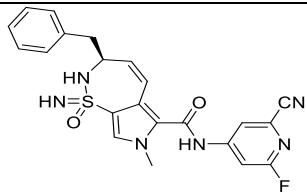
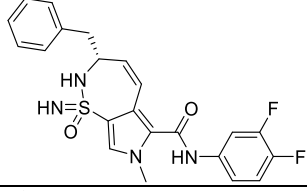
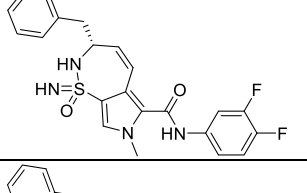
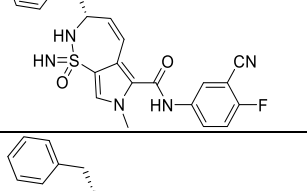
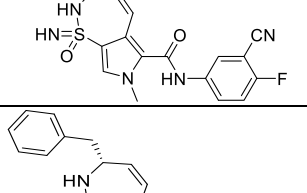
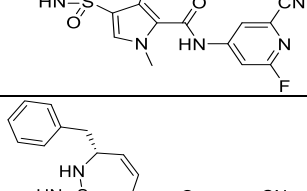
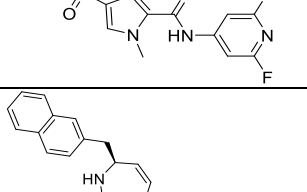
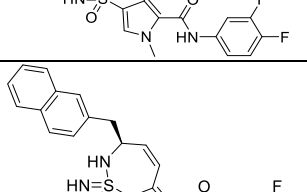
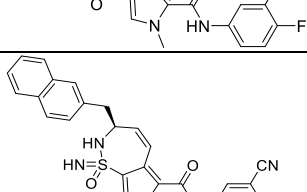
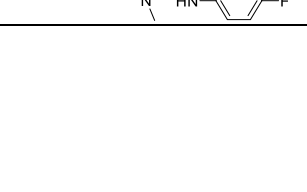
10t1		417	Peak1 (HPLC)
10t2		417	Peak2 (HPLC)
10u1		409	Peak1 (HPLC)
10u2		409	Peak2 (HPLC)
10v1		416	Peak1 (HPLC)
10v2		416	Peak2 (HPLC)
10w1		417	Peak1 (HPLC)
10w2		417	Peak2 (HPLC)
10x1		424	Peak1 (HPLC)

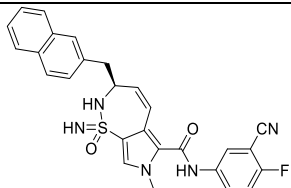
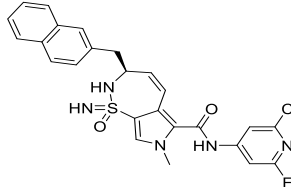
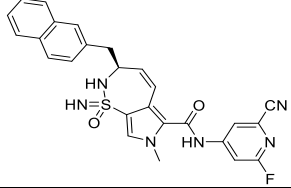
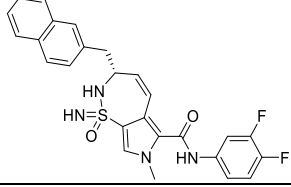
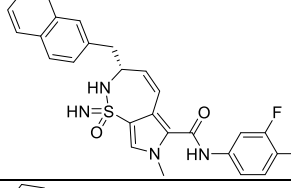
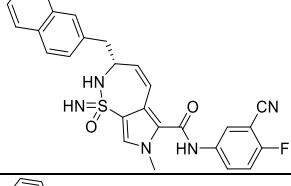
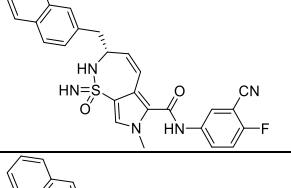
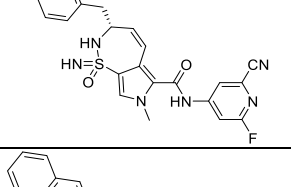
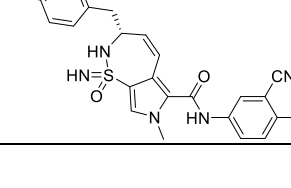
10x2		424	Peak2 (HPLC)
10y1		409	Peak1 (HPLC)
10y2		409	Peak2 (HPLC)
10z1		374	Peak1 (HPLC)
10z2		374	Peak2 (HPLC)
10aa1		417	Peak1 (HPLC)
10aa2		417	Peak2 (HPLC)
10bb1		435	Peak1 (HPLC)
10bb2		435	Peak2 (HPLC)
10cc1		442	Peak1 (HPLC)

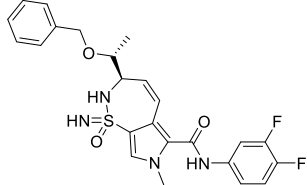
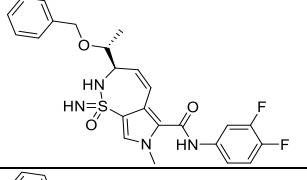
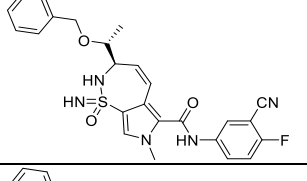
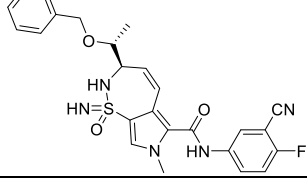
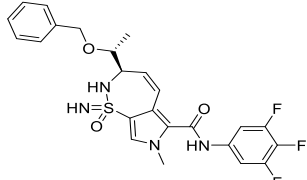
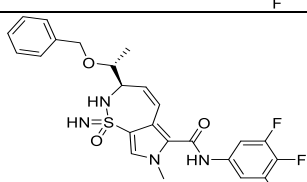
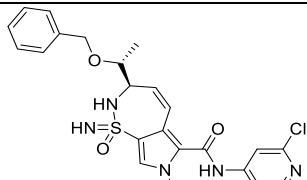
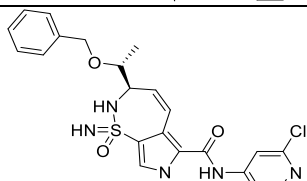
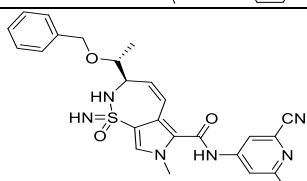
10cc2		442	Peak2 (HPLC)
10dd1		443	Peak1 (HPLC)
10dd2		443	Peak2 (HPLC)
10ee1		450	Peak1 (HPLC)
10ee2		450	Peak2 (HPLC)
10ff1		435	Peak1 (HPLC)
10ff2		435	Peak2 (HPLC)
10gg1		400	Peak1 (HPLC)
10gg2		400	Peak2 (HPLC)

10hh1		443	Peak1 (HPLC)
10hh2		443	Peak2 (HPLC)
10ii1		429	Peak1 (HPLC)
10ii2		429	Peak2 (HPLC)
10jj1		436	Peak1 (HPLC)
10jj2		436	Peak2 (HPLC)
10kk1		437	Peak1 (HPLC)
10kk2		437	Peak2 (HPLC)
10mm1		429	Peak1 (HPLC)
10mm2		429	Peak2 (HPLC)

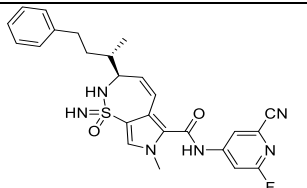
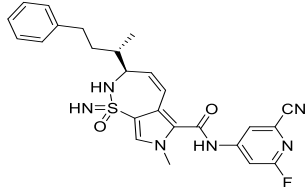
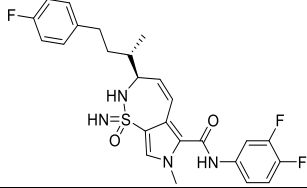
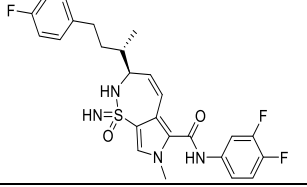
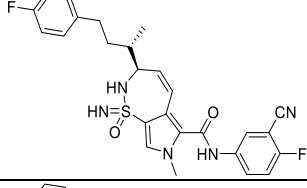
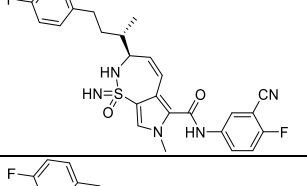
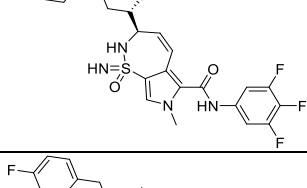
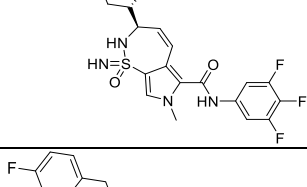
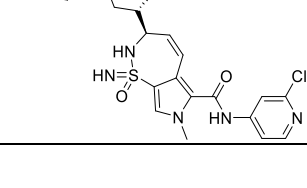
10nn1		436	Peak1 (HPLC)
10nn2		436	Peak2 (HPLC)
10oo1		437	Peak1 (HPLC)
10oo2		437	Peak2 (HPLC)
10pp1		443	Peak1 (HPLC)
10pp2		443	Peak2 (HPLC)
10qq1		450	Peak1 (HPLC)
10qq2		450	Peak2 (HPLC)
10rr1		451	Peak1 (HPLC)

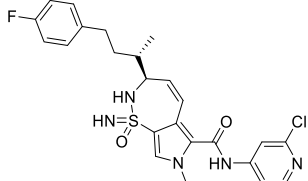
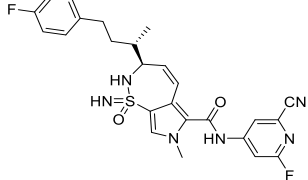
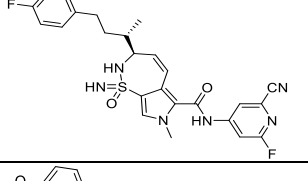
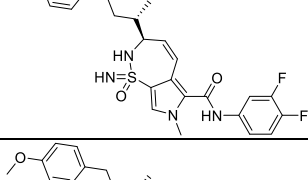
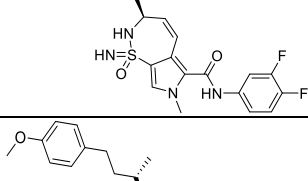
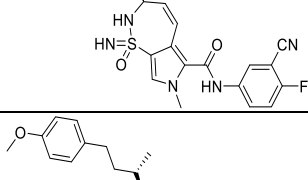
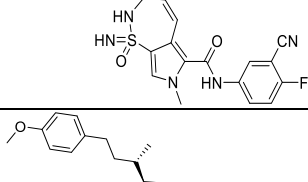
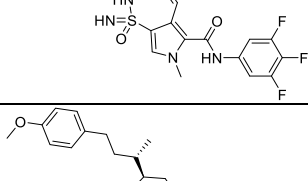
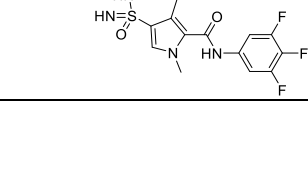
10rr2		451	Peak2 (HPLC)
10ss1		443	Peak1 (HPLC)
10ss2		443	Peak2 (HPLC)
10tt1		450	Peak1 (HPLC)
10tt2		450	Peak2 (HPLC)
10uu1		451	Peak1 (HPLC)
10uu2		451	Peak2 (HPLC)
10vv1		493	Peak1 (HPLC)
10vv2		493	Peak2 (HPLC)
10ww1		500	Peak1 (HPLC)

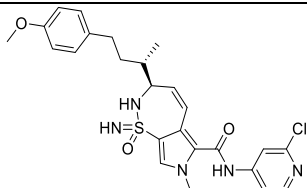
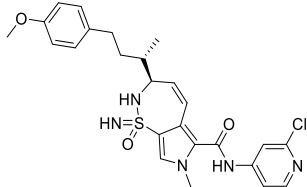
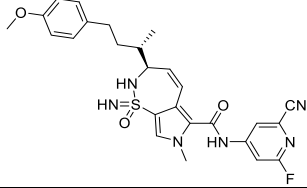
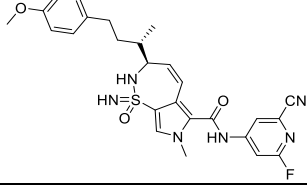
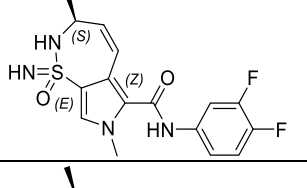
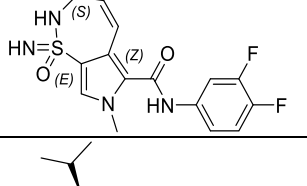
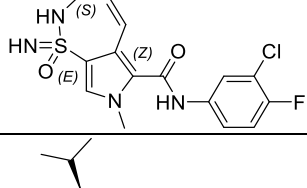
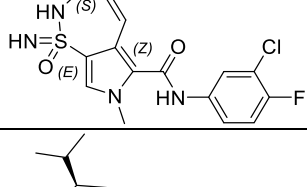
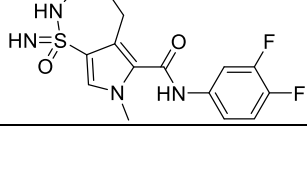
10ww2		500	Peak2 (HPLC)
10xx1		501	Peak1 (HPLC)
10xx2		501	Peak2 (HPLC)
10yy1		493	Peak1 (HPLC)
10yy2		493	Peak2 (HPLC)
10zz1		500	Peak1 (HPLC)
10zz2		500	Peak2 (HPLC)
10aaa1		501	Peak1 (HPLC)
10aaa2		501	Peak2 (HPLC)

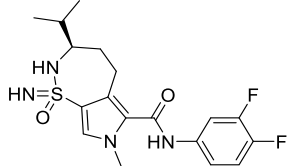
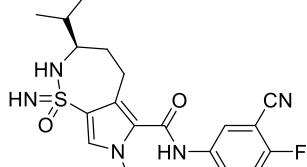
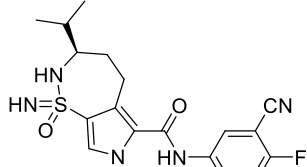
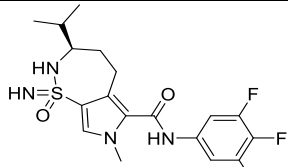
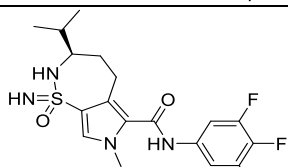
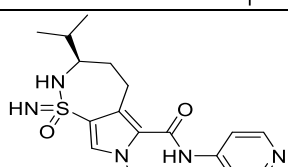
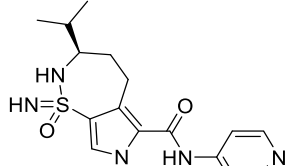
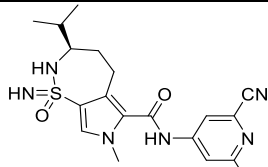
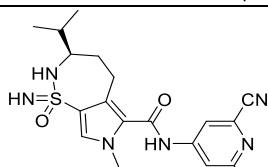
10bbb1		487	Peak1 (HPLC)
10bbb2		487	Peak2 (HPLC)
10ccc1		494	Peak1 (HPLC)
10ccc2		494	Peak2 (HPLC)
10ddd1		505	Peak1 (HPLC)
10ddd2		505	Peak2 (HPLC)
10eee1		486	Peak1 (HPLC)
10eee2		486	Peak2 (HPLC)
10fff1		495	Peak1 (HPLC)

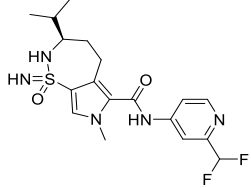
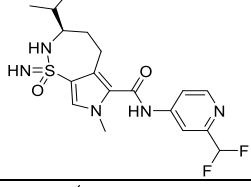
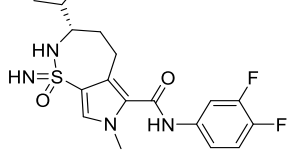
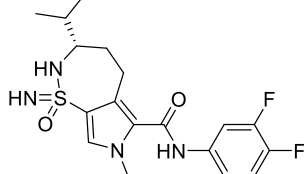
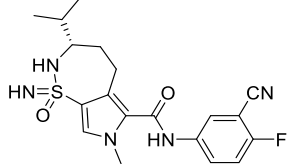
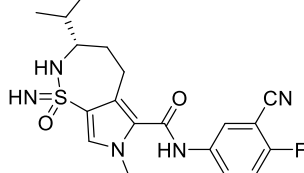
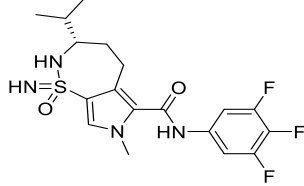
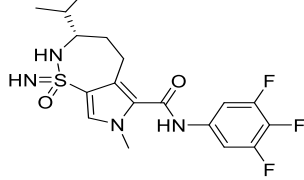
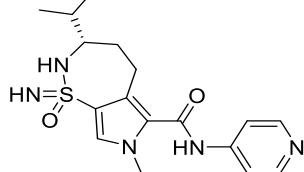
10fff2		495	Peak2 (HPLC)
10ggg1		485	Peak1 (HPLC)
10ggg2		485	Peak2 (HPLC)
10hhh1		492	Peak1 (HPLC)
10hhh2		492	Peak2 (HPLC)
10iii1		503	Peak1 (HPLC)
10iii2		503	Peak2 (HPLC)
10jjj1		484	Peak1 (HPLC)
10jjj2		484	Peak2 (HPLC)

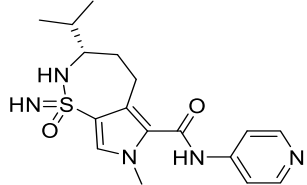
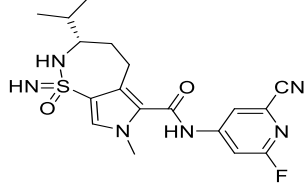
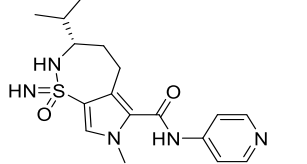
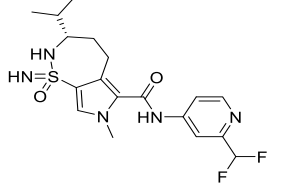
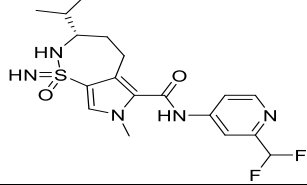
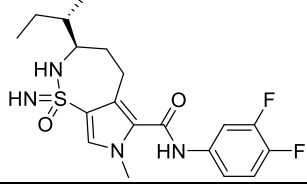
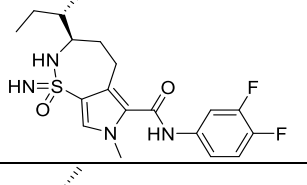
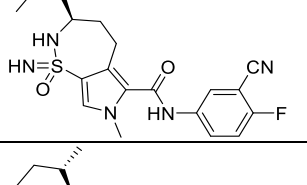
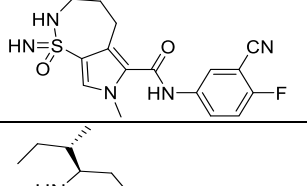
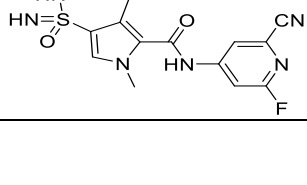
10kkk1		493	Peak1 (HPLC)
10kkk2		493	Peak2 (HPLC)
10mmm1		503	Peak1 (HPLC)
10mmm2		503	Peak2 (HPLC)
10nnn1		510	Peak1 (HPLC)
10nnn2		510	Peak2 (HPLC)
10ooo1		521	Peak1 (HPLC)
10ooo2		521	Peak2 (HPLC)
10ppp1		502	Peak1 (HPLC)

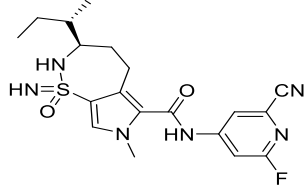
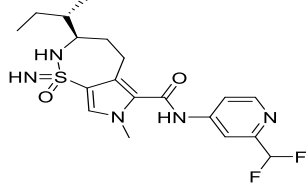
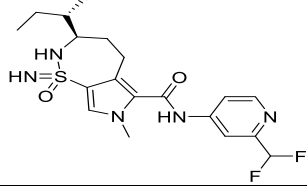
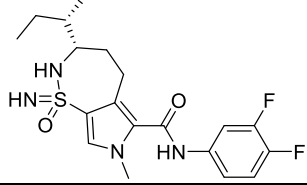
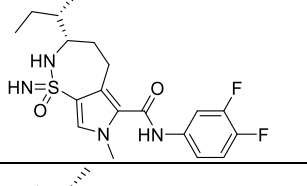
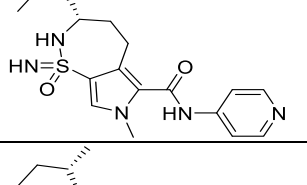
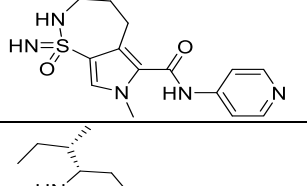
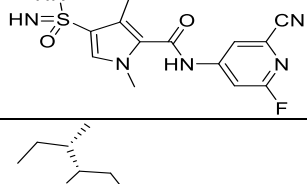
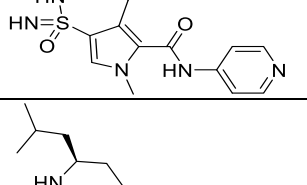
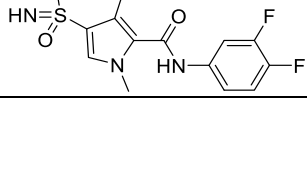
10ppp2		502	Peak2 (HPLC)
10qqq1		511	Peak1 (HPLC)
10qqq2		511	Peak2 (HPLC)
10rrr1		515	Peak1 (HPLC)
10rrr2		515	Peak2 (HPLC)
10sss1		522	Peak1 (HPLC)
10sss2		522	Peak2 (HPLC)
10ttt1		533	Peak1 (HPLC)
10ttt2		533	Peak2 (HPLC)

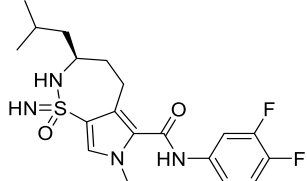
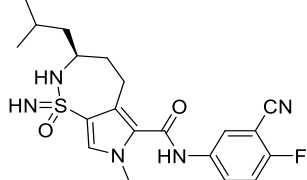
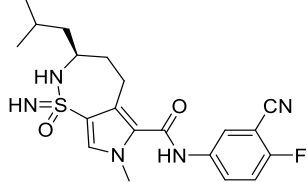
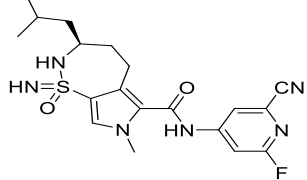
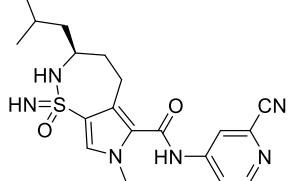
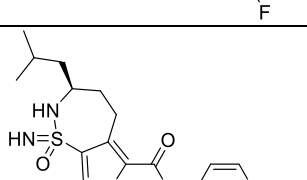
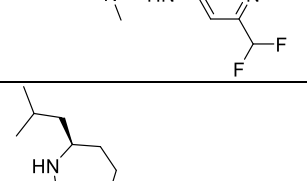
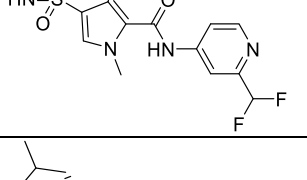
10uuu1		514	Peak1 (HPLC)
10uuu2		514	Peak2 (HPLC)
10vvv1		523	Peak1 (HPLC)
10vvv2		523	Peak2 (HPLC)
10www1		367	Peak1 (HPLC)
10www2		367	Peak2 (HPLC)
10xxx1		411	Peak1 (HPLC)
10xxx2		411	Peak2 (HPLC)
20a1		397	Peak1 (HPLC)

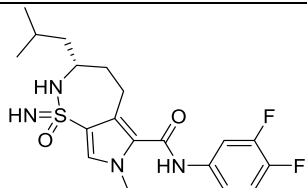
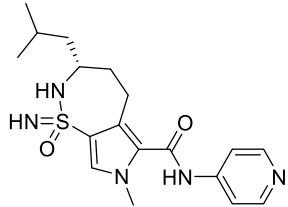
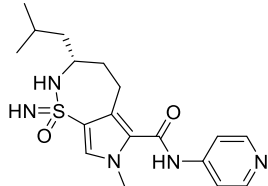
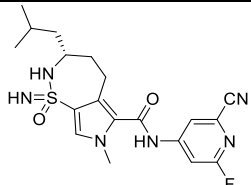
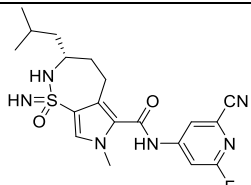
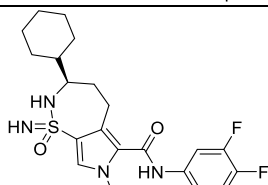
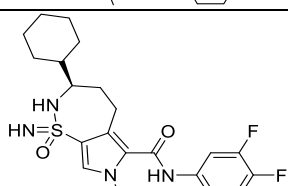
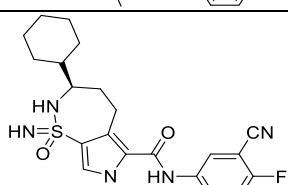
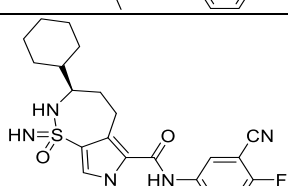
20a2		397	Peak2 (HPLC)
20b1		404	Peak1 (HPLC)
20b2		404	Peak2 (HPLC)
20c1		415	Peak1 (HPLC)
20c2		415	Peak2 (HPLC)
20d1		362	Peak1 (HPLC)
20d2		362	Peak2 (HPLC)
20e1		405	Peak1 (HPLC)
20e2		405	Peak2 (HPLC)

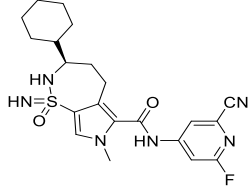
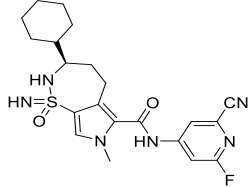
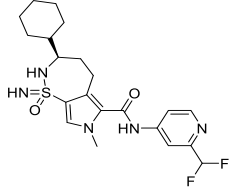
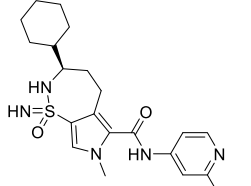
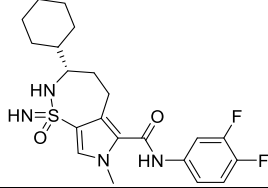
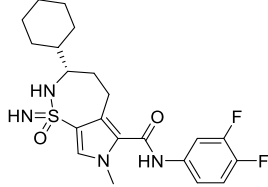
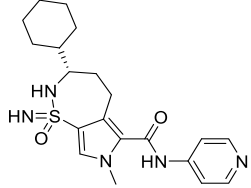
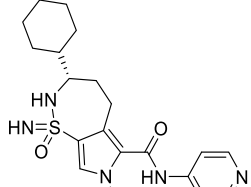
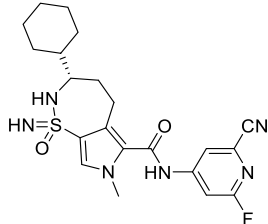
20f1		412	Peak1 (HPLC)
20f2		412	Peak2 (HPLC)
20g1		397	Peak1 (HPLC)
20g2		397	Peak2 (HPLC)
20h1		404	Peak1 (HPLC)
20h2		404	Peak2 (HPLC)
20i1		415	Peak1 (HPLC)
20i2		415	Peak2 (HPLC)
20j1		362	Peak1 (HPLC)

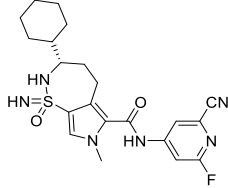
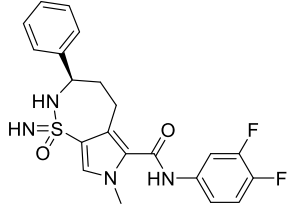
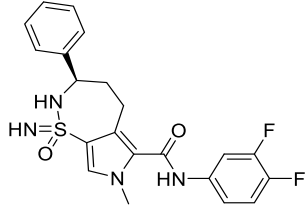
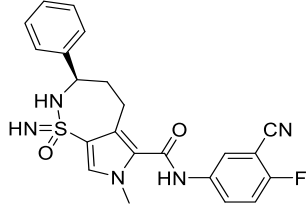
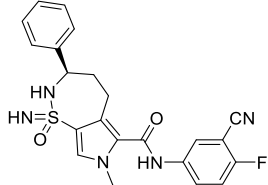
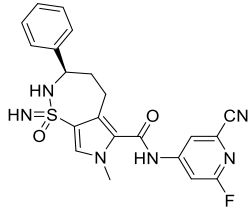
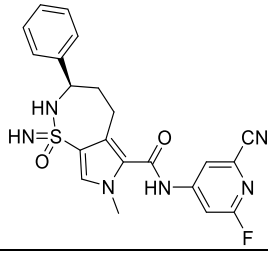
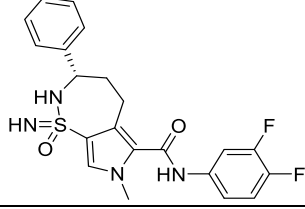
20j2		362	Peak2 (HPLC)
20k1		405	Peak1 (HPLC)
20k2		405	Peak2 (HPLC)
20m1		412	Peak1 (HPLC)
10m2		412	Peak2 (HPLC)
20n1		411	Peak1 (HPLC)
20n2		411	Peak2 (HPLC)
20o1		418	Peak1 (HPLC)
20o2		418	Peak2 (HPLC)
20p1		419	Peak1 (HPLC)

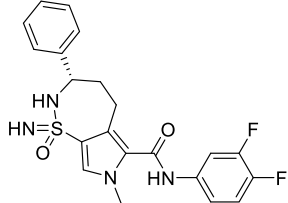
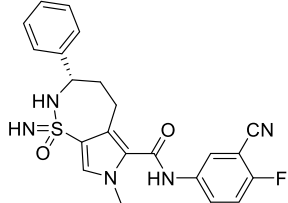
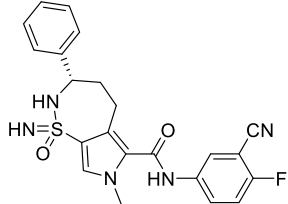
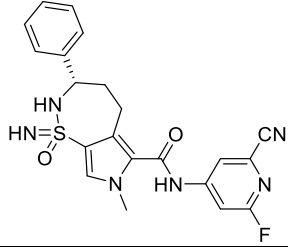
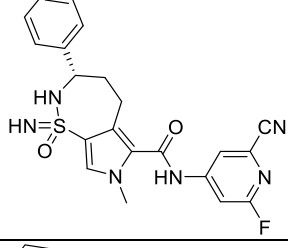
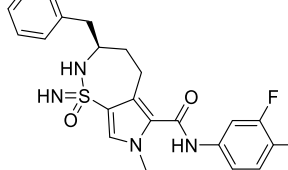
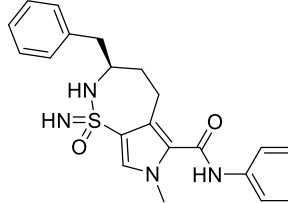
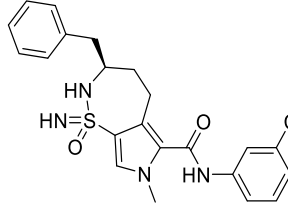
20p2		419	Peak2 (HPLC)
20q1		426	Peak1 (HPLC)
20q2		426	Peak2 (HPLC)
20r1		411	Peak1 (HPLC)
20r2		411	Peak2 (HPLC)
20s1		376	Peak1 (HPLC)
20s2		376	Peak2 (HPLC)
20t1		419	Peak1 (HPLC)
20t2		419	Peak2 (HPLC)
20u1		411	Peak1 (HPLC)

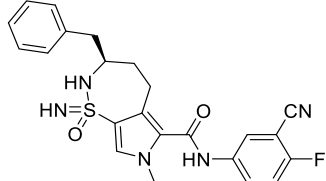
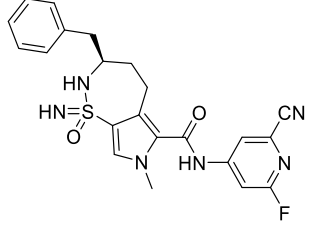
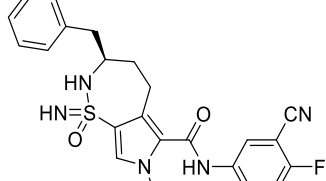
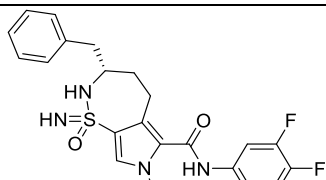
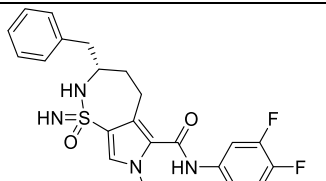
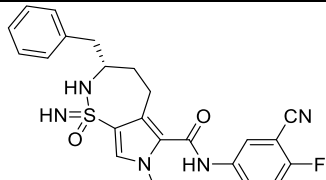
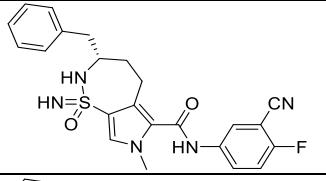
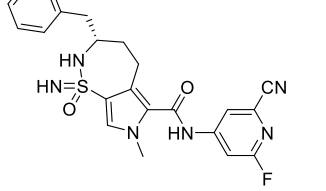
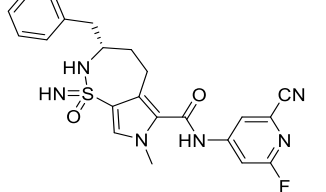
20u2		411	Peak2 (HPLC)
20v1		418	Peak1 (HPLC)
20v2		418	Peak2 (HPLC)
20w1		419	Peak1 (HPLC)
20w2		419	Peak2 (HPLC)
20x1		426	Peak1 (HPLC)
20x2		426	Peak2 (HPLC)
20y1		411	Peak1 (HPLC)

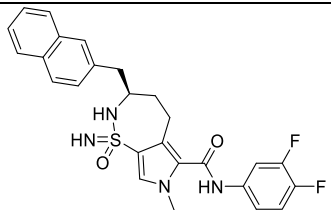
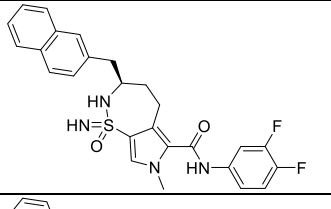
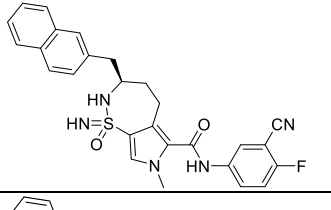
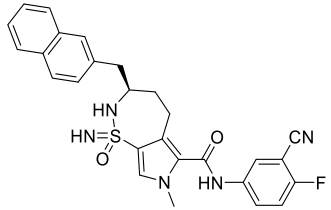
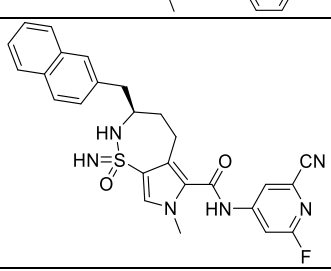
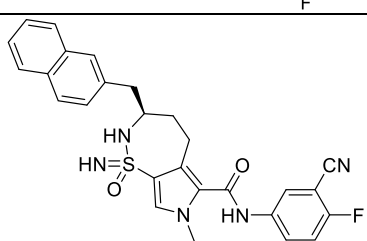
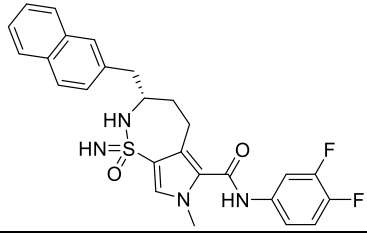
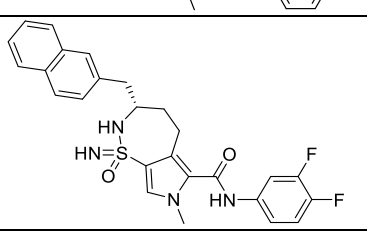
20y2		411	Peak2 (HPLC)
20z1		376	Peak1 (HPLC)
20z2		376	Peak2 (HPLC)
20aa1		419	Peak1 (HPLC)
20aa2		419	Peak2 (HPLC)
20bb1		437	Peak1 (HPLC)
20bb2		437	Peak2 (HPLC)
20cc1		444	Peak1 (HPLC)
20cc2		444	Peak2 (HPLC)

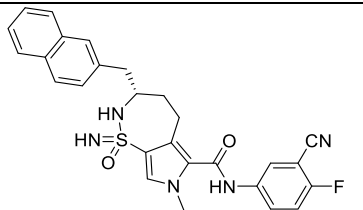
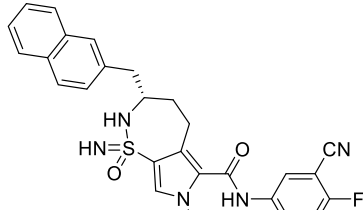
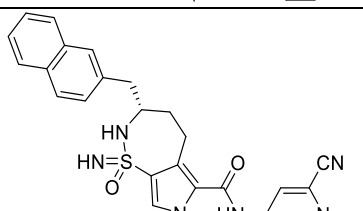
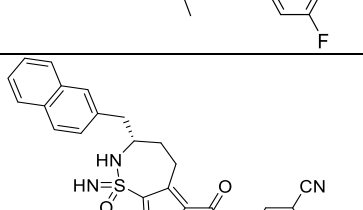
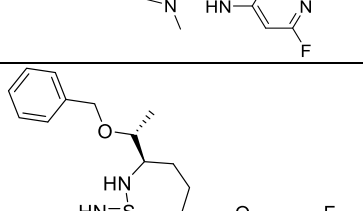
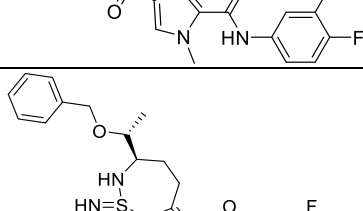
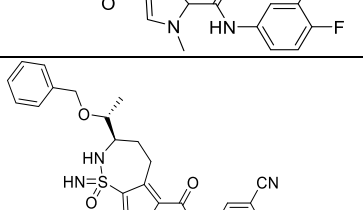
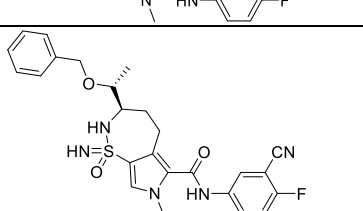
20dd1		445	Peak1 (HPLC)
20dd2		445	Peak2 (HPLC)
20ee1		452	Peak1 (HPLC)
20ee2		452	Peak2 (HPLC)
20ff1		437	Peak1 (HPLC)
20ff2		437	Peak2 (HPLC)
20gg1		402	Peak1 (HPLC)
20gg2		402	Peak2 (HPLC)
20hh1		445	Peak1 (HPLC)

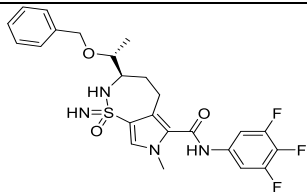
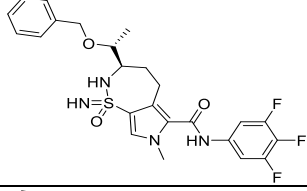
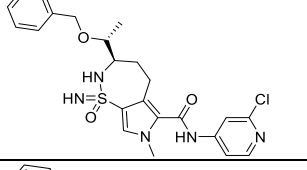
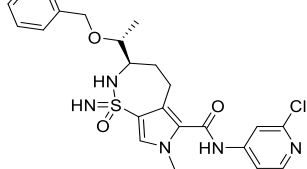
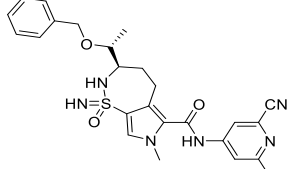
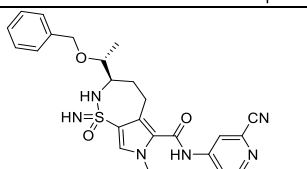
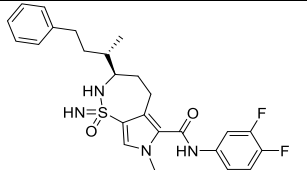
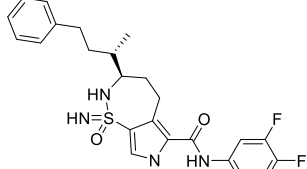
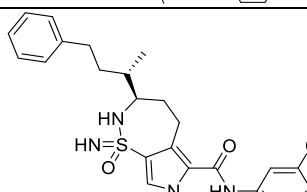
20hh2		445	Peak2 (HPLC)
20ii1		431	Peak1 (HPLC)
20ii2		431	Peak2 (HPLC)
20jj1		438	Peak1 (HPLC)
20jj2		438	Peak2 (HPLC)
20kk1		439	Peak1 (HPLC)
20kk2		439	Peak2 (HPLC)
20mm1		431	Peak1 (HPLC)

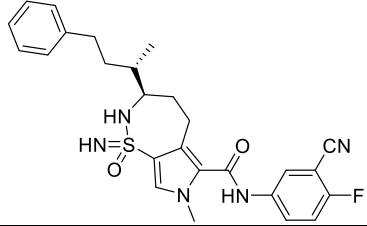
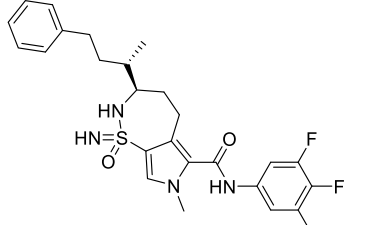
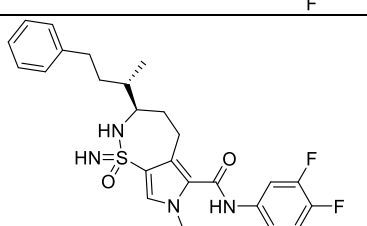
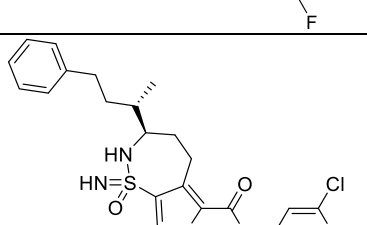
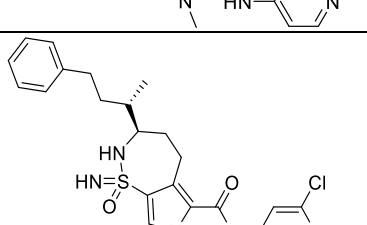
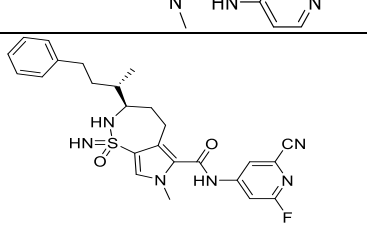
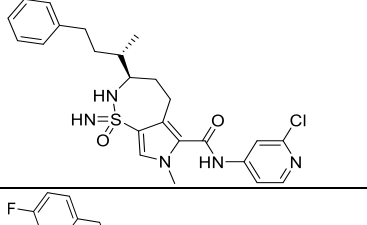
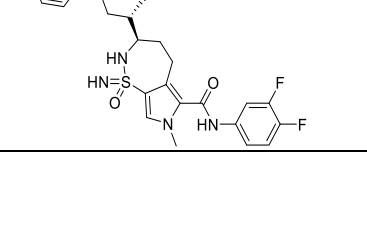
20mm2		431	Peak2 (HPLC)
20nn1		438	Peak1 (HPLC)
20nn2		438	Peak2 (HPLC)
20oo1		439	Peak1 (HPLC)
20oo2		439	Peak2 (HPLC)
20pp1		445	Peak1 (HPLC)
20pp2		445	Peak2 (HPLC)
20qq1		452	Peak1 (HPLC)

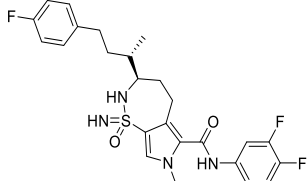
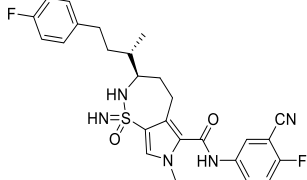
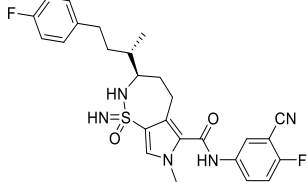
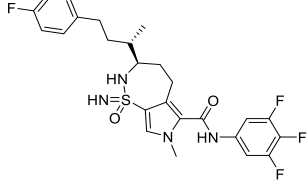
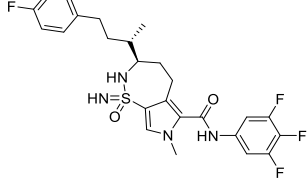
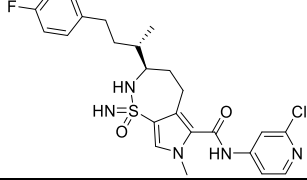
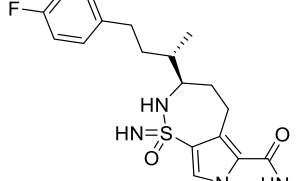
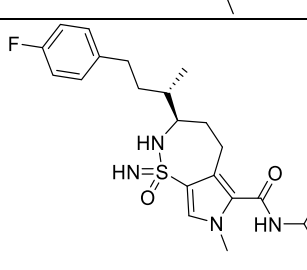
20qq2		452	Peak2 (HPLC)
20rr1		453	Peak1 (HPLC)
20rr2		453	Peak2 (HPLC)
20ss1		445	Peak1 (HPLC)
20ss2		445	Peak2 (HPLC)
20tt1		452	Peak1 (HPLC)
20tt2		452	Peak2 (HPLC)
20uu1		453	Peak1 (HPLC)
20uu2		453	Peak2 (HPLC)

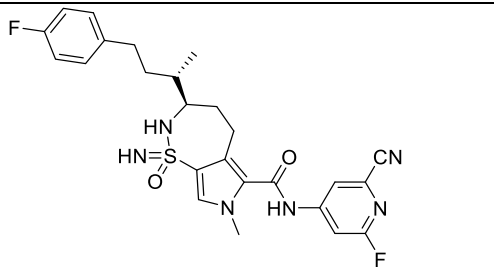
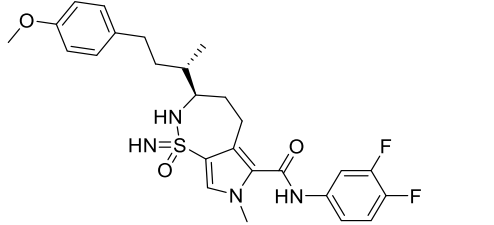
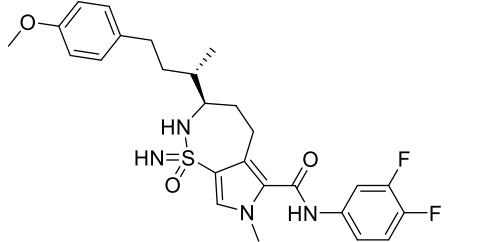
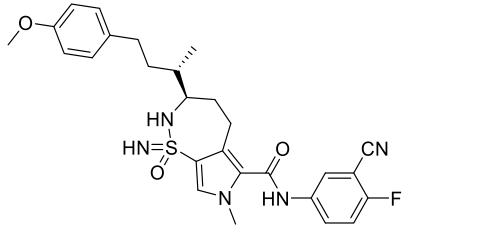
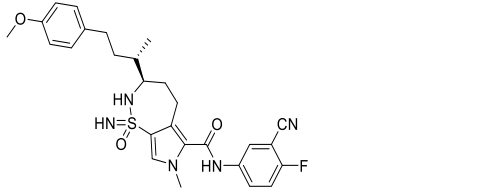
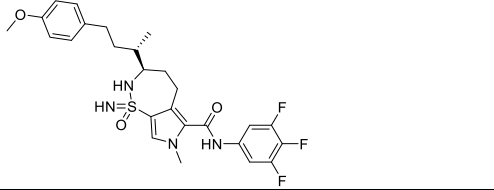
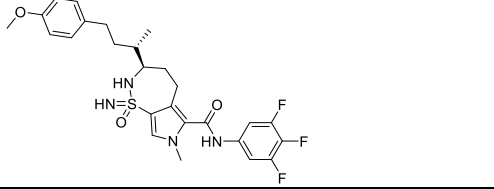
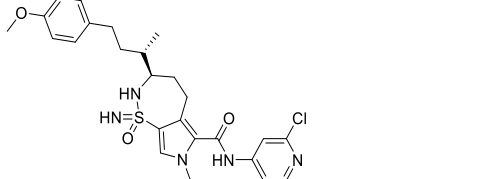
20vv1		495	Peak1 (HPLC)
20vv2		495	Peak2 (HPLC)
20ww1		502	Peak1 (HPLC)
20ww2		502	Peak2 (HPLC)
20xx1		503	Peak1 (HPLC)
20xx2		503	Peak2 (HPLC)
20yy1		495	Peak1 (HPLC)
20yy2		495	Peak2 (HPLC)

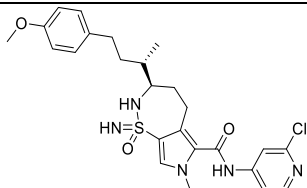
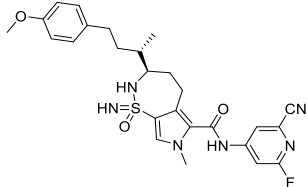
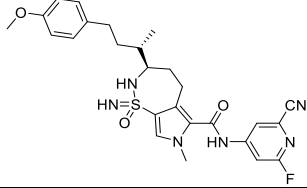
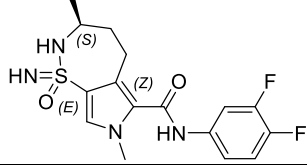
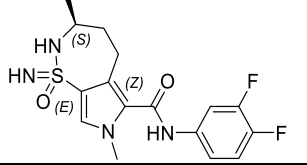
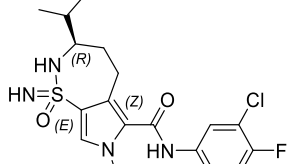
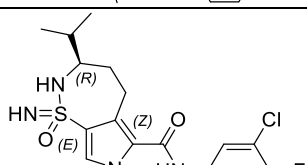
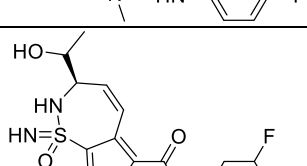
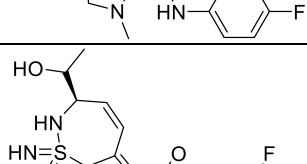
20zz1		502	Peak1 (HPLC)
20zz2		502	Peak2 (HPLC)
20aaa1		503	Peak1 (HPLC)
20aaa2		503	Peak2 (HPLC)
20bbb1		489	Peak1 (HPLC)
20bbb2		489	Peak2 (HPLC)
20ccc1		496	Peak1 (HPLC)
20ccc2		496	Peak2 (HPLC)

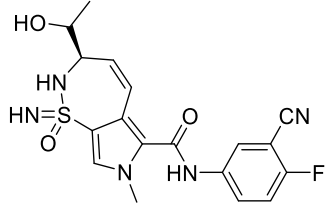
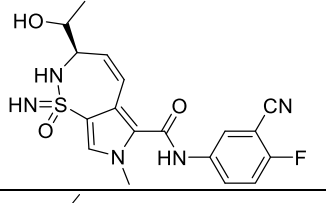
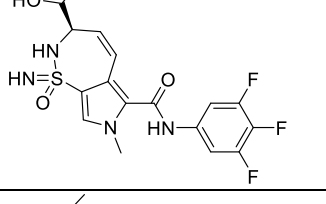
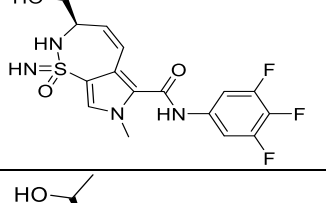
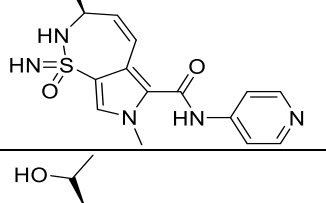
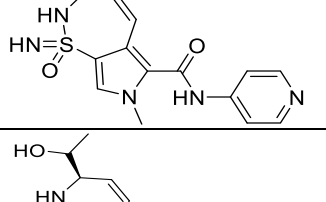
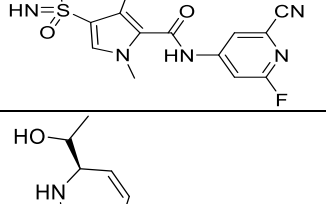
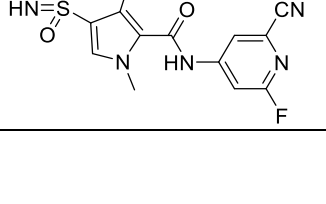
20ddd1		507	Peak1 (HPLC)
20ddd2		507	Peak2 (HPLC)
20eee1		488	Peak1 (HPLC)
20eee2		488	Peak2 (HPLC)
20fff1		497	Peak1 (HPLC)
20fff2		497	Peak2 (HPLC)
20ggg1		486	Peak1 (HPLC)
20ggg2		486	Peak2 (HPLC)
20hhh1		494	Peak1 (HPLC)

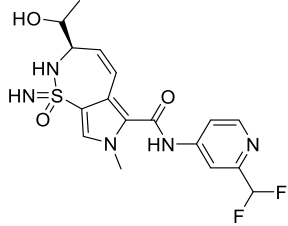
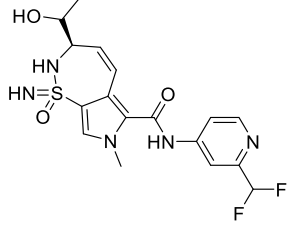
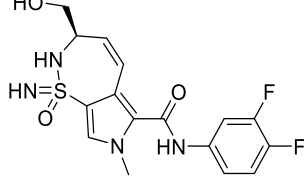
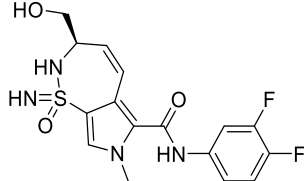
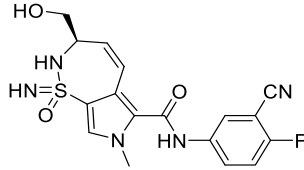
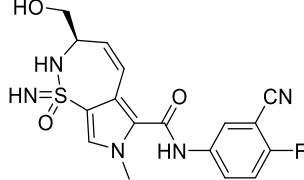
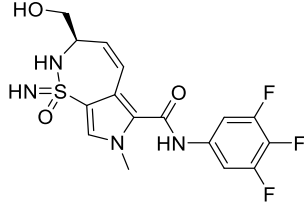
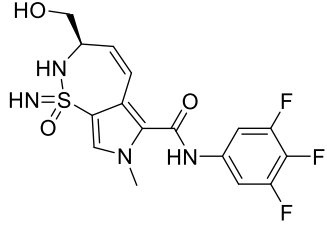
20hhh2		494	Peak2 (HPLC)
20iii1		505	Peak1 (HPLC)
20iii2		505	Peak2 (HPLC)
20jjj1		486	Peak1 (HPLC)
20jjj2		486	Peak2 (HPLC)
20kkk1		495	Peak1 (HPLC)
20kkk2		495	Peak2 (HPLC)
20mmm1		505	Peak1 (HPLC)

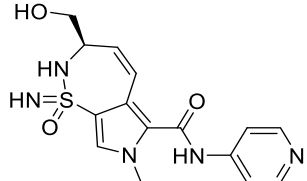
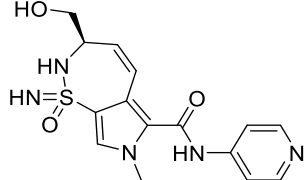
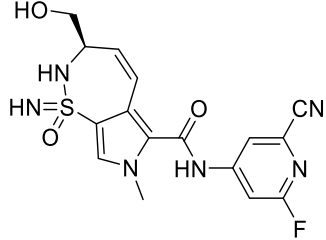
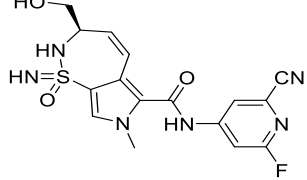
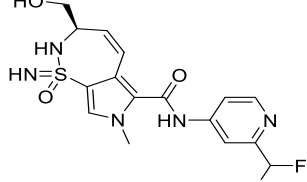
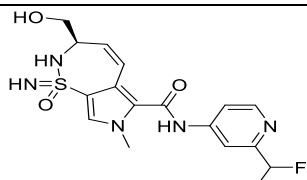
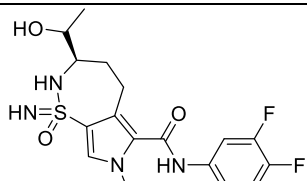
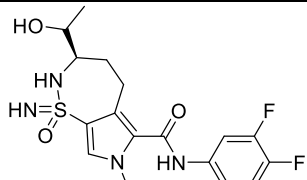
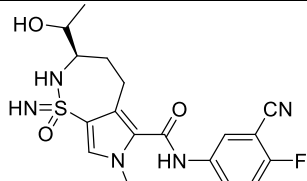
20mmm2		505	Peak2 (HPLC)
20nnn1		512	Peak1 (HPLC)
20nnn2		512	Peak2 (HPLC)
20ooo1		523	Peak1 (HPLC)
20ooo2		523	Peak2 (HPLC)
20ppp1		504	Peak1 (HPLC)
20ppp2		504	Peak2 (HPLC)
20qqq1		513	Peak1 (HPLC)

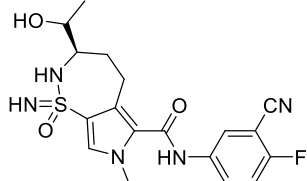
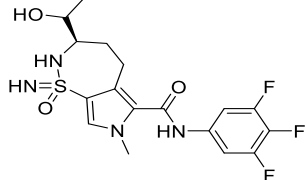
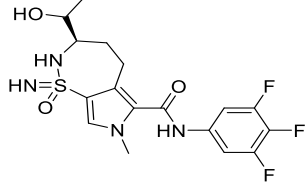
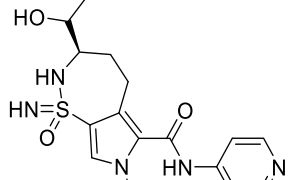
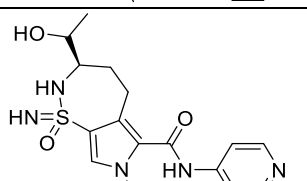
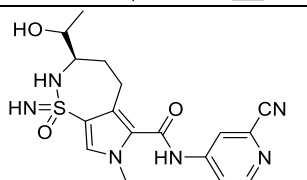
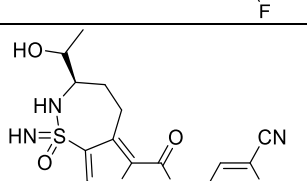
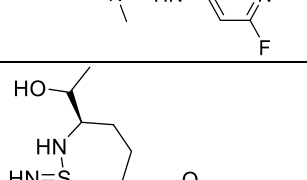
20qqq2		513	Peak2 (HPLC)
20rrr1		517	Peak1 (HPLC)
20rrr2		517	Peak2 (HPLC)
20sss1		524	Peak1 (HPLC)
20sss2		524	Peak2 (HPLC)
20ttt1		535	Peak1 (HPLC)
20ttt2		535	Peak2 (HPLC)
20uuu1		516	Peak1 (HPLC)

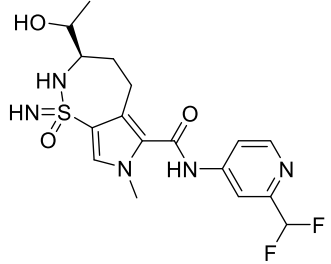
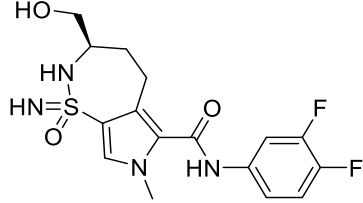
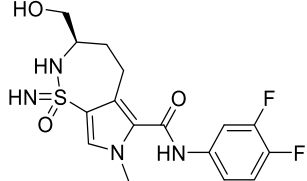
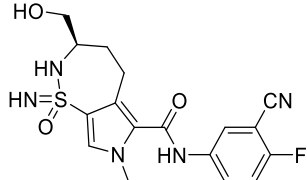
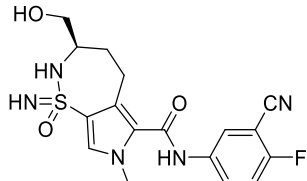
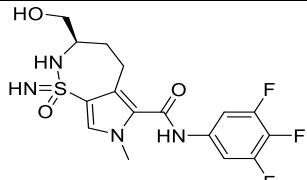
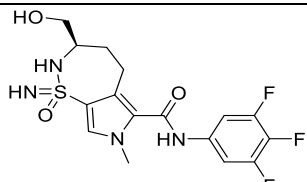
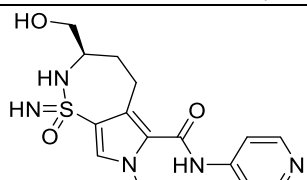
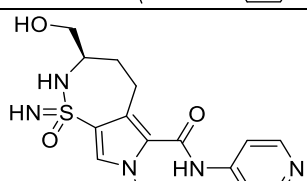
20uuu2		516	Peak2 (HPLC)
20vvv1		525	Peak1 (HPLC)
20vvv2		525	Peak2 (HPLC)
20www1		369	Peak1 (HPLC)
20www2		369	Peak2 (HPLC)
20xxx1		413	Peak1 (HPLC)
20xxx2		413	Peak2 (HPLC)
30a1		397	Peak1 (HPLC)
30a2		397	Peak2 (HPLC)

30b1		404	Peak1 (HPLC)
30b2		404	Peak2 (HPLC)
30c1		415	Peak1 (HPLC)
30c2		415	Peak2 (HPLC)
30d1		362	Peak1 (HPLC)
30d2		362	Peak2 (HPLC)
30e1		405	Peak1 (HPLC)
30e2		405	Peak2 (HPLC)

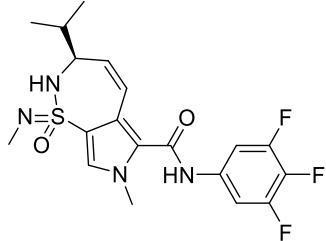
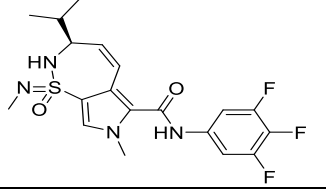
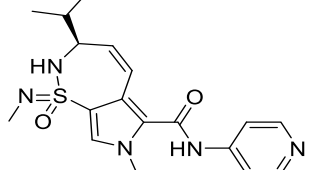
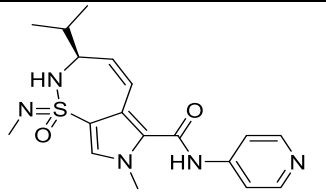
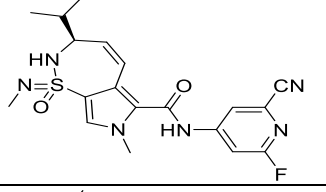
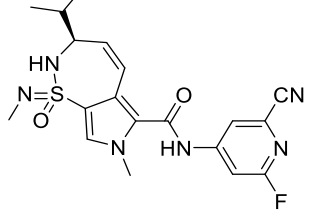
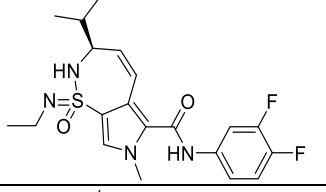
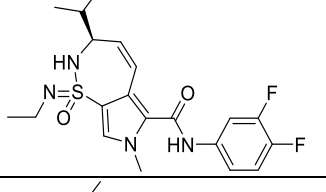
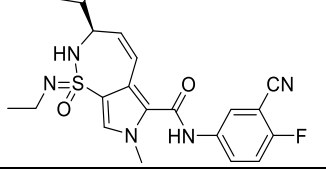
30f1		412	Peak1 (HPLC)
30f2		412	Peak2 (HPLC)
30g1		383	Peak1 (HPLC)
30g2		383	Peak2 (HPLC)
30h1		390	Peak1 (HPLC)
30h2		390	Peak2 (HPLC)
30i1		401	Peak1 (HPLC)
30i2		401	Peak2 (HPLC)

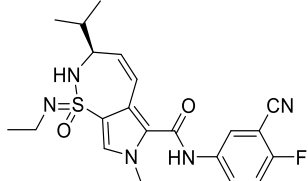
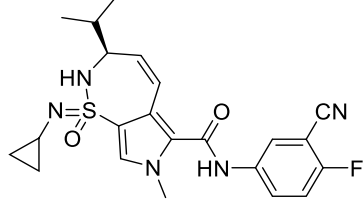
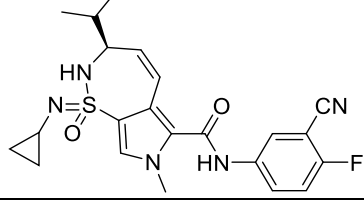
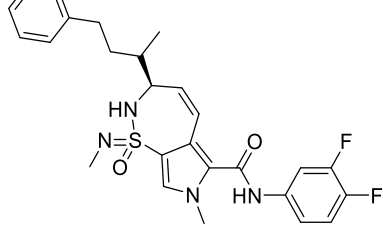
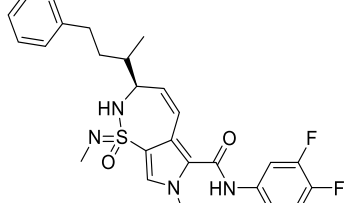
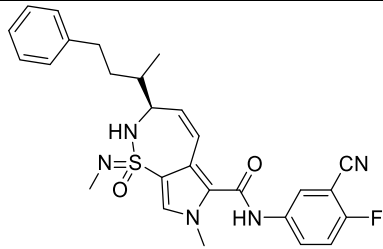
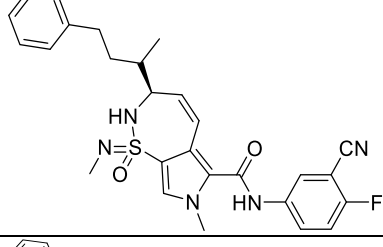
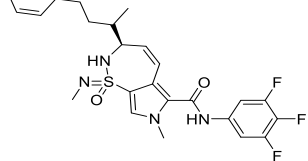
30j1		348	Peak1 (HPLC)
30j2		348	Peak2 (HPLC)
30k1		391	Peak1 (HPLC)
30k2		391	Peak2 (HPLC)
30m1		398	Peak1 (HPLC)
30m2		398	Peak2 (HPLC)
40a1		399	Peak1 (HPLC)
40a2		399	Peak2 (HPLC)
40b1		406	Peak1 (HPLC)

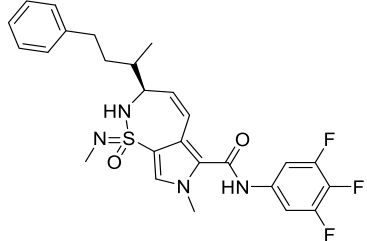
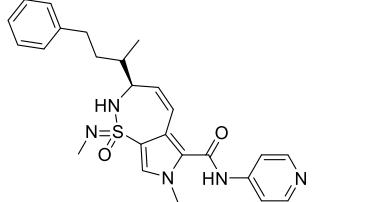
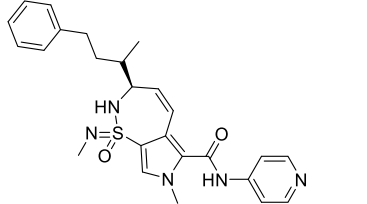
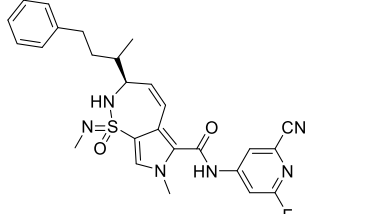
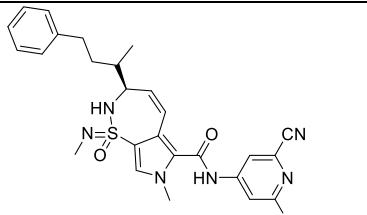
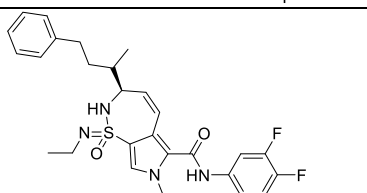
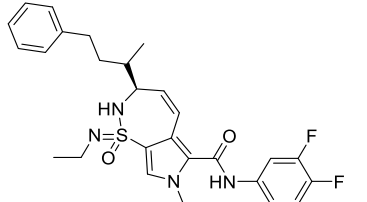
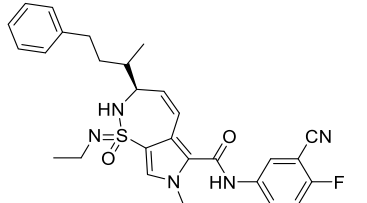
40b2		406	Peak2 (HPLC)
40c1		417	Peak1 (HPLC)
40c2		417	Peak2 (HPLC)
40d1		364	Peak1 (HPLC)
40d2		364	Peak2 (HPLC)
40e1		407	Peak1 (HPLC)
40e2		407	Peak2 (HPLC)
40f1		414	Peak1 (HPLC)

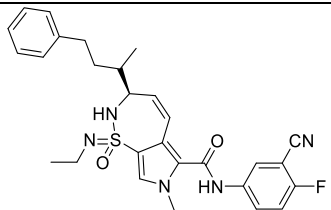
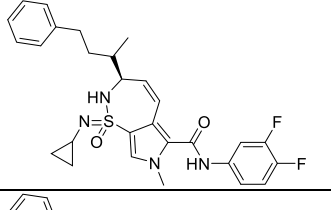
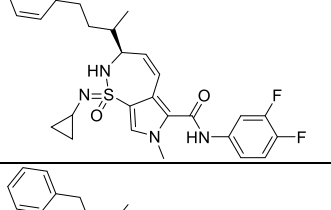
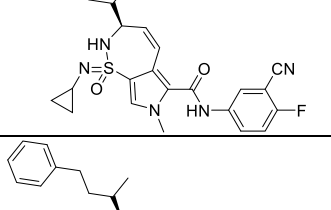
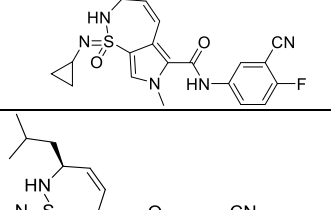
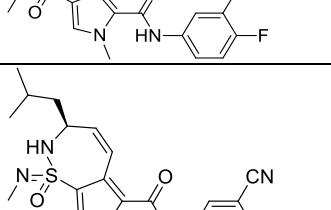
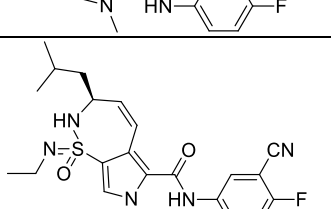
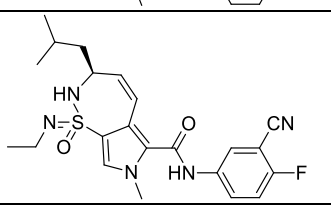
40f2		414	Peak2 (HPLC)
40g1		385	Peak1 (HPLC)
40g2		385	Peak2 (HPLC)
40h1		392	Peak1 (HPLC)
40h2		392	Peak2 (HPLC)
40i1		403	Peak1 (HPLC)
40i2		403	Peak2 (HPLC)
40j1		350	Peak1 (HPLC)
40j2		350	Peak2 (HPLC)

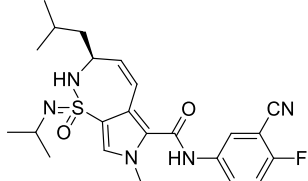
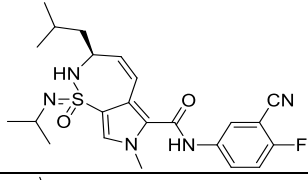
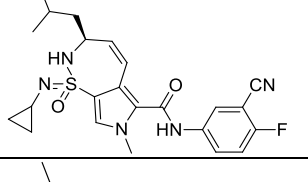
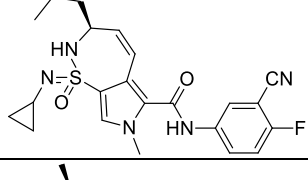
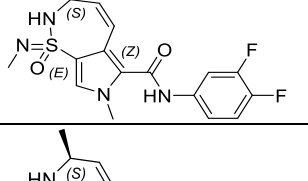
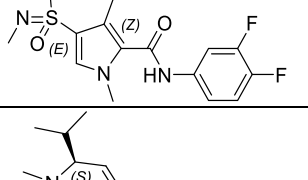
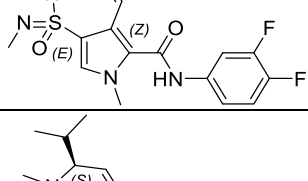
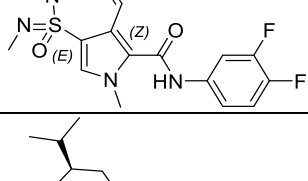
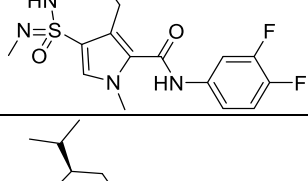
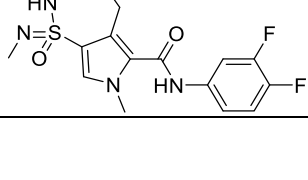
40k1		393	Peak1 (HPLC)
40k2		393	Peak2 (HPLC)
40m1		400	Peak1 (HPLC)
40m2		400	Peak2 (HPLC)
50a1		409	Peak1 (HPLC)
50a2		409	Peak2 (HPLC)
50b1		416	Peak1 (HPLC)
50b2		416	Peak2 (HPLC)

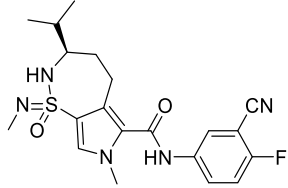
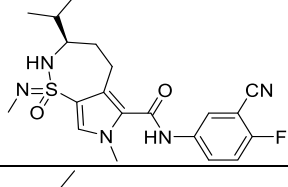
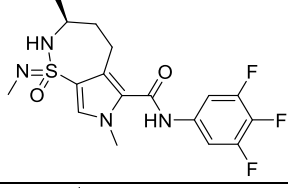
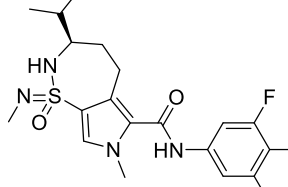
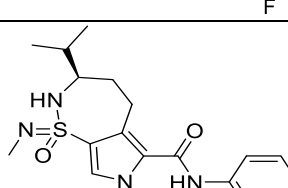
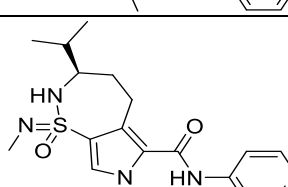
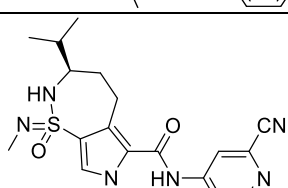
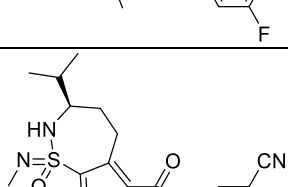
50c1		413	Peak1 (HPLC)
50c2		427	Peak2 (HPLC)
50d1		374	Peak1 (HPLC)
50d2		360	Peak2 (HPLC)
50e1		417	Peak1 (HPLC)
50e2		417	Peak2 (HPLC)
50f1		423	Peak1 (HPLC)
50f2		423	Peak2 (HPLC)
50g1		430	Peak1 (HPLC)

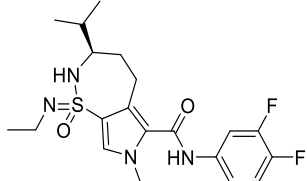
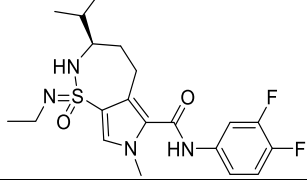
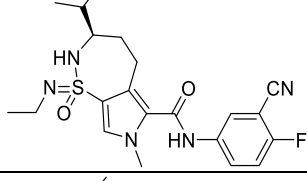
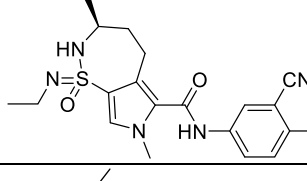
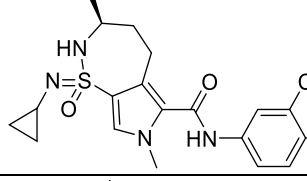
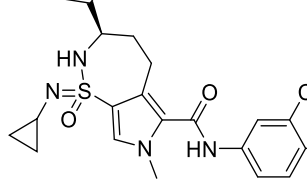
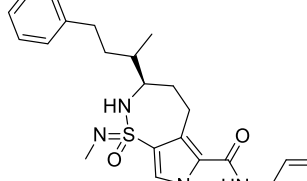
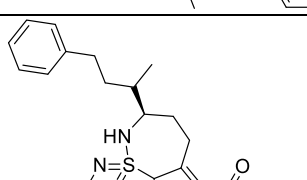
50g2		430	Peak2 (HPLC)
50h1		442	Peak1 (HPLC)
50h2		442	Peak2 (HPLC)
50i1		499	Peak1 (HPLC)
50i2		499	Peak2 (HPLC)
50j1		506	Peak1 (HPLC)
50j2		506	Peak2 (HPLC)
50k1		517	Peak1 (HPLC)

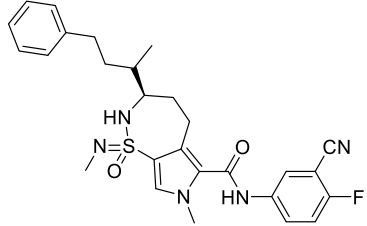
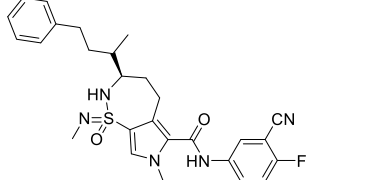
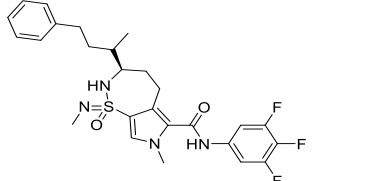
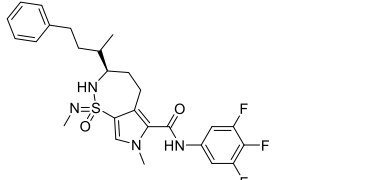
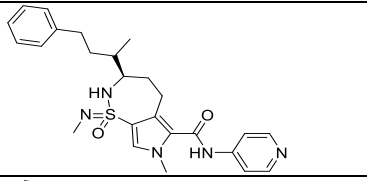
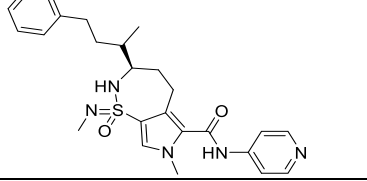
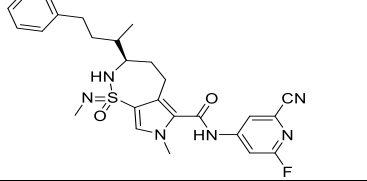
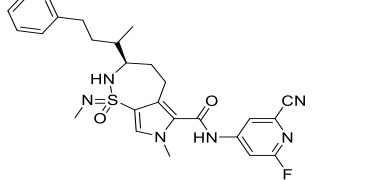
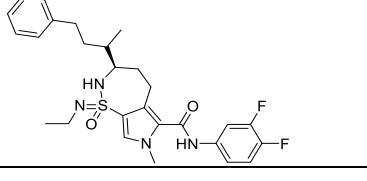
50k2		427	Peak2 (HPLC)
50m1		464	Peak1 (HPLC)
50m2		464	Peak2 (HPLC)
50n1		507	Peak1 (HPLC)
50n2		507	Peak2 (HPLC)
50o1		513	Peak1 (HPLC)
50o2		513	Peak2 (HPLC)
50p1		520	Peak1 (HPLC)

50p2		520	Peak2 (HPLC)
50q1		525	Peak1 (HPLC)
50q2		525	Peak2 (HPLC)
50r1		532	Peak1 (HPLC)
50r2		532	Peak2 (HPLC)
50s1		430	Peak1 (HPLC)
50s2		430	Peak2 (HPLC)
50t1		444	Peak1 (HPLC)
50t2		444	Peak2 (HPLC)

50u1		458	Peak1 (HPLC)
50u2		458	Peak2 (HPLC)
50v1		456	Peak1 (HPLC)
50v2		456	Peak2 (HPLC)
50w1		381	Peak1 (HPLC)
50w2		381	Peak2 (HPLC)
50x1		423	Peak1 (HPLC)
50x2		423	Peak2 (HPLC)
60a1		411	Peak1 (HPLC)
60a2		411	Peak2 (HPLC)

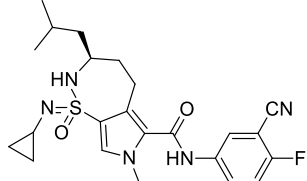
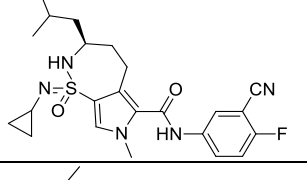
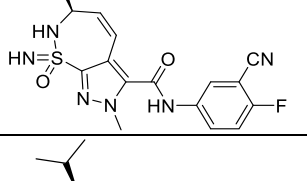
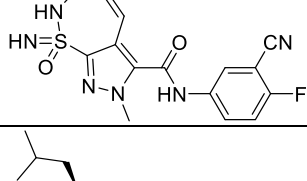
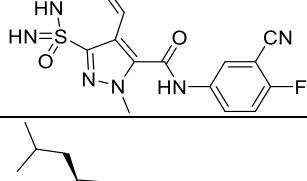
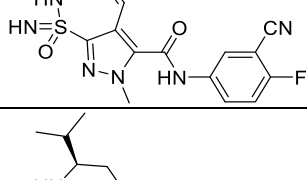
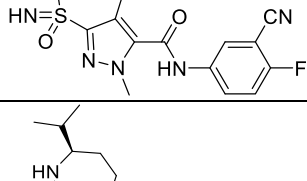
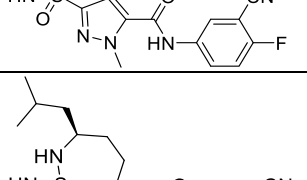
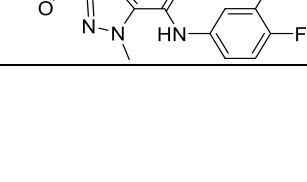
60b1		418	Peak1 (HPLC)
60b2		418	Peak2 (HPLC)
60c1		429	Peak1 (HPLC)
60c2		429	Peak2 (HPLC)
60d1		376	Peak1 (HPLC)
60d2		376	Peak2 (HPLC)
60e1		419	Peak1 (HPLC)
60e2		419	Peak2 (HPLC)

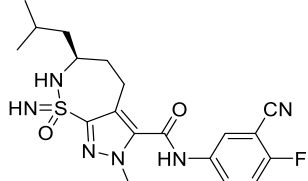
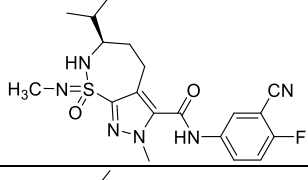
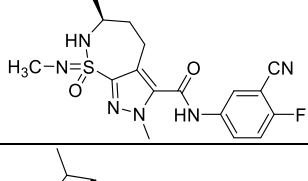
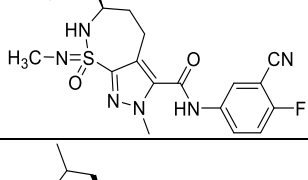
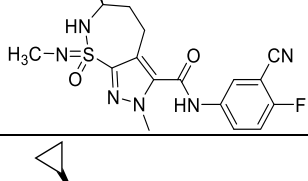
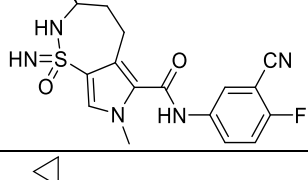
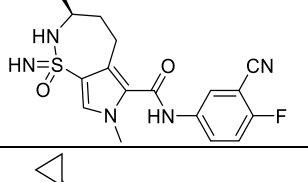
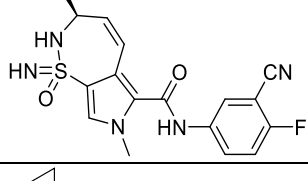
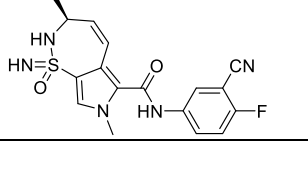
60f1		425	Peak1 (HPLC)
60f2		425	Peak2 (HPLC)
60g1		432	Peak1 (HPLC)
60g2		432	Peak2 (HPLC)
60h1		446	Peak1 (HPLC)
60h2		446	Peak2 (HPLC)
60i1		501	Peak1 (HPLC)
60i2		501	Peak2 (HPLC)

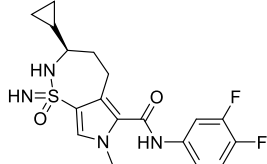
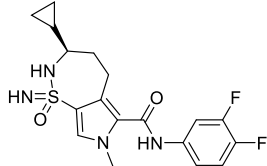
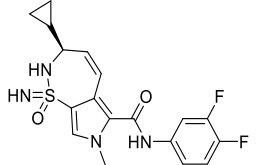
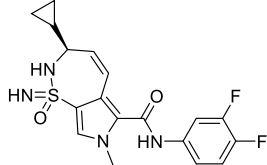
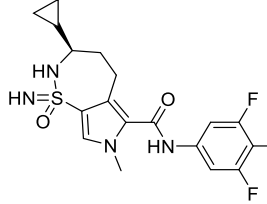
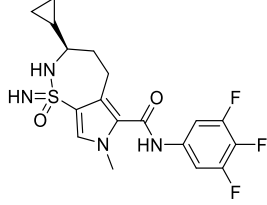
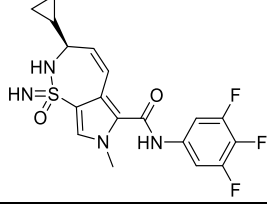
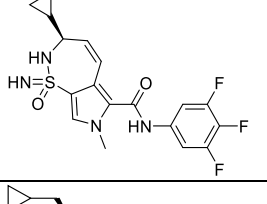
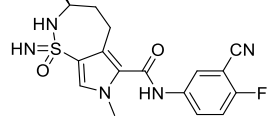
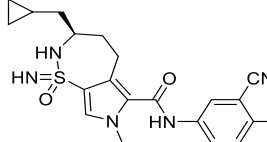
60j1		508	Peak1 (HPLC)
60j2		508	Peak2 (HPLC)
60k1		519	Peak1 (HPLC)
60k2		519	Peak2 (HPLC)
60m1		466	Peak1 (HPLC)
60m2		466	Peak2 (HPLC)
60n1		509	Peak1 (HPLC)
60n2		509	Peak2 (HPLC)
60o1		515	Peak1 (HPLC)

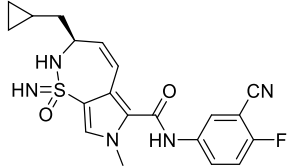
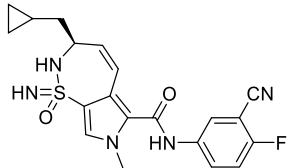
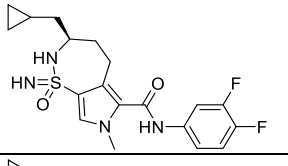
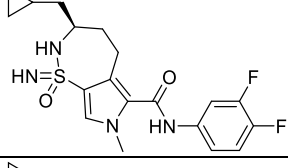
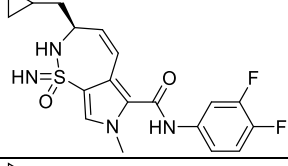
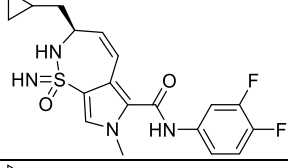
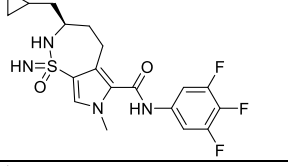
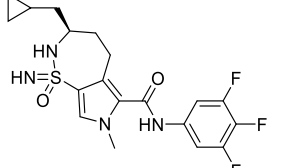
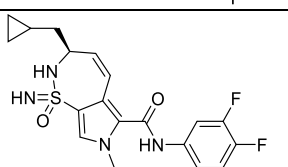
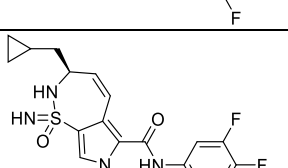
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60p1		522	Peak1 (HPLC)
60p2		522	Peak2 (HPLC)
60q1		527	Peak1 (HPLC)
60q2		527	Peak2 (HPLC)
60r1		534	Peak1 (HPLC)
60r2		534	Peak2 (HPLC)
60s1		383	Peak1 (HPLC)
60s2		383	Peak2 (HPLC)

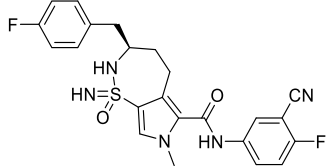
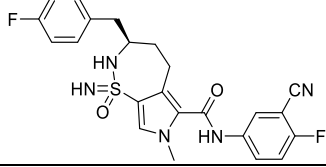
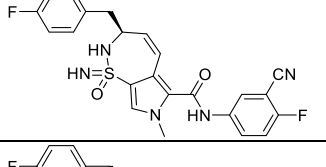
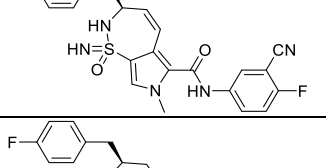
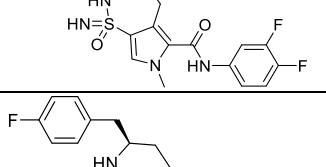
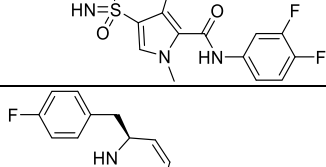
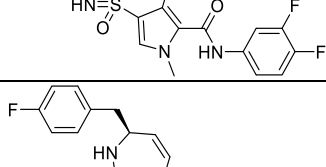
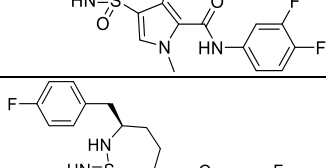
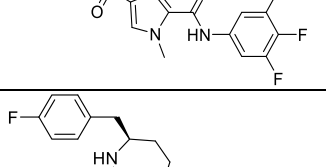
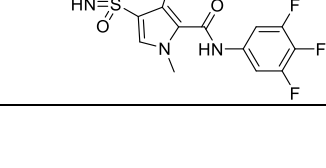
60t1		425	Peak1 (HPLC)
60t2		425	Peak2 (HPLC)
60u1		451	Peak1 (HPLC)
60u2		451	Peak2 (HPLC)
60v1		432	Peak1 (HPLC)
60v2		432	Peak2 (HPLC)
60w1		446	Peak1 (HPLC)
60w2		446	Peak2 (HPLC)
60x1		460	Peak1 (HPLC)
60x2		460	Peak2 (HPLC)

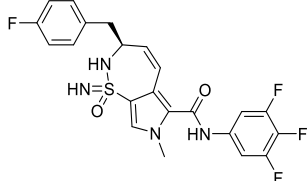
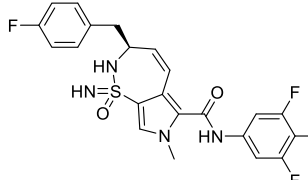
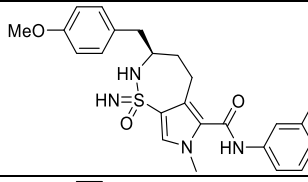
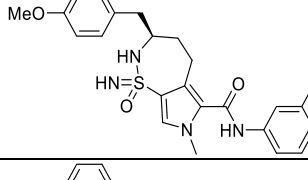
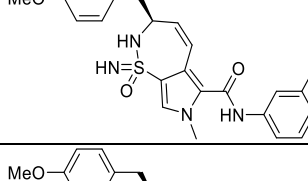
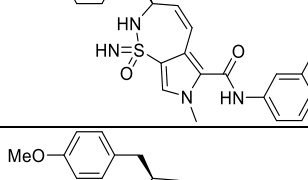
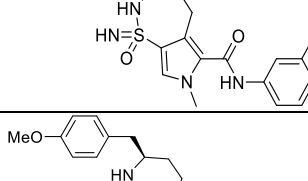
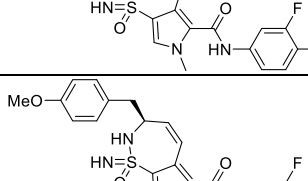
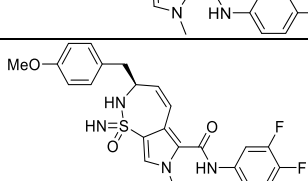
60y1		458	Peak1 (HPLC)
60y2		458	Peak2 (HPLC)
70a1		403	Peak1 (HPLC)
70a2		403	Peak2 (HPLC)
70b1		417	Peak1 (HPLC)
70b2		417	Peak2 (HPLC)
80a1		405	Peak1 (HPLC)
80a2		405	Peak2 (HPLC)
80b1		419	Peak1 (HPLC)

80b2		419	Peak2 (HPLC)
90a1		419	Peak1 (HPLC)
90a2		419	Peak2 (HPLC)
90b1		433	Peak1 (HPLC)
90b2		433	Peak2 (HPLC)
100a01		402	Peak1 (HPLC)
100a02		402	Peak2 (HPLC)
100a03		400	Peak1 (HPLC)
100a04		400	Peak2 (HPLC)

100a05		395	Peak1 (HPLC)
100a06		395	Peak2 (HPLC)
100a07		393	Peak1 (HPLC)
100a08		393	Peak2 (HPLC)
100a09		413	Peak1 (HPLC)
100a10		413	Peak2 (HPLC)
100a11		411	Peak1 (HPLC)
100a12		411	Peak2 (HPLC)
100b01		416	Peak1 (HPLC)
100b02		416	Peak2 (HPLC)

100b03		414	Peak1 (HPLC)
100b04		414	Peak2 (HPLC)
100b05		409	Peak1 (HPLC)
100b06		409	Peak2 (HPLC)
100b07		407	Peak1 (HPLC)
100b08		407	Peak2 (HPLC)
100b09		427	Peak1 (HPLC)
100b10		427	Peak2 (HPLC)
100b11		425	Peak1 (HPLC)
100b12		425	Peak2 (HPLC)

100c01		470	Peak1 (HPLC)
100c02		470	Peak2 (HPLC)
100c03		468	Peak1 (HPLC)
100c04		468	Peak2 (HPLC)
100c05		463	Peak1 (HPLC)
100c06		463	Peak2 (HPLC)
100c07		461	Peak1 (HPLC)
100c08		461	Peak2 (HPLC)
100c09		481	Peak1 (HPLC)
100c10		481	Peak2 (HPLC)

100c11		479	Peak1 (HPLC)
100c12		479	Peak2 (HPLC)
100c13		482	Peak1 (HPLC)
100c14		482	Peak2 (HPLC)
100c15		480	Peak1 (HPLC)
100c16		480	Peak2 (HPLC)
100c17		475	Peak1 (HPLC)
100c18		475	Peak2 (HPLC)
100c19		473	Peak1 (HPLC)
100c20		473	Peak2 (HPLC)

PHARMACEUTICAL COMPOSITION AND ADMINISTRATION MODE

Since the compounds of the present invention have excellent inhibitory activity against hepatitis B virus (HBV), the various compounds of the present invention, pharmaceutically acceptable inorganic or organic salts, hydrates or solvates thereof, and a pharmaceutical composition containing a compound of the present invention as a main active ingredient can be used for the prevention and/or treatment (stabilization, alleviation or cure) of hepatitis B virus infection or for prevention and/or treatment (stabilization, alleviation or cure) hepatitis B virus-related diseases (for example, hepatitis B, progressive liver fibrosis, inflammation and necrosis which cause cirrhosis, end-stage liver disease, hepatitis B cancer).

The pharmaceutical composition of the invention comprises the compound of the present invention in a safe and effective dosage range and a pharmaceutically acceptable excipient or carrier. The term "safe and effective dosage" means that the amount of compound is sufficient to significantly improve the condition without causing serious side effects. Generally, the pharmaceutical composition contains 1-2000 mg compound of the invention per dose, preferably, 10-200mg compound of the invention per dose. Preferably, the "one dose" is one capsule or one tablet.

"Pharmaceutically acceptable carrier" means one or more compatible solid or liquid fillers, or gelatinous materials which are suitable for human use and should be of sufficient purity and sufficiently low toxicity. "Compatibility" means that each component in the composition can be admixed with the compounds of the present invention and with each other without significantly reducing the efficacy of the compounds. Some examples of pharmaceutically acceptable carriers include cellulose and the derivatives thereof (such as sodium carboxymethyl cellulose, sodium ethyl cellulose, cellulose acetate, etc.), gelatin, talc, solid lubricants (such as stearic acid, magnesium stearate), calcium sulfate, vegetable oils (such as soybean oil, sesame oil, peanut oil, olive oil, etc.), polyols (such as propylene glycol, glycerol, mannitol, sorbitol, etc.), emulsifiers (such as Tween®), wetting agent (such as sodium dodecyl sulfate), coloring agents, flavoring agents, stabilizers, antioxidants, preservatives, pyrogen-free water, etc.

There is no special limitation on administration mode for the compound or pharmaceutical composition of the present invention, and the representative administration mode includes (but is not limited to): oral, parenteral (intravenous, intramuscular or subcutaneous) administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In these solid dosage forms, the active compounds are mixed with at least one conventional inert excipient (or carrier), such as sodium citrate or CaHPO_4 , or mixed with any of the following components: (a) fillers or compatibilizer, for example, starch, lactose, sucrose, glucose, mannitol and silicic acid; (b) binders, for example, hydroxymethyl cellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and arabic gum; (c) humectant, such as, glycerol; (d) disintegrating agents such as agar, calcium carbonate, potato starch or tapioca starch, alginic acid, certain composite silicates, and sodium carbonate; (e)

dissolution-retarding agents, such as paraffin; (f) absorption accelerators, for example, quaternary ammonium compounds; (g) wetting agents, such as cetyl alcohol and glyceryl monostearate; (h) adsorbents, for example, kaolin; and (i) lubricants such as talc, stearin calcium, magnesium stearate, solid polyethylene glycol, sodium lauryl sulfate, or the mixtures thereof. In capsules, tablets and pills, the dosage forms may also contain buffering agents.

The solid dosage forms such as tablets, sugar pills, capsules, pills and granules can be prepared by using coating and shell materials, such as enteric coatings and any other materials known in the art. They can contain an opaque agent. The release of the active compounds or compounds in the compositions can be released in a delayed mode in a given portion of the digestive tract. Examples of the embedding components include polymers and waxes. If necessary, the active compounds and one or more above excipients can form microcapsules.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups or tinctures. In addition to the active compounds, the liquid dosage forms may contain any conventional inert diluents known in the art such as water or other solvents, solubilizers and emulsifiers, for example, ethanol, isopropanol, ethyl carbonate, ethyl acetate, propylene glycol, 1,3-butanediol, dimethyl formamide, as well as oil, in particular, cottonseed oil, peanut oil, corn germ oil, olive oil, castor oil and sesame oil, or the combination thereof.

Besides these inert diluents, the composition may also contain additives such as wetting agents, emulsifiers, and suspending agent, sweetener, flavoring agents and perfume.

In addition to the active compounds, the suspension may contain suspending agent, for example, ethoxylated isooctadecanol, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, methanol aluminum and agar, or the combination thereof.

The compositions for parenteral injection may comprise physiologically acceptable sterile aqueous or anhydrous solutions, dispersions, suspensions or emulsions, and sterile powders which can be re-dissolved into sterile injectable solutions or dispersions. Suitable aqueous and non-aqueous carriers, diluents, solvents or excipients include water, ethanol, polyols and any suitable mixtures thereof.

The compounds of the present invention can be administrated alone, or in combination with any other pharmaceutically acceptable compounds (such as anti-HBV agents).

In the case of co-administration, the pharmaceutical composition can also include one or more (2, 3, 4, or more) other pharmaceutically acceptable compounds (such as anti-HBV agents). One or more (2, 3, 4, or more) other pharmaceutically acceptable compounds (e.g., anti-HBV agents) may be used simultaneously, separately or sequentially with the compound of the present invention so as to prevent and/or treat HBV infection or HBV related diseases.

When the pharmaceutical composition is used, a safe and effective amount of compound of the present invention is administered to a mammal (such as human) in need of, wherein the dose of administration is a pharmaceutically effective dose. For a person weighed 60 kg, the daily dose is usually 1-2000 mg, preferably 20-500mg. Of course, the particular dose should also depend on various factors, such as the route of administration, patient healthy status, which are well within the skills of an experienced physician.

The main advantages of the present invention include:

(1) The compounds of the present invention are novel in structure and have an excellent anti-hepatitis B virus infection effect. In this application, the existing endocyclic sulfoxide amide-arylamide compounds are transformed into endocyclic sulfonimid amide-arylamide compounds in order to better interfering with the assembly process of the capsid protein, thus inhibiting the activity or expression of HBV.

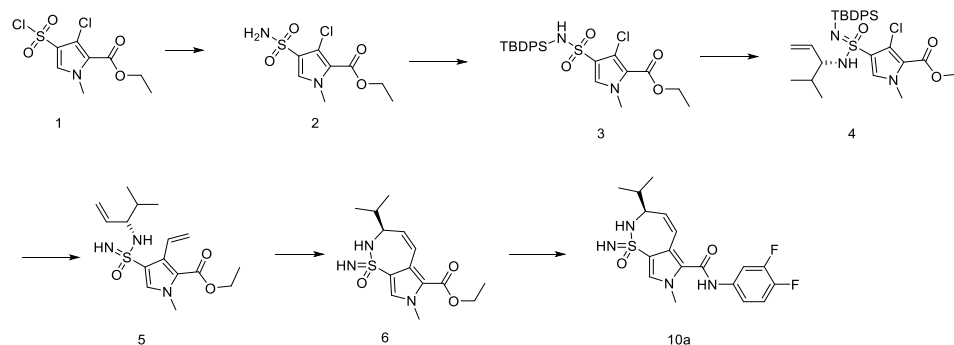
(2) The compounds of the present invention have very low toxicity to normal cells, and therefore can be applied to a subject in a large dose range.

(3) The compounds of the present invention have good drug ability. Compared with the existing compounds, the compounds of the present invention have better solubility and have shown good bioavailability in *in vivo* experiments. The bioavailability of some compounds has reached 70% or above. Meanwhile, the compounds of the present invention are extremely easy to make into pharmaceutically acceptable salts compared to existing compounds, and thus contribute to the further formation of formulations.

(4) The compound of the present invention and a pharmaceutical composition containing the compound of the present invention as a main active ingredient can be used for prevention and/or treatment of hepatitis B virus-related diseases (for example, hepatitis B, progressive liver fibrosis, inflammation and necrosis leading to liver cirrhosis, end-stage liver diseases, hepatitis B liver cancer).

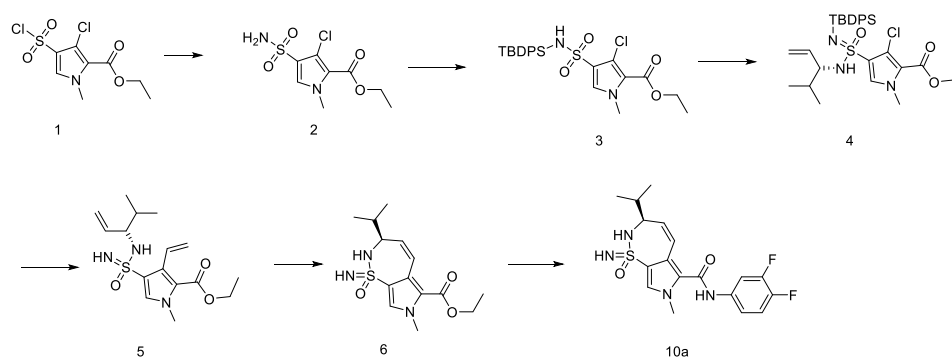
The present invention will be further illustrated below with reference to the specific examples. It should be understood that these examples are only to illustrate the invention but not to limit the scope of the invention. The experimental methods with no specific conditions described in the following examples are generally performed under the conventional conditions, or according to the manufacturer's instructions. Unless indicated otherwise, parts and percentage are calculated by weight. Unless otherwise specified, the raw materials or instruments used in the embodiments of the present invention are commercially available. 10 classes of compounds are prepared by the following scheme:

Example 1: synthesis of compound 10a

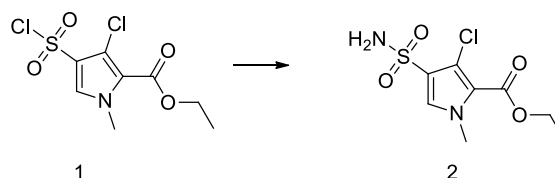


the **synthesis** of 10 types of compounds:

Example 1: Synthesis of compound 10a

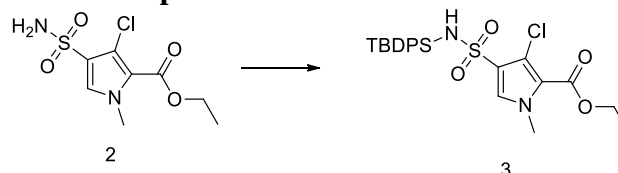


Step 1: Synthesis of Compound 2



Compound 1 (10 g) was dissolved in dichloromethane (40 mL), and ammonia water (30 mL) was added dropwise to the reaction system at room temperature. The reaction was carried out for 5 h at room temperature, then vacuum filtrated, and the filter cake was washed with water (5mL) to provide 5g of light yellow solid, MS ($M + 1 = 267$).

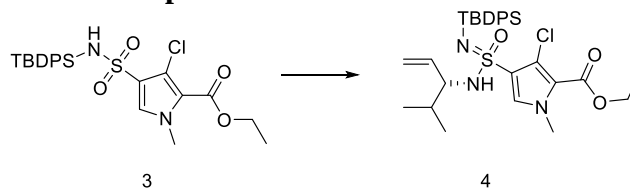
Step 2: Synthesis of Compound 3



The substrate 2 (5 g) was dissolved in DMF (10 mL), sodium hydride (1.5 g) was added into the reaction system at 0 °C, and stirred for 15 min. TBDPSCl was then added to the reaction system, and reacted for 18 h. The reaction system was poured into ice water, and extracted with ethyl acetate (3 * 30 mL), and the organic phase was dried, the solvent was evaporated in vacuum. Crude product

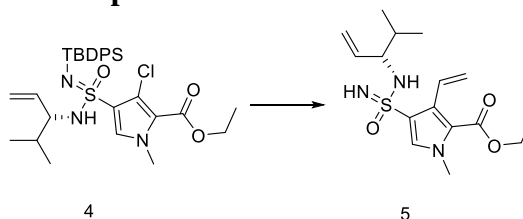
was purified via column chromatography (n-heptane: ethyl acetate = 1: 4) to provide the product **3** (3 g). MS ($M + 1 = 505$).

Step 3: Synthesis of Compound 4



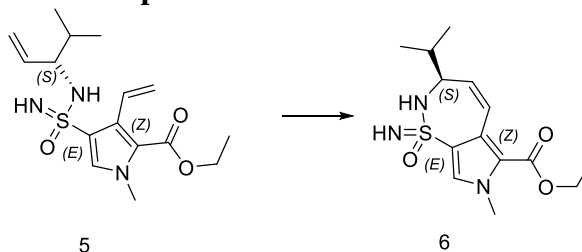
The PPh_3Cl_2 chloroform solution (80 mL) was cooled to 0 °C, and then triethylamine (7 mL) was added, stirred for 10 minutes and then compound **3** was added at 0 °C. After stirred for 20 minutes, 2-isopropyl-3-propenylamine was added to the reaction system and reacted at room temperature for 18h. Water (20 mL) and ethyl acetate (3 * 25mL) were added to the reaction system for extraction. The organic phase was dried and the solvent was evaporated in vacuum. Crude product was purified via column chromatography (n-heptane: ethyl acetate = 1: 5) to provide the product **4** (1.9 g). MS ($M + 1 = 586$).

Step 4: Synthesis of Compound 5



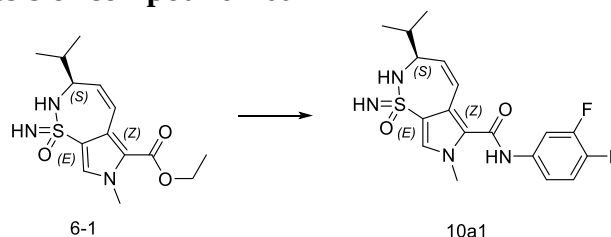
Compound **4** (1.8 g), Tetrakis (triphenylphosphine) palladium (100 mg), pinacol vinylboronate (900 mg), and cesium carbonate (2.7 g) were dissolved in DMF (410 mL), and the mixture was reacted at 100 °C under nitrogen for 15 h. The reaction was quenched with aqueous solution, extracted with ethyl acetate, and the organic phase was dried and the solvent was evaporated in vacuum. The resulting crude product was purified by column chromatography (n-heptane: ethyl acetate = 1: 5) to provide compound **5** (1.0 g). MS ($M + 1 = 340$).

Step 5: Synthesis of Compound 6



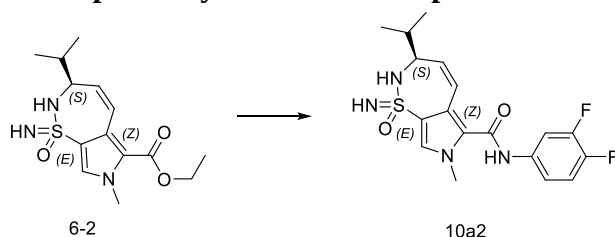
Compound **5** (1.0 g) was dissolved in dichloromethane (500 ml), and then the Zhan Catalyst (0.1 g) was added to the reaction system and stirred overnight. The solvent of reaction solution was evaporated in vacuum and crude product was purified via column chromatography (n-heptane: ethyl acetate = 1: 3) to provide compound **6**. The lower point indicated by TLC was 6-1 (0.22 g), and the upper point indicated by TLC was 6-2 (0.27 g), MS ($M + 1 = 312$).

Step 6: Synthesis of compound 10a1



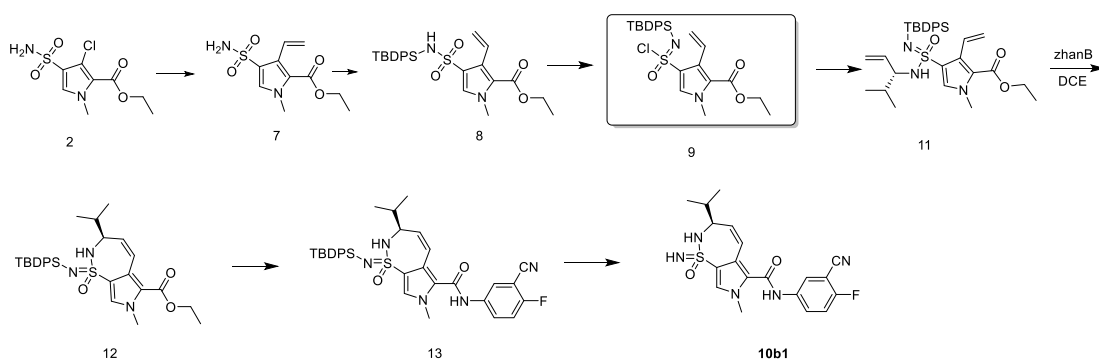
Compound 6-1 (30 mg) and 4-fluoro-3-cyanoaniline (20 mg) were dissolved in THF (5 mL), the solution was cooled to 0 °C, and then NaHMDS (0.2 mL) solution was added to the reaction system. The reaction was stirred at room temperature for 16 h, and water was added to the reaction system. The mixture was extracted with ethyl acetate (3 * 15 mL). The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuum. The crude product was subjected to column chromatography (n-heptane: ethyl acetate = 1: 3) to provide target product 10a1 (11mg). ¹H NMR (400 MHz, DMSO-d₆) δ 10.78 (s, 1H), 7.89 – 7.83 (m, 1H), 7.71 (s, 1H), 7.44 (qd, J = 4.7, 4.2, 2.5 Hz, 2H), 6.54 (dd, J = 12.4, 2.7 Hz, 1H), 5.75 (dd, J = 12.4, 2.8 Hz, 1H), 4.0 (dq, J = 7.8, 2.6 Hz, 1H), 3.74 (s, 3H), 1.97-1.89 (m, 1H), 0.98 (dd, J = 12.6, 6.7 Hz, 6H). MS(M+1=395).

Example 2: Synthesis of Compound 10a2

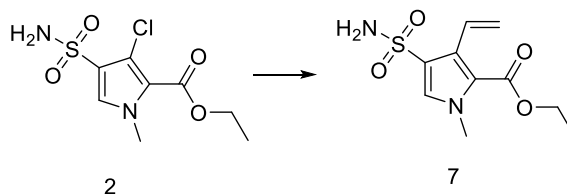


The reaction was carried out according to the step 6 of example 1, all the conditions were the same except the compound 6-2 was used instead of 6-1, column chromatography (n-heptane: ethyl acetate = 1: 1) purified to provide target product 10a2 (8mg). ¹H NMR (400 MHz, DMSO-d₆) δ 10.69 (s, 1H), 7.89 – 7.83 (m, 1H), 7.51 (s, 1H), 7.44 (qd, J = 4.7, 4.2, 2.5 Hz, 2H), 6.53 (dd, J = 12.4, 2.7 Hz, 1H), 5.72 (dd, J = 12.4, 2.8 Hz, 1H), 3.87 (dq, J = 7.8, 2.6 Hz, 1H), 3.72 (s, 3H), 1.91-1.85 (m, 1H), 0.96 (dd, J = 12.6, 6.7 Hz, 6H). MS(M+1=395).

Example 3: Synthesis of Compound 10b1

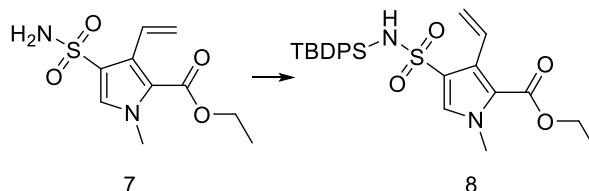


Step 1: Synthesis of Compound 7



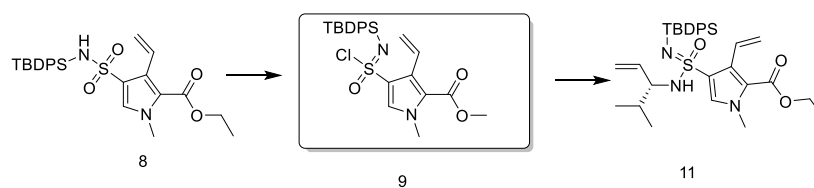
Compound 2 (2.5 g), vinyl borate (1.5 g), sodium carbonate (3.5 g), palladium acetate (120 mg) and Xphos (500 mg) were dissolved in DMF. Under nitrogen protection, the reaction system was placed in a pre-heated 100°C oil bath to react for 6 hours. Water (50 mL) was added to the reaction system, and extracted with ethyl acetate (3 * 60 mL), dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuum. Purified via column chromatography to provide 1.2 g of yellow solid. MS ($M + 1 = 259$).

Step 2: Synthesis of Compound 8



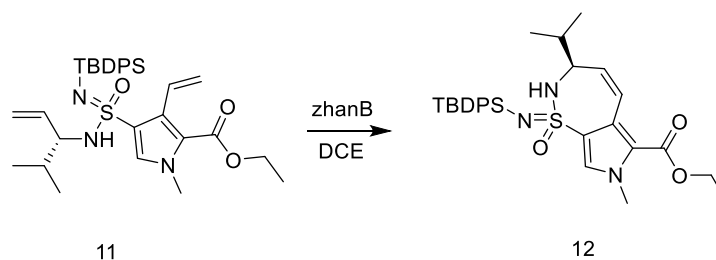
The reaction system was cooled to 0 °C, sodium hydride (180 mg) was added to DMF, and then stirred for 10 min. TBDPSCl (2.7 g) and 7 (1.1 g) in DMF was added dropwise to the reaction system at 0 °C, and reacted at room temperature for 1.5 h. The reaction liquid was added dropwise to a mixed solution of 1N HCl and saturated ammonium chloride, extracted with ethyl acetate (3 * 50mL), dried over anhydrous sodium sulfate, the organic phase was evaporated in vacuum, and 800 mg of white solid was obtained by column chromatography, MS ($M + 1 = 497$). ^1H NMR (400 MHz, DMSO- d_6) δ 10.78 (s, 1H), 7.62 – 7.59 (m, 1H), 7.45 – 7.41(m, 1H), 7.33 – 7.29 (m, 3H), 7.13 (qd, $J = 4.7, 4.2, 2.5$ Hz, 2H), 6.16 (dd, $J = 12.4, 2.7$ Hz, 1H), 5.58 (dd, $J = 12.4, 2.8$ Hz, 1H), 5.09 (s, 1H), 4.35-4.40 (m, 2), 3.56 (s, 3H), 1.45-1.40 (m,3), 1.04 (s, 9H).

Step 3: Synthesis of Compound 11



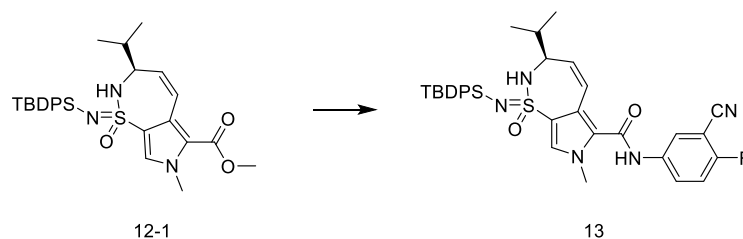
The PPh_3Cl_2 mixture was cooled to 0 °C, and then triethylamine (3mL) was added into the reaction system. After the addition, the mixture was reacted at 0 °C for 10 minutes, and then solid 8 (500mg) was added in one batch to the system, and stirred at 0 °C for 20 min. Finally, the chloroform solution of isopropylallylamine (200 mg) was added to the reaction system, and reacted at room temperature for 18 h. The silica gel was directly added to the reaction system, and purified via column chromatography to provide 650 mg of pale yellow oil. MS(M+1=578) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.81 – 7.73 (m, 4H), 7.38-7.32 (m, 7H), 7.06 – 6.91 (m, 2H), 6.01-5.89 (m, 1 H), 5.48-5.33 (m, 2 H), 4.92-4.70 (m, 2 H), 4.36-4.30 (m, 2 H), 3.79 (s, 1.55H), 3.76 (s, 1.36H), 3.50-3.41(m, 1H),1.71-1.66 (m, 0. 5H),1.56-1.51 (m, 0. 5H), 1.40-1.35 (m, 3),1.14 (s, 4.2H), 1.12 (s, 4.5H),0.76-0.73 (m,3H), 0.68-0.64 (m,3H).

Step 4: Synthesis of Compound 12



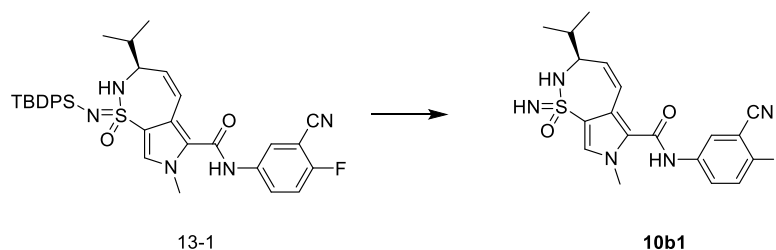
Compound 11 (650mg) was dissolved in 1,2-dichloroethane, and Zhan 1B was added to the reaction system. Under the protection of nitrogen, the system was warmed to 70 °C and stirred for 24h. Silica gel was directly added to the reaction system, and purified by column chromatography, after the solvent was evaporated in vacuum to provide pale yellow oil 12: The lower point of the TLC display was 12-1 (0.22 g), and the upper point of the TLC display was 12-2 (0.27 g), MS (M + 1 = 550). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.81 – 7.74 (m, 5H), 7.40-7.37 (m, 7H), 7.28-7.21 (m, 1H), 6.01-5.89 (m, 1 H), 6.99 (s, 1H), 5.77-5.73 (m, 1 H), 4.42-4.35 (m, 2 H), 4.15-4.11 (m, 1 H), 3.80 (s, 3H), 1.91-1.86 (m, 1H), 1.43-1.39 (m, 3), 1.14 (s, 9H), 0.87-0.78 (m,6H).

Step 5: Synthesis of Compound 13



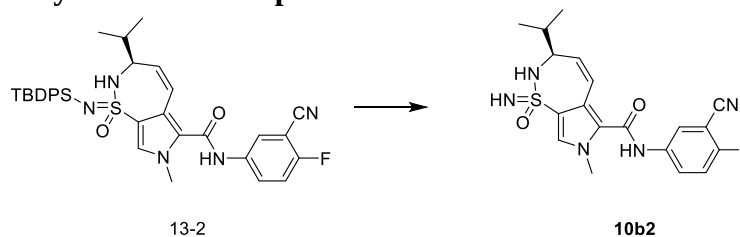
Compound 12-1 (90 mg) (lower point shown by TLC) and 3,4-difluoroaniline (43 mg) was dissolved in THF (8 mL), then the system was cooled to 0 °C, and 6 eq of NaHMDS was added to the reaction system to react at 0 °C for 1 h. Water (20 mL) was added to the reaction system, and extracted with ethyl acetate (3 * 30 mL), dried over anhydrous sodium sulfate, the solvent was evaporated in vacuum, and purified via column chromatography to provide 80 mg of yellow oil. MS ($M + 1 = 640$).

Step 6: Synthesis of compound 10b1



Compound 13-1 (40 mg) (lower point shown by TLC) was dissolved in THF (3mL), then 120 eq of 3HF.TEA was added dropwise into the reaction system, reacted at room temperature for 3 days, separated by preparation TLC, and freeze-dried to obtain white solid 10b1 (4.5 mg). ^1H NMR (400 MHz, DMSO- d_6) δ 10.90 (s, 1H), 8.18 (dd, $J = 5.8, 2.7$ Hz, 1H), 7.99(ddd, $J = 9.2, 4.8, 2.7$ Hz, 1H), 7.78– 7.70 (m, 2H), 7.57 (d, $J = 10.3$ Hz, 1H), 6.57 (dd, $J = 12.4, 2.7$ Hz, 1H), 5.77 (dd, $J = 12.4, 2.8$ Hz, 1H), 4.07 (ddt, $J = 10.6, 5.4, 2.7$ Hz, 1H), 3.76 (s, 3H), 1.92 (tq, $J = 12.1, 6.7, 5.6$ Hz, 1H), 0.99 (dd, $J = 12.0, 6.7$ Hz, 6H). **Ms** (ESI) $m/z = 402(M+1)$

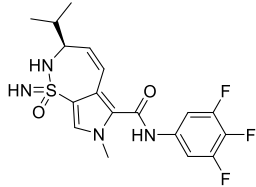
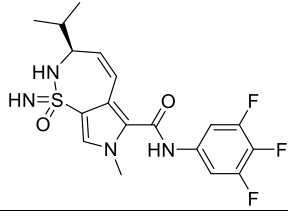
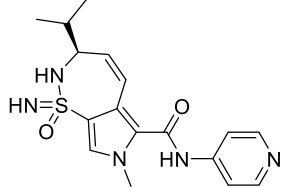
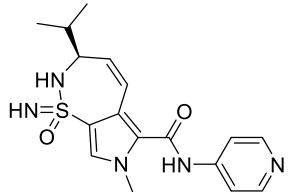
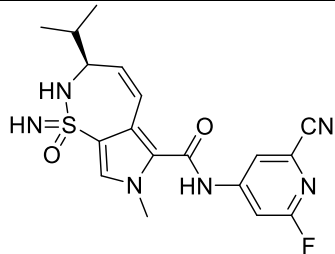
Example 4: Synthesis of compound 10b2

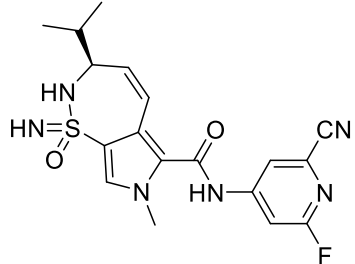
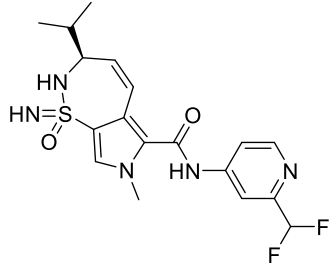
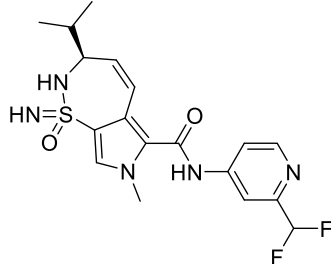
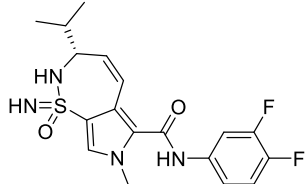
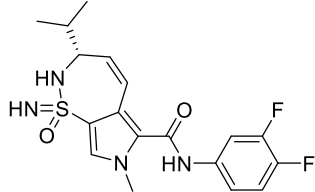
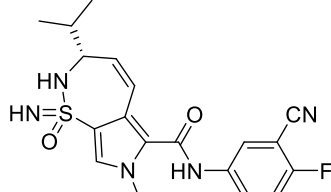
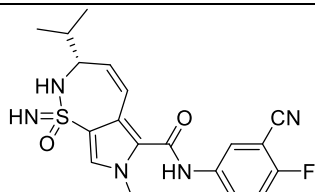


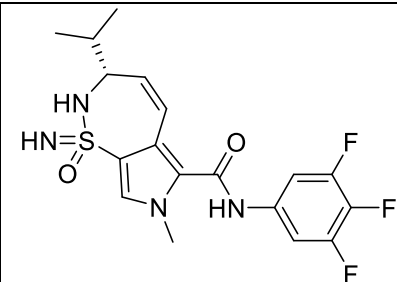
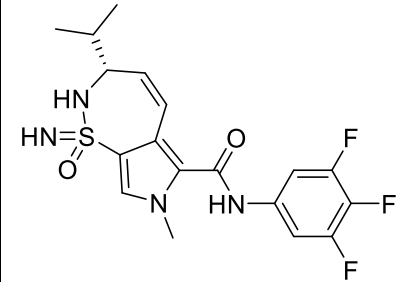
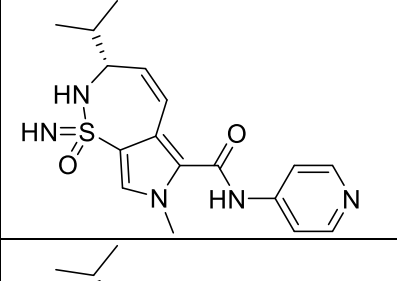
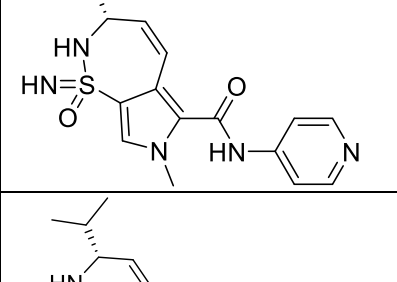
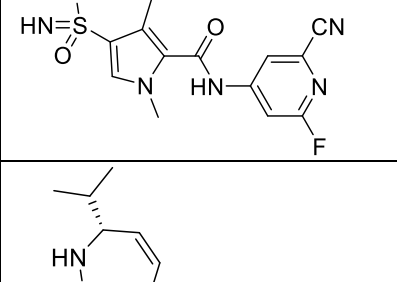
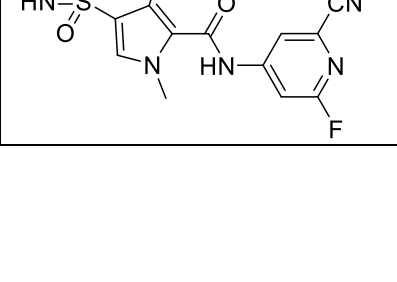
The reaction was carried out according to the step 6 of example 3, all the conditions were the same except the compound 13-2 (upper point shown by TLC) was used instead of compound 13-1 (lower point shown by TLC), purified by column chromatography (n-heptane: ethyl acetate = 1: 1) to provide target

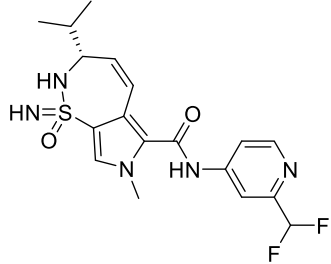
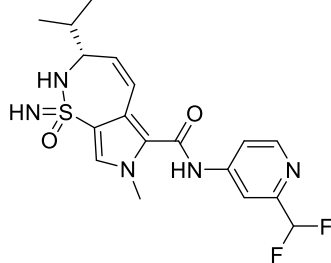
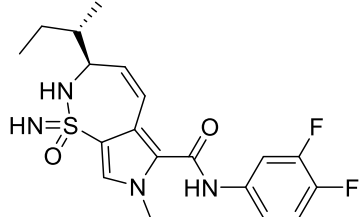
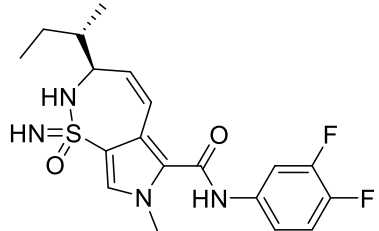
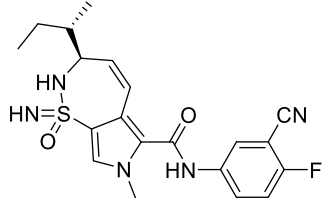
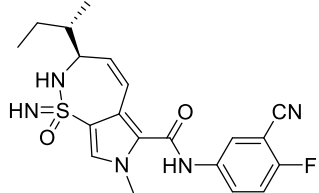
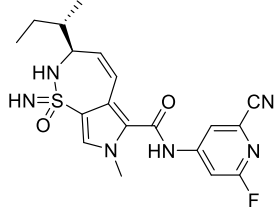
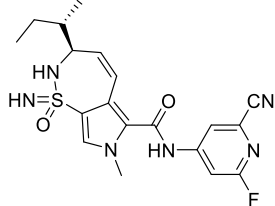
product 10b2 (8mg). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.89 (s, 1H), 8.20 (dd, J = 5.8, 2.7 Hz, 1H), 7.97(ddd, J = 9.2, 4.8, 2.7 Hz, 1H), 7.90– 7.88 (m, 2H), 7.56 (d, J = 10.3 Hz, 1H), 6.65(dd, J = 12.4, 2.7 Hz, 1H), 5.91 (dd, J = 12.4, 2.8 Hz, 1H), 3.80 (s, 3H), 3.69-3.63(m, 1H), 1.95 (tq, J = 12.1, 6.7, 5.6 Hz, 1H), 0.99 (dd, J = 12.0, 6.7 Hz, 6H). **Ms (ESI)** m/z = 402(M+1)

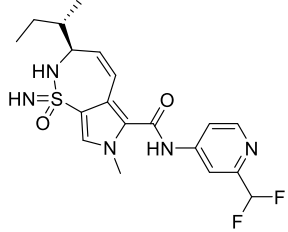
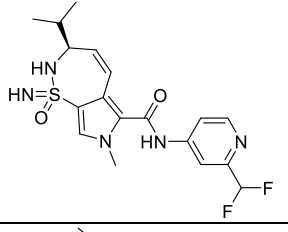
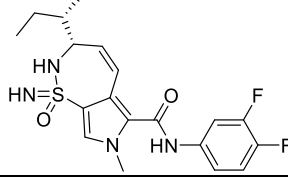
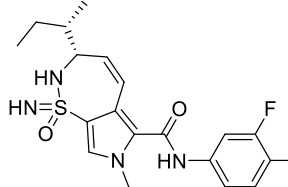
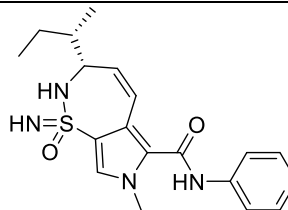
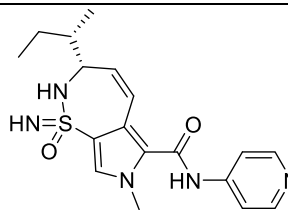
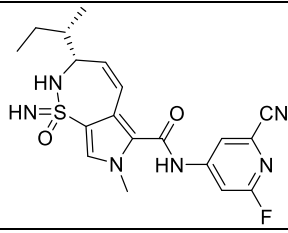
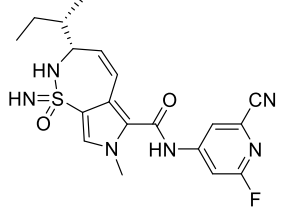
The following 10 and 30 series compounds were synthesized according to the method of example 3:

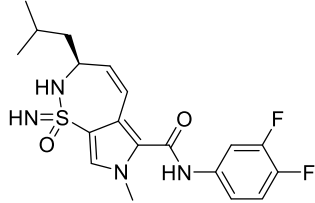
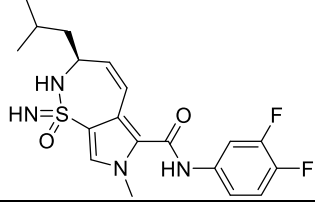
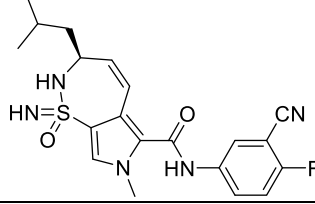
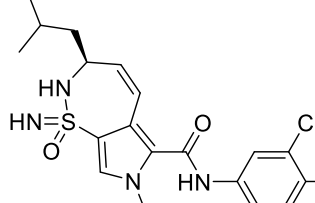
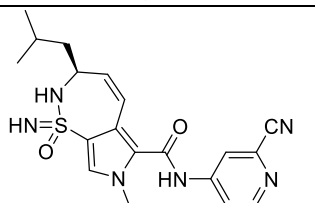
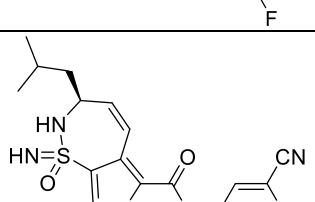
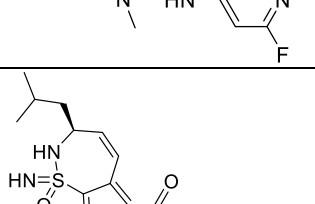
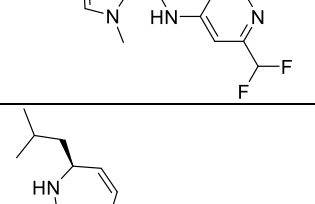
No.	Structure	Mass Spectrum ESI-MS, (M + H)	Remark
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10c2		413	Peak2 (HPLC)
10d1		360	Peak1 (HPLC)
10d2		360	Peak2 (HPLC)
10e1		403	Peak1 (HPLC)

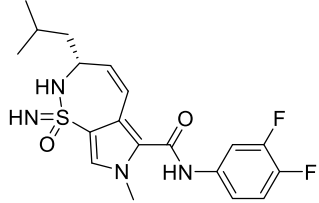
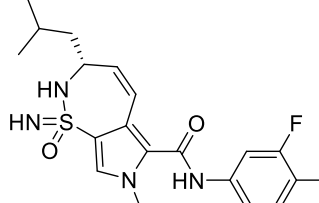
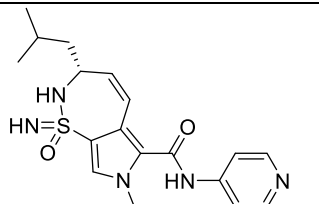
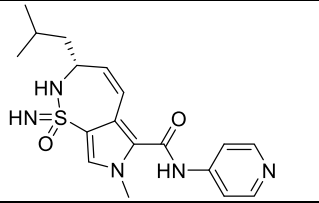
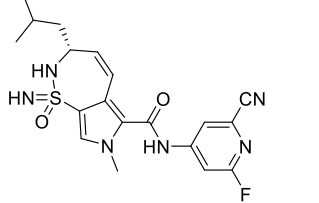
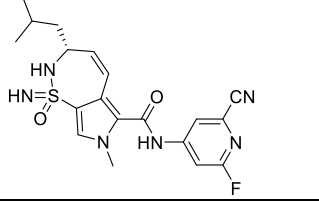
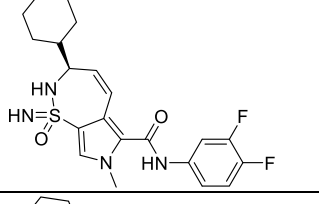
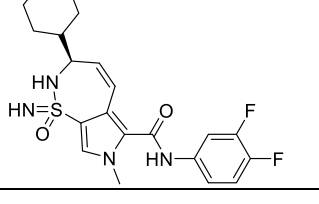
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10f2		410	Peak2 (HPLC)
10g1		395	Peak1 (HPLC)
10g2		395	Peak2 (HPLC)
10h1		402	Peak1 (HPLC)
10h2		402	Peak2 (HPLC)

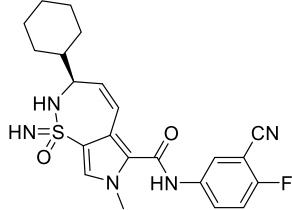
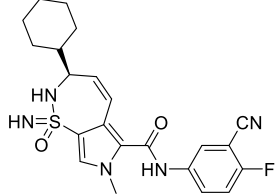
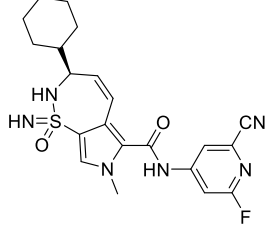
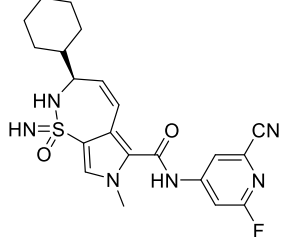
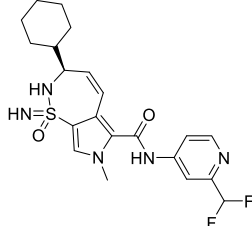
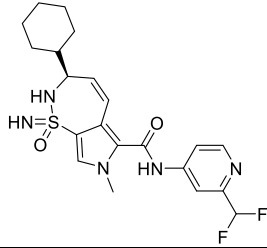
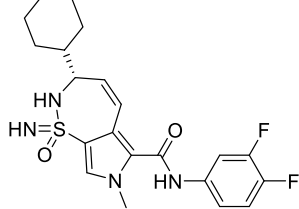
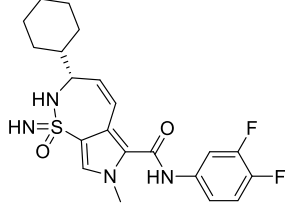
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10j1		360	Peak1 (HPLC)
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10k1		403	Peak1 (HPLC)
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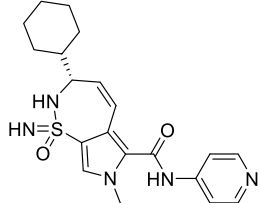
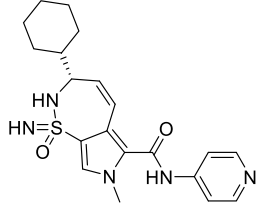
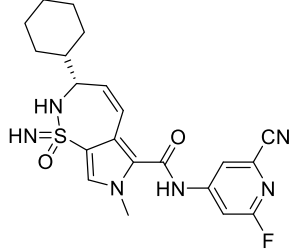
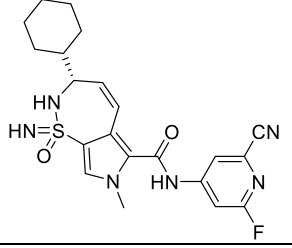
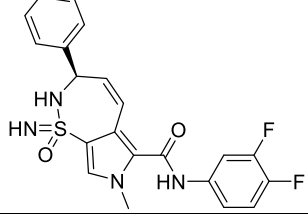
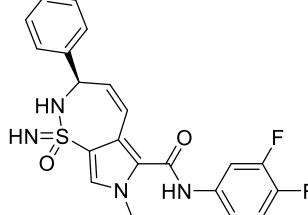
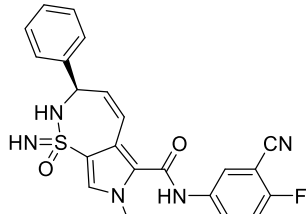
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10n2		409	Peak2 (HPLC)
10o1		416	Peak1 (HPLC)
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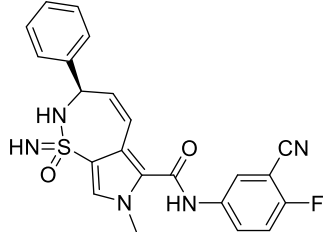
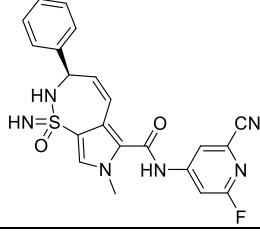
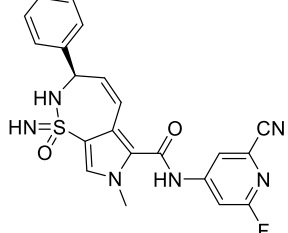
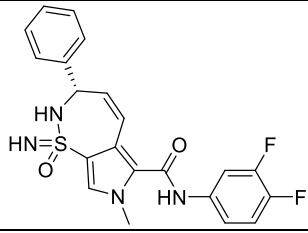
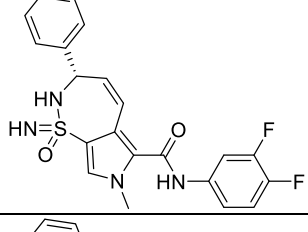
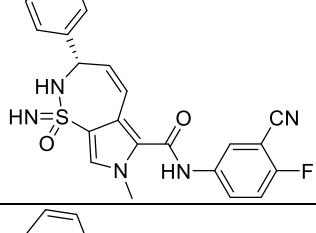
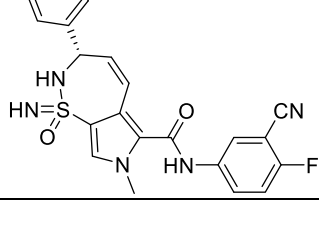
10q1		424	Peak1 (HPLC)
10q2		424	Peak2 (HPLC)
10r1		409	Peak1 (HPLC)
10r2		409	Peak2 (HPLC)
10s1		374	Peak1 (HPLC)
10s2		374	Peak2 (HPLC)
10t1		417	Peak1 (HPLC)
10t2		417	Peak2 (HPLC)

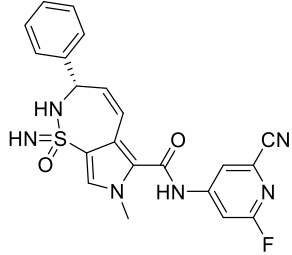
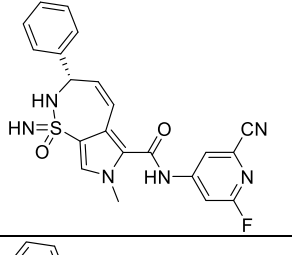
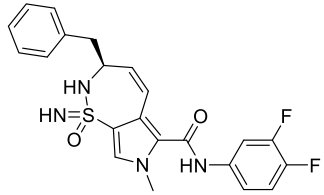
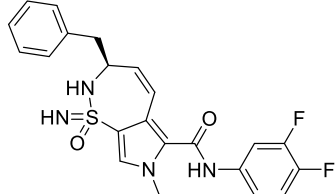
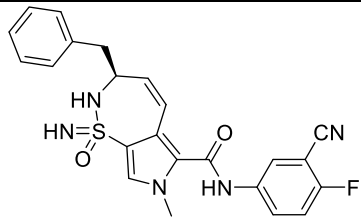
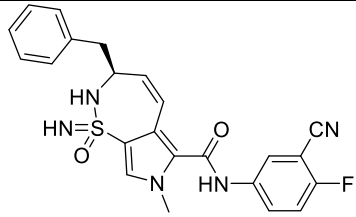
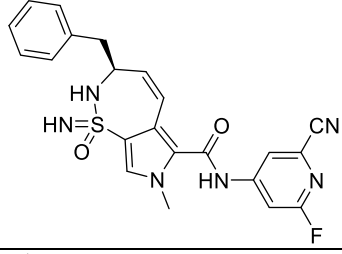
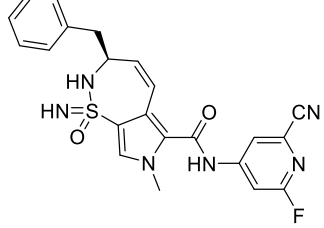
10u1		409	Peak1 (HPLC)
10u2		409	Peak2 (HPLC)
10v1		416	Peak1 (HPLC)
10v2		416	Peak2 (HPLC)
10w1		417	Peak1 (HPLC)
10w2		417	Peak2 (HPLC)
10x1		424	Peak1 (HPLC)
10x2		424	Peak2 (HPLC)

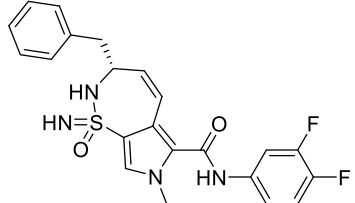
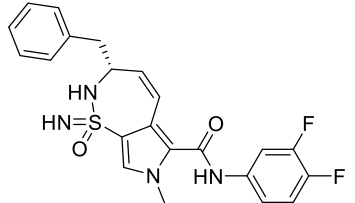
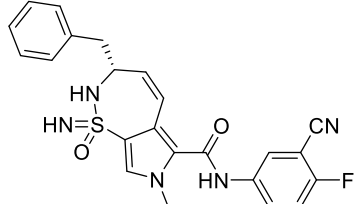
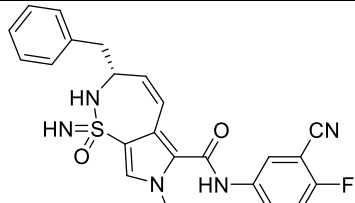
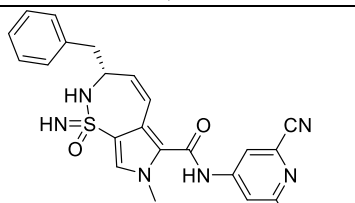
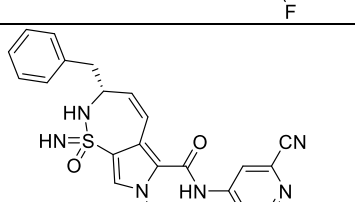
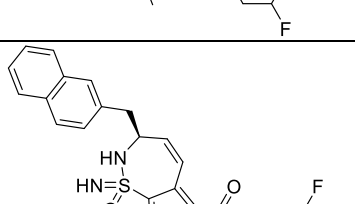
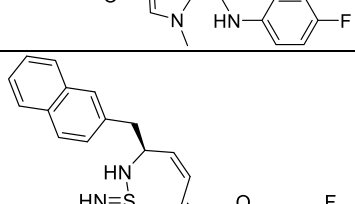
10y1		409	Peak1 (HPLC)
10y2		409	Peak2 (HPLC)
10z1		374	Peak1 (HPLC)
10z2		374	Peak2 (HPLC)
10aa1		417	Peak1 (HPLC)
10aa2		417	Peak2 (HPLC)
10bb1		435	Peak1 (HPLC)
10bb2		435	Peak2 (HPLC)

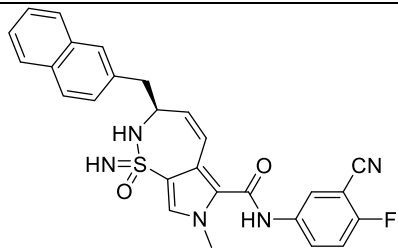
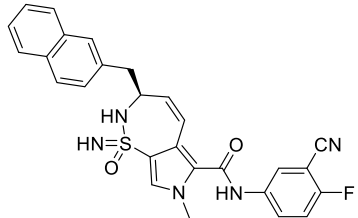
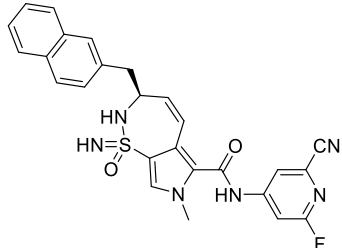
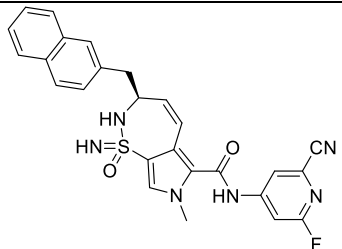
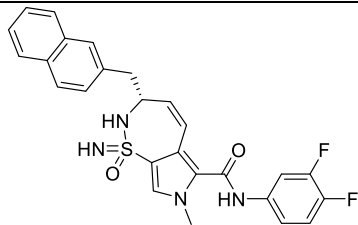
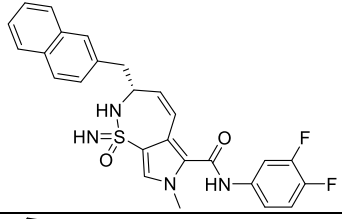
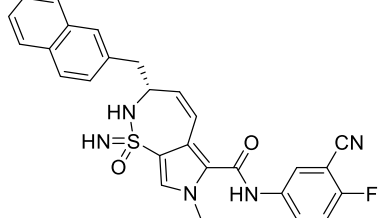
10cc1		442	Peak1 (HPLC)
10cc2		442	Peak2 (HPLC)
10dd1		443	Peak1 (HPLC)
10dd2		443	Peak2 (HPLC)
10ee1		450	Peak1 (HPLC)
10ee2		450	Peak2 (HPLC)
10ff1		435	Peak1 (HPLC)
10ff2		435	Peak2 (HPLC)

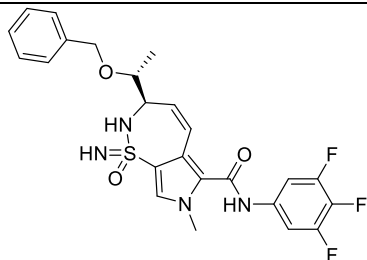
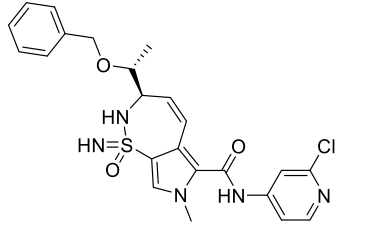
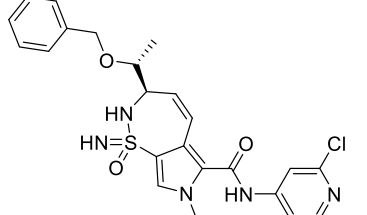
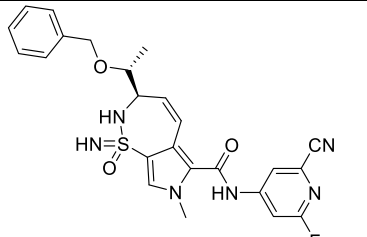
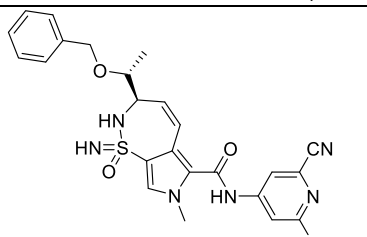
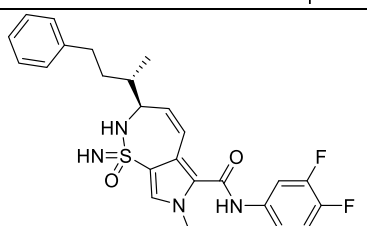
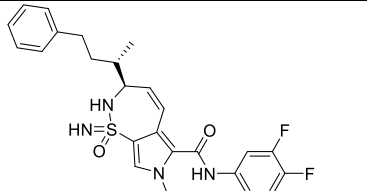
10gg1		400	Peak1 (HPLC)
10gg2		400	Peak2 (HPLC)
10hh1		443	Peak1 (HPLC)
10hh2		443	Peak2 (HPLC)
10ii1		429	Peak1 (HPLC)
10ii2		429	Peak2 (HPLC)
10jj1		436	Peak1 (HPLC)

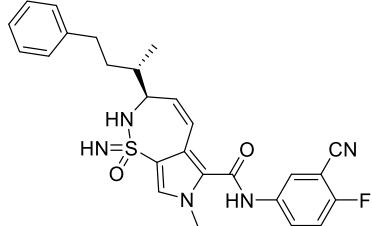
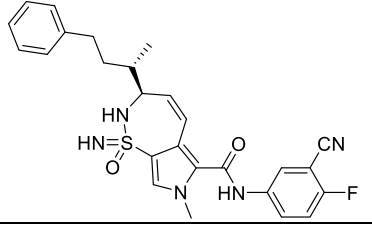
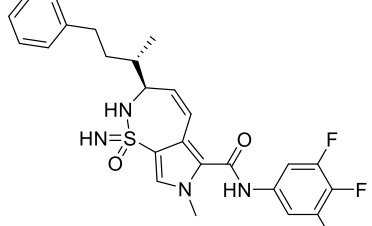
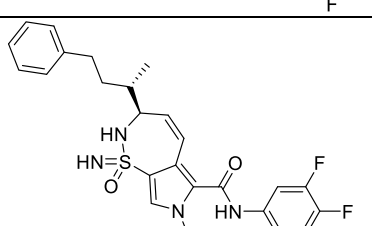
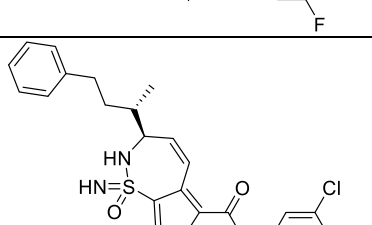
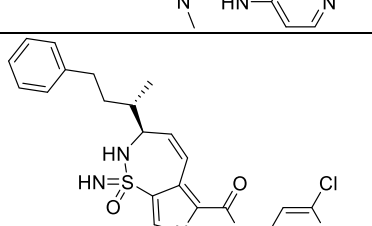
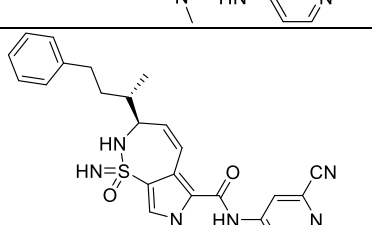
10jj2		436	Peak2 (HPLC)
10kk1		437	Peak1 (HPLC)
10kk2		437	Peak2 (HPLC)
10mm1		429	Peak1 (HPLC)
10mm2		429	Peak2 (HPLC)
10nn1		436	Peak1 (HPLC)
10nn2		436	Peak2 (HPLC)

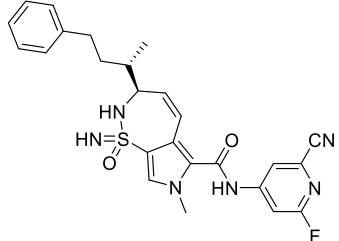
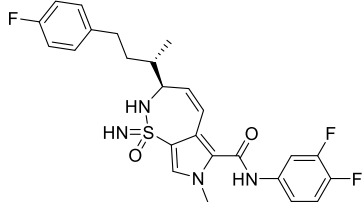
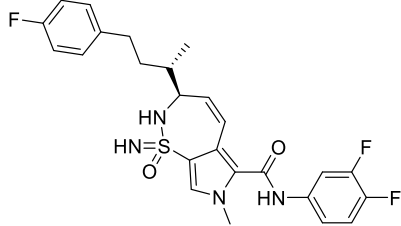
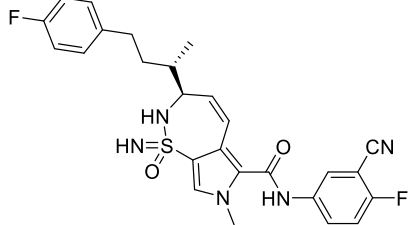
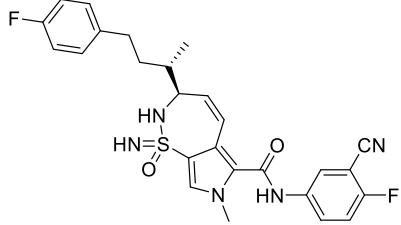
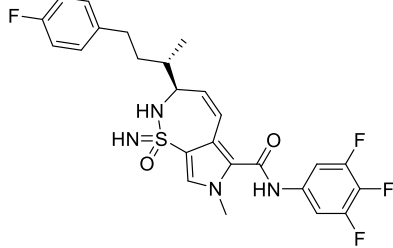
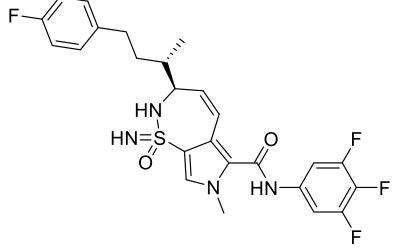
10oo1		437	Peak1 (HPLC)
10oo2		437	Peak2 (HPLC)
10pp1		443	Peak1 (HPLC)
10pp2		443	Peak2 (HPLC)
10qq1		450	Peak1 (HPLC)
10qq2		450	Peak2 (HPLC)
10rr1		451	Peak1 (HPLC)
10rr2		451	Peak2 (HPLC)

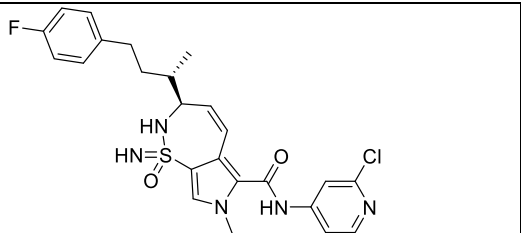
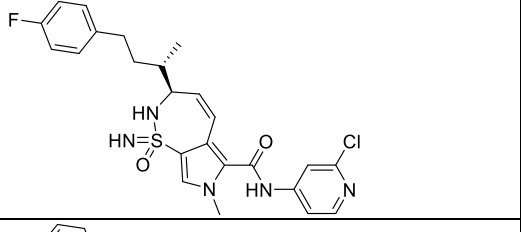
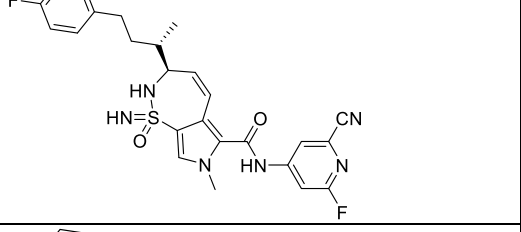
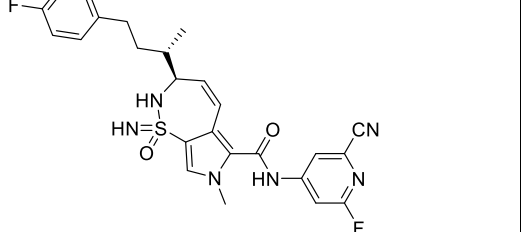
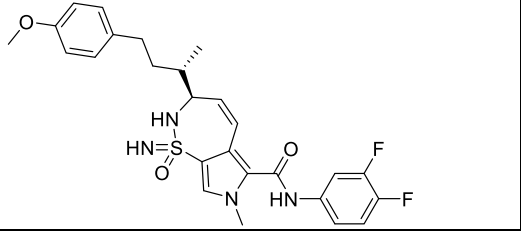
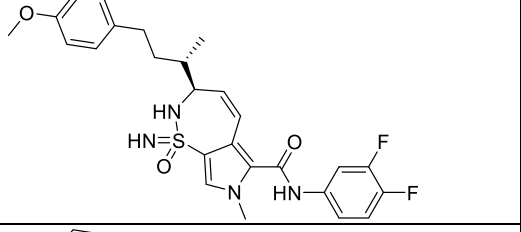
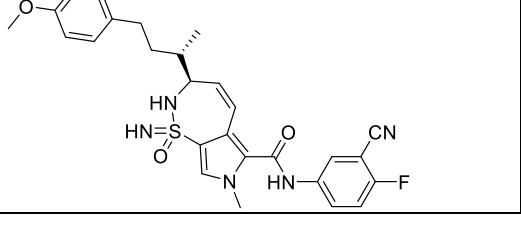
10ss1		443	Peak1 (HPLC)
10ss2		443	Peak2 (HPLC)
10tt1		450	Peak1 (HPLC)
10tt2		450	Peak2 (HPLC)
10uu1		451	Peak1 (HPLC)
10uu2		451	Peak2 (HPLC)
10vv1		493	Peak1 (HPLC)
10vv2		493	Peak2 (HPLC)

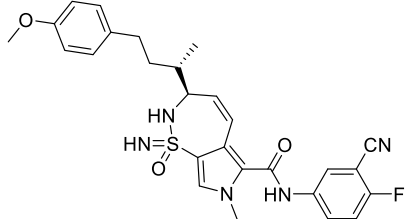
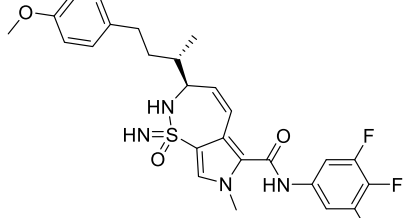
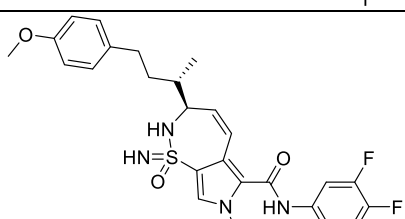
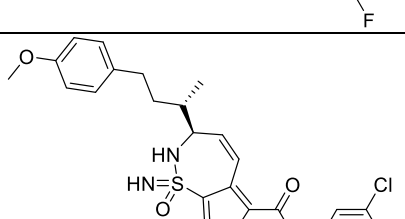
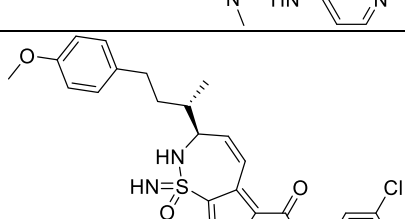
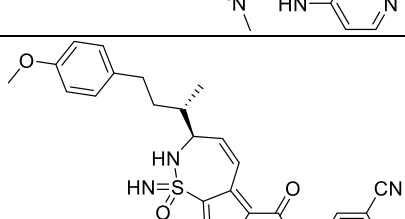
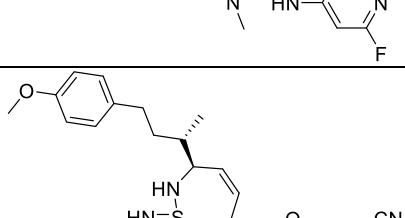
10ww1		500	Peak1 (HPLC)
10ww2		500	Peak2 (HPLC)
10xx1		501	Peak1 (HPLC)
10xx2		501	Peak2 (HPLC)
10yy1		493	Peak1 (HPLC)
10yy2		493	Peak2 (HPLC)
10zz1		500	Peak1 (HPLC)

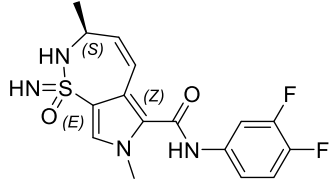
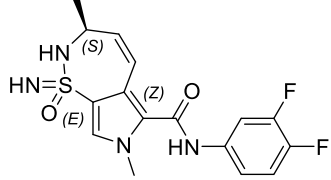
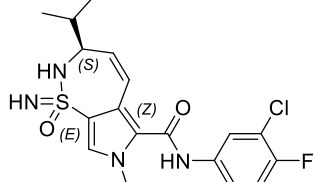
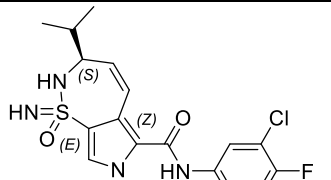
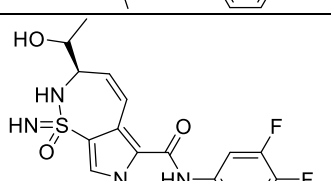
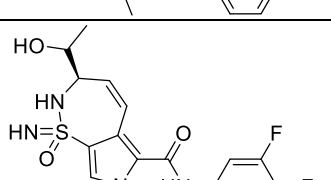
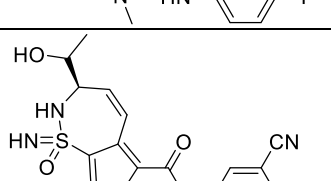
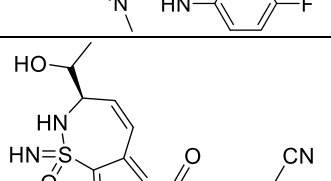
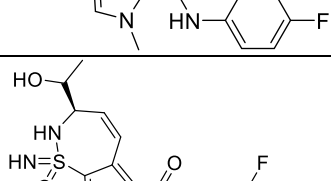
10ddd2		505	Peak2 (HPLC)
10eee1		486	Peak1 (HPLC)
10eee2		486	Peak2 (HPLC)
10fff1		495	Peak1 (HPLC)
10fff2		495	Peak2 (HPLC)
10ggg1		485	Peak1 (HPLC)
10ggg2		485	Peak2 (HPLC)

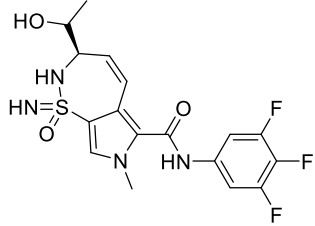
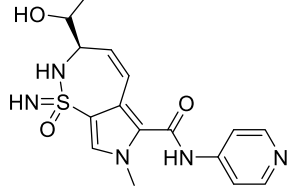
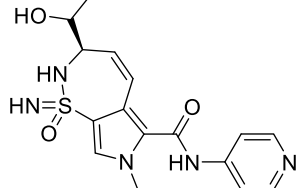
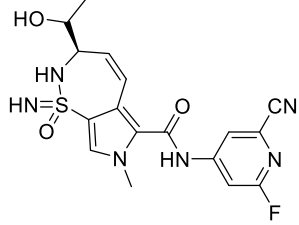
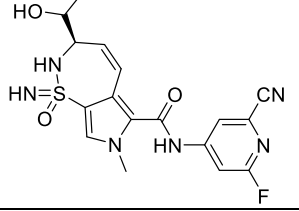
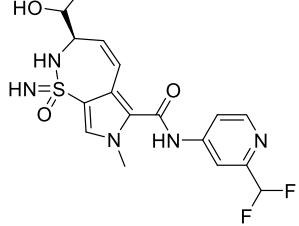
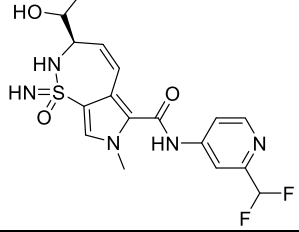
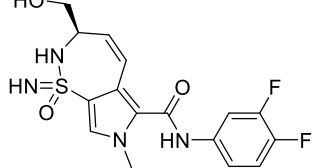
10hhh1		492	Peak1 (HPLC)
10hhh2		492	Peak2 (HPLC)
10iii1		503	Peak1 (HPLC)
10iii2		503	Peak2 (HPLC)
10jjj1		484	Peak1 (HPLC)
10jjj2		484	Peak2 (HPLC)
10kkk1		493	Peak1 (HPLC)

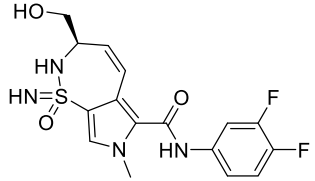
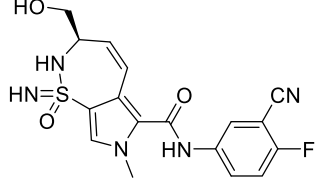
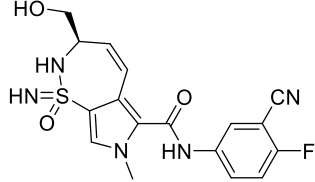
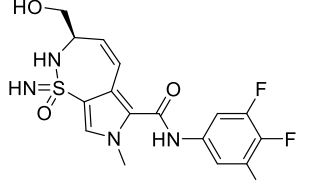
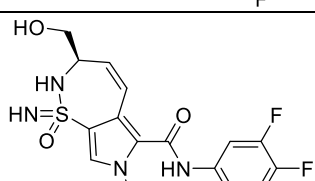
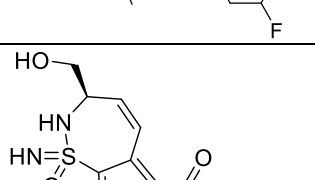
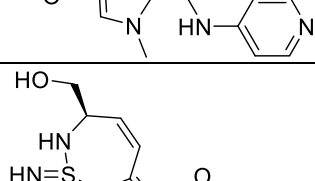
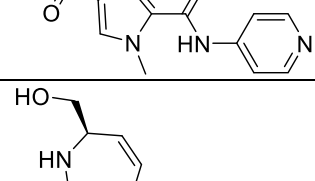
10kkk2		493	Peak2 (HPLC)
10mmm1		503	Peak1 (HPLC)
10mmm2		503	Peak2 (HPLC)
10nnn1		510	Peak1 (HPLC)
10nnn2		510	Peak2 (HPLC)
10ooo1		521	Peak1 (HPLC)
10ooo2		521	Peak2 (HPLC)

10ppp1		502	Peak1 (HPLC)
10ppp2		502	Peak2 (HPLC)
10qqq1		511	Peak1 (HPLC)
10qqq2		511	Peak2 (HPLC)
10rrr1		515	Peak1 (HPLC)
10rrr2		515	Peak2 (HPLC)
10sss1		522	Peak1 (HPLC)

10sss2		522	Peak2 (HPLC)
10ttt1		533	Peak1 (HPLC)
10ttt2		533	Peak2 (HPLC)
10uuu1		514	Peak1 (HPLC)
10uuu2		514	Peak2 (HPLC)
10vvv1		523	Peak1 (HPLC)
10vvv2		523	Peak2 (HPLC)

10www1		367	Peak1 (HPLC)
10www2		367	Peak2 (HPLC)
10xxx1		411	Peak1 (HPLC)
10xxx2		411	Peak2 (HPLC)
30a1		397	Peak1 (HPLC)
30a2		397	Peak2 (HPLC)
30b1		404	Peak1 (HPLC)
30b2		404	Peak2 (HPLC)
30c1		415	Peak1 (HPLC)

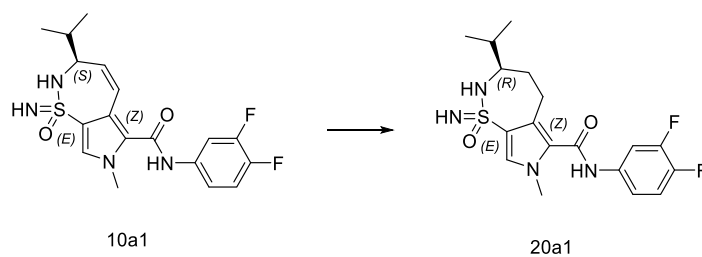
30c2		415	Peak2 (HPLC)
30d1		362	Peak1 (HPLC)
30d2		362	Peak2 (HPLC)
30e1		405	Peak1 (HPLC)
30e2		405	Peak2 (HPLC)
30f1		412	Peak1 (HPLC)
30f2		412	Peak2 (HPLC)
30g1		383	Peak1 (HPLC)

30g2		383	Peak2 (HPLC)
30h1		390	Peak1 (HPLC)
30h2		390	Peak2 (HPLC)
30i1		401	Peak1 (HPLC)
30i2		401	Peak2 (HPLC)
30j1		348	Peak1 (HPLC)
30j2		348	Peak2 (HPLC)
30k1		391	Peak1 (HPLC)

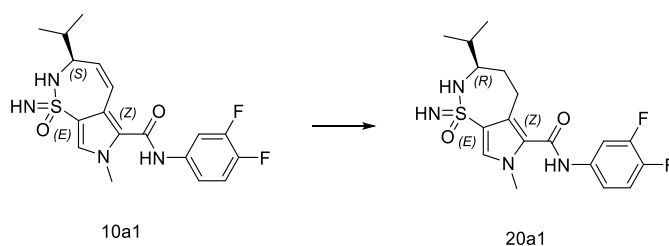
30k2		391	Peak2 (HPLC)
30m1		398	Peak1 (HPLC)
30m2		398	Peak2 (HPLC)

The following are the synthesis of 20 series compounds:

Example 72: Synthesis of compound 20a1



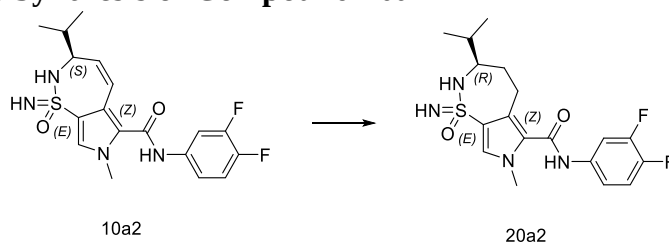
Step 1



Compound 10a1 (20 mg) was dissolved in methanol (5 mL), and then Pd/C (5 mg) was added to the reaction system. The reaction was performed in hydrogen atmosphere at room temperature for 6 h. The crude product was column chromatography (n-heptane: ethyl acetate = 1: 3) purified to provide the target product 20a1 (11 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.56 (s, 1H), 7.88–7.83 (m, 1H), 7.63 (s, 2H), 7.46–7.42 (m, 1H), 7.21–6.96 (m, 1H), 3.72 (s, 3H), 3.12 – 3.09 (m, 1H), 3.00 (dd, *J* = 15.0, 6.7 Hz, 1H), 2.89 – 2.78(m, 1H), 1.89–

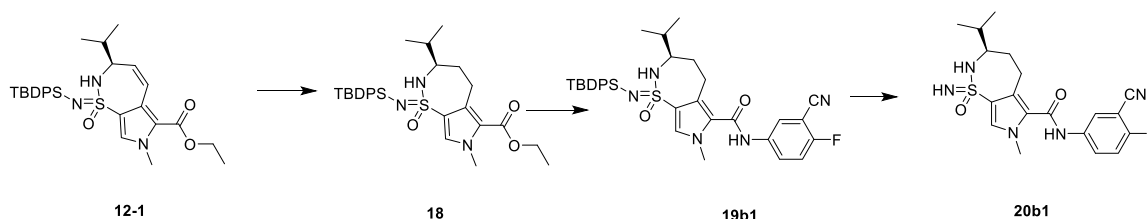
1.85 (m, 1H), 1.69-1.50 (m, 1H), 1.43 (q, $J = 12.0$ Hz, 1H), 0.92 (dd, $J = 6.8, 3.5$ Hz, 6H). MS ($M+1=397$).

Example 73: Synthesis of Compound 20a2

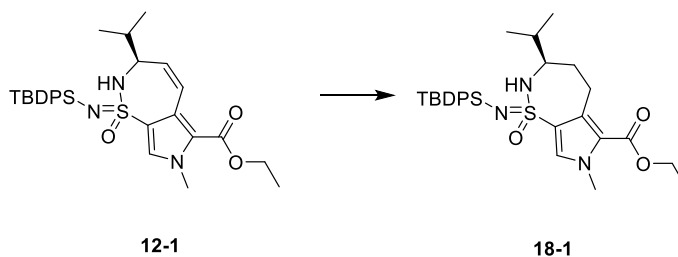


The reaction was carried out according to the step 6 of example 1, all the conditions were the same except the compound 10a2 was used instead of 10a1, purified via column chromatography (n-heptane: ethyl acetate = 1: 1) to provide target product 20a2 (8mg). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.67 (s, 1H), 8.20– 8.18 (m, 1H), 7.97 (d, $J = 3.7$ Hz, 1H), 7.68– 7.59 (m, 1H), 7.55 (d, $J = 10.3$ Hz, 1H), 3.76 (s, 3H), 3.04 – 2.92 (m, 2H), 2.85 (dd, $J = 15.0, 6.7$ Hz, 1H), 1.90 – 1.83 (m, 1H), 1.73 (dd, $J = 14.3, 6.7$ Hz, 1H), 1.69-1.50 (m, 1H), 1.45 (q, $J = 12.0$ Hz, 1H), 0.89 (dd, $J = 6.8, 3.5$ Hz, 6H). MS ($M+1=397$).

Example 74: Synthesis of compound 20b1



Step 1

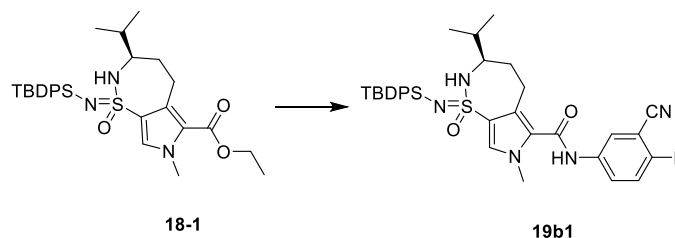


Compound 1 (150 mg) was dissolved in methanol (8 mL), and Pd / C (30 mg) was added to the reaction system, and purged with nitrogen for three times, then purged with hydrogen for three times. The reaction was carried out at room temperature (25 °C) for 18h with a hydrogen balloon, and the raw material was monitored to have been consumed with TLC. The reaction was suction filtrated, and the solvent was evaporated in vacuum, and purified via column chromatography (n-heptane: ethyl acetate = 5: 1) to obtain the target product 130

mg.

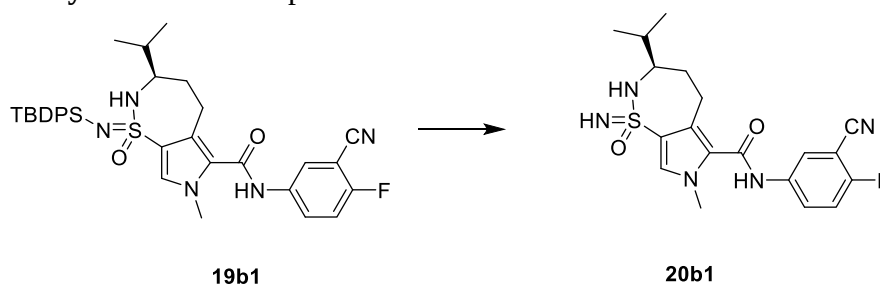
MS ($M + 1 = 552$).

Step 2



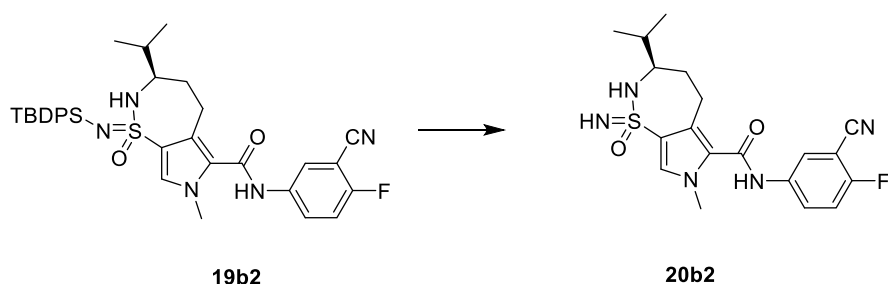
Compound 12-1 (45 mg) (lower point shown by TLC) and 3-cyano-4-fluoroaniline (23 mg) was dissolved in THF (6 mL), then the system was cooled to 0 °C. 8 eq of NaHMDS was added to the reaction system to react at 0 °C for 1 h. Water (20 mL) was added to the reaction system, and extracted with ethyl acetate (3 * 30 mL), dried over anhydrous sodium sulfate, the solvent was evaporated in vacuum, and purified by column chromatography to provide 18 mg of yellow oil. MS ($M + 1 = 640$).

Step 3: Synthesis of compound 20b1



Compound 2 (18 mg) was dissolved in THF (3 mL), and 50 eq of 3HF.TEA was added dropwise to the reaction system. The reaction was performed at room temperature for 3 days. The mixture was purified by preparation TLC and freeze-dried to obtain 4.0 mg of the target product as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 10.77(s, 1H), 8.20 (dd, $J = 5.8, 2.7$ Hz, 1H), 7.98 (ddd, $J = 9.2, 4.9, 2.7$ Hz, 1H), 7.90 (s, 1H), 7.51 (t, $J = 9.1$ Hz, 1H), 3.77 (s, 3H), 3.11 – 3.02 (m, 2H), 2.89 – 2.87 (m, 1H), 1.97-1.92 (m, 1H), 1.78-1.73 (m, 1H), 1.60-1.51 (m, 1H), 0.96 (dd, $J = 6.8, 3.4$ Hz, 6H). **Ms(ESI)** $m/z = 404(M+1)$

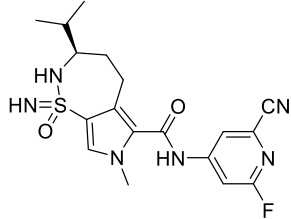
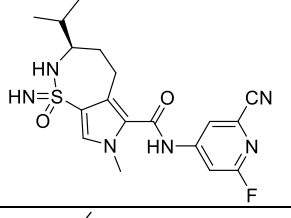
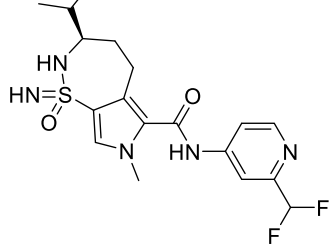
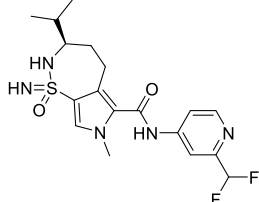
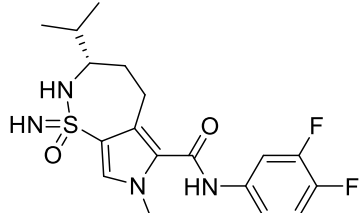
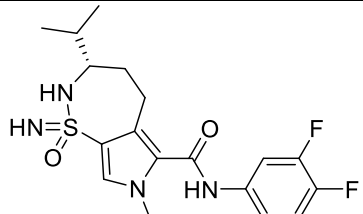
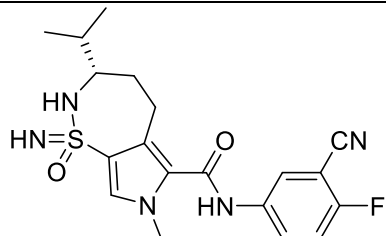
Example 75: Synthesis of compound 20b2



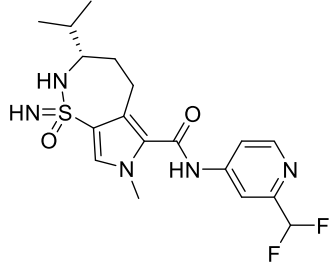
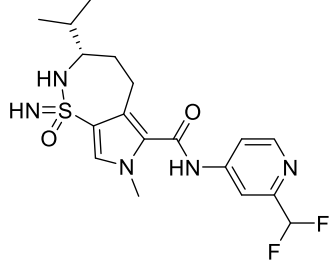
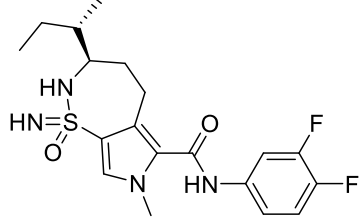
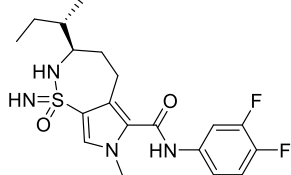
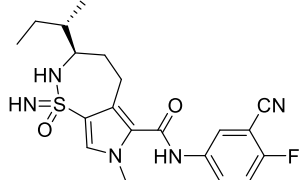
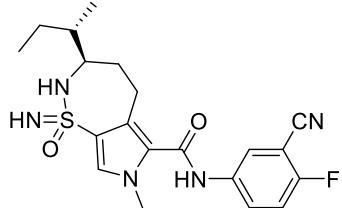
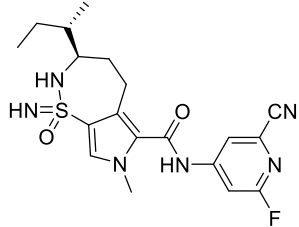
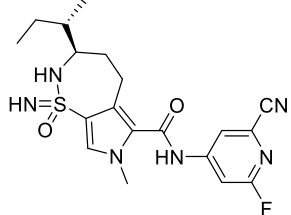
The reaction was carried out according to the step 3 of example 74, all the conditions were the same except the compound 19b2 was used instead of 19b1, column chromatography (n-heptane: ethyl acetate = 1: 1) purified to provide target product 20b2 (8mg). ^1H NMR (400 MHz, DMSO- d_6) δ 10.67 (s, 1H), 8.19 (dd, J = 5.8, 2.7 Hz, 1H), 7.97 (ddd, J = 9.2, 4.9, 2.7 Hz, 1H), 7.68 (s, 1H), 7.57 (t, J = 9.1 Hz, 1H), 3.76 (s, 3H), 3.04-2.92(m, 2H), 2.85 – 2.83 (m, 1H), 1.90-1.83 (m, 1H), 1.74-1.69 (m, 1H), 1.67-1.46 (m, 1H), 0.89 (dd, J = 6.8, 3.4 Hz, 6H). Ms(ESI) m/z = 404(M+1)

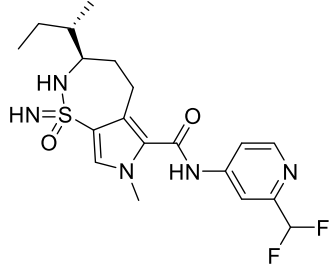
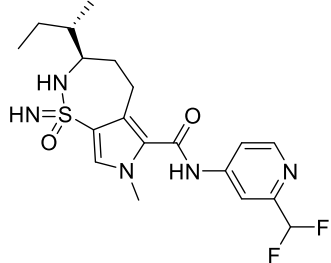
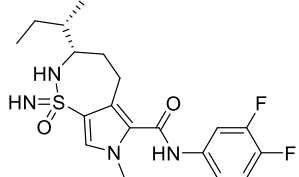
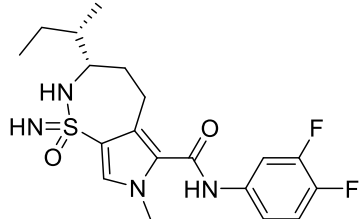
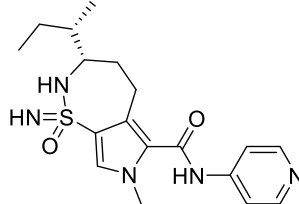
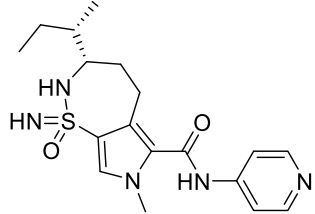
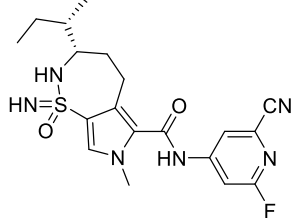
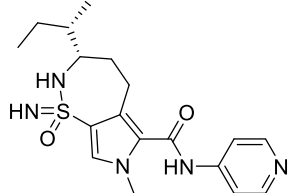
The following 20 and 40 series compounds are synthesized according to the method of example 72 or 74:

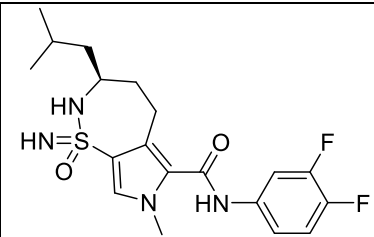
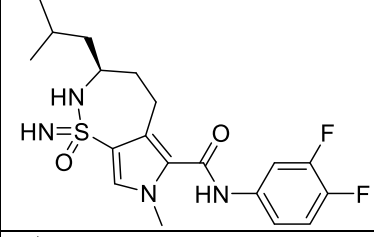
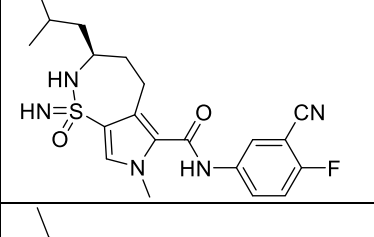
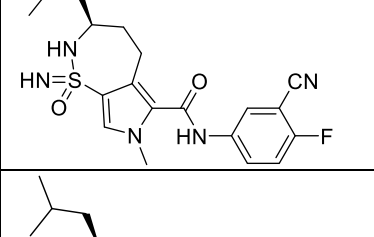
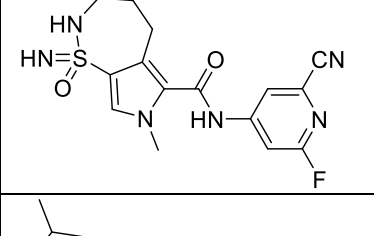
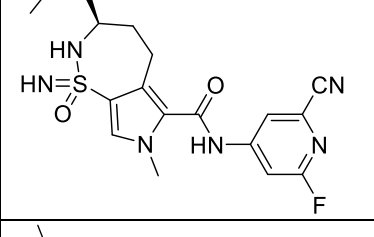
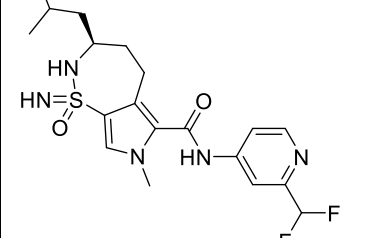
No.	Structure	Mass Spectrum ESI-MS, (M + H)	Remark
20c1		415	Peak1 (HPLC)
20c2		415	Peak2 (HPLC)
20d1		362	Peak1 (HPLC)
20d2		362	Peak2 (HPLC)

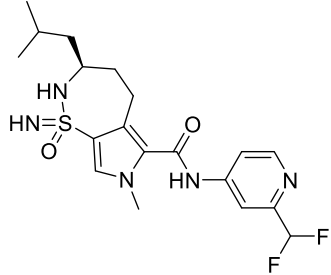
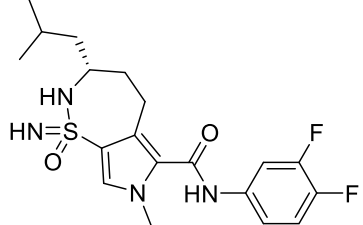
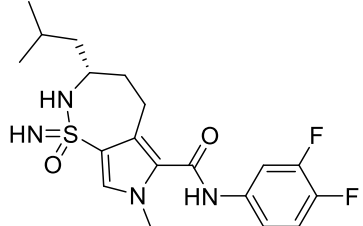
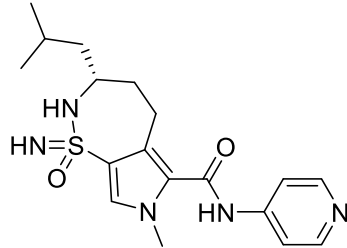
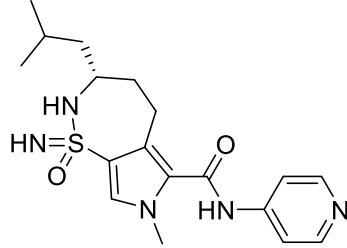
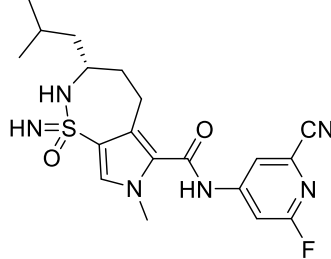
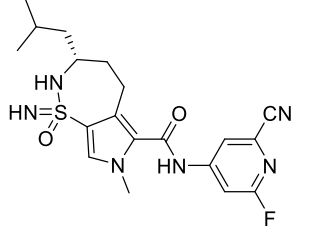
20e1		405	Peak1 (HPLC)
20e2		405	Peak2 (HPLC)
20f1		412	Peak1 (HPLC)
20f2		412	Peak2 (HPLC)
20g1		397	Peak1 (HPLC)
20g2		397	Peak2 (HPLC)
20h1		404	Peak1 (HPLC)

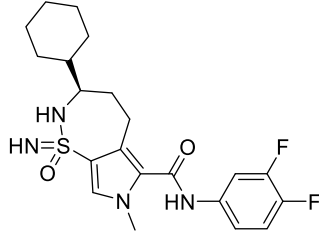
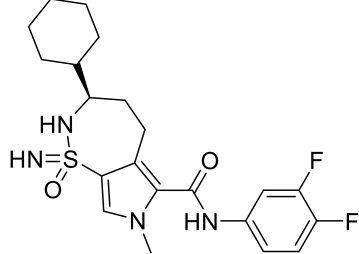
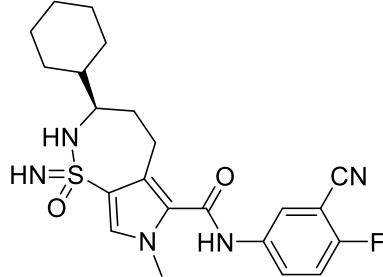
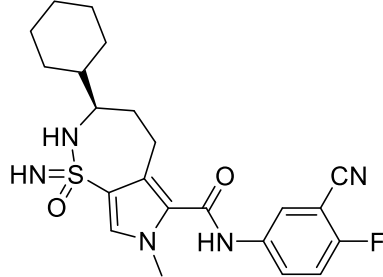
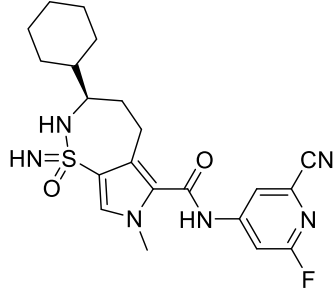
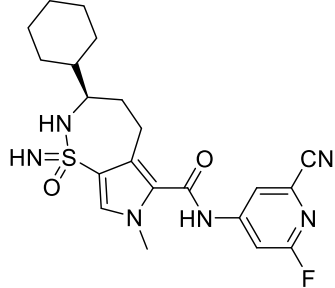
20h2		404	Peak2 (HPLC)
20i1		415	Peak1 (HPLC)
20i2		415	Peak2 (HPLC)
20j1		362	Peak1 (HPLC)
20j2		362	Peak2 (HPLC)
20k1		405	Peak1 (HPLC)
20k2		405	Peak2 (HPLC)

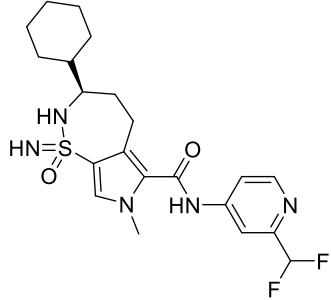
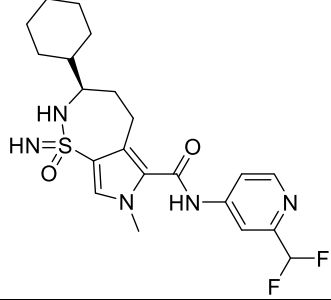
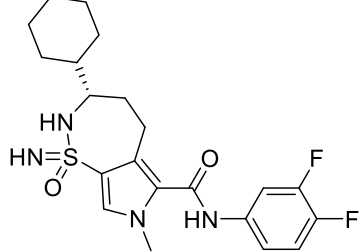
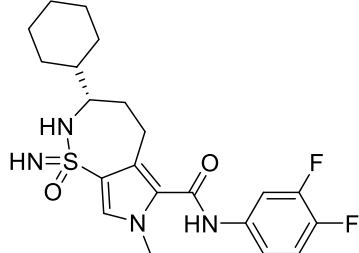
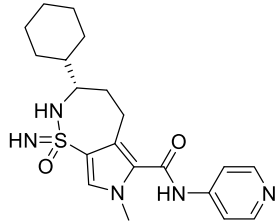
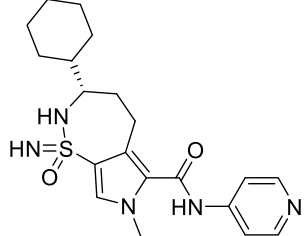
20m1		412	Peak1 (HPLC)
10m2		412	Peak2 (HPLC)
20n1		411	Peak1 (HPLC)
20n2		411	Peak2 (HPLC)
20o1		418	Peak1 (HPLC)
20o2		418	Peak2 (HPLC)
20p1		419	Peak1 (HPLC)
20p2		419	Peak2 (HPLC)

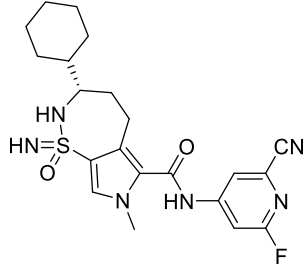
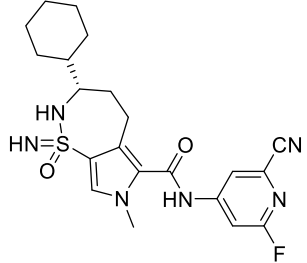
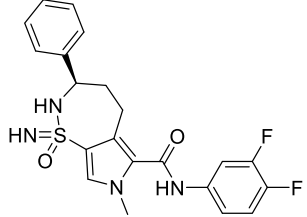
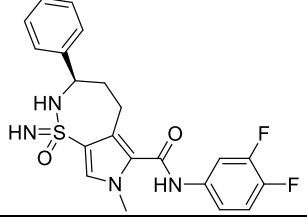
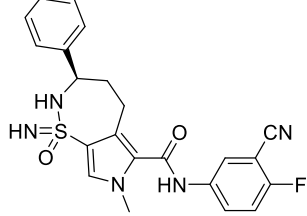
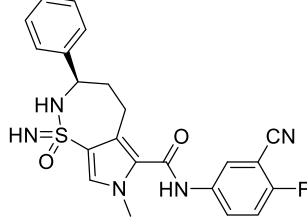
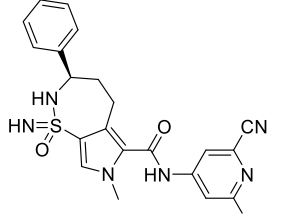
20q1		426	Peak1 (HPLC)
20q2		426	Peak2 (HPLC)
20r1		411	Peak1 (HPLC)
20r2		411	Peak2 (HPLC)
20s1		376	Peak1 (HPLC)
20s2		376	Peak2 (HPLC)
20t1		419	Peak1 (HPLC)
20t2		419	Peak2 (HPLC)

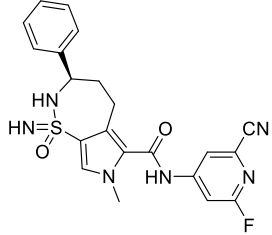
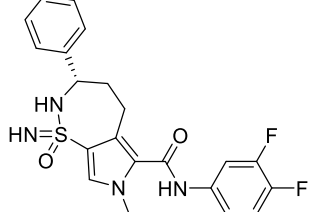
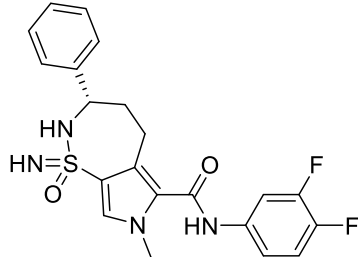
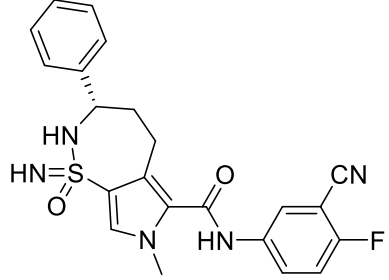
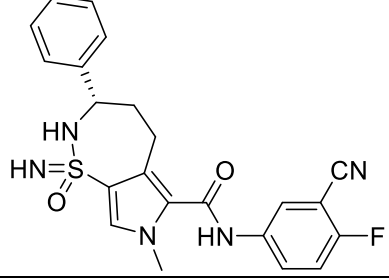
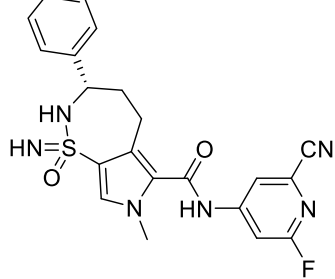
20u1		411	Peak1 (HPLC)
20u2		411	Peak2 (HPLC)
20v1		418	Peak1 (HPLC)
20v2		418	Peak2 (HPLC)
20w1		419	Peak1 (HPLC)
20w2		419	Peak2 (HPLC)
20x1		426	Peak1 (HPLC)

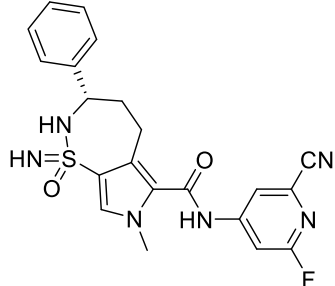
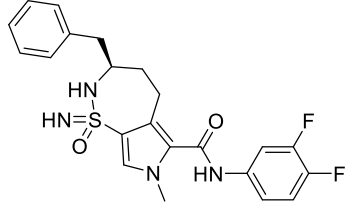
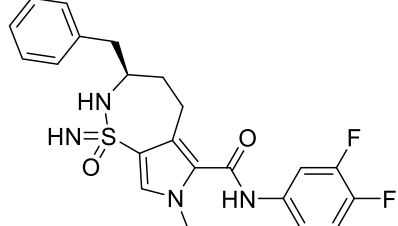
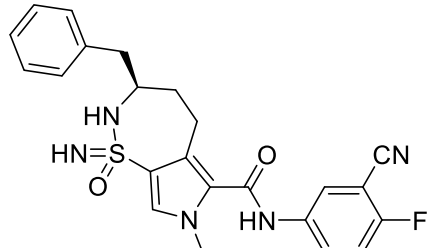
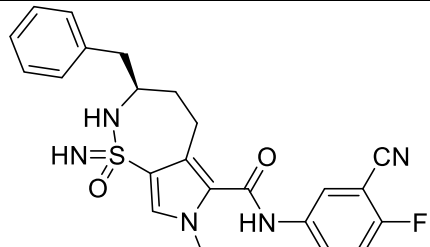
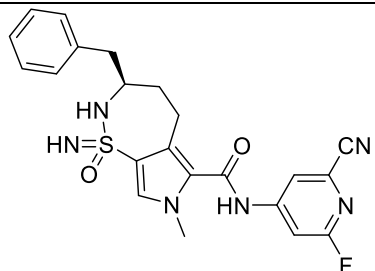
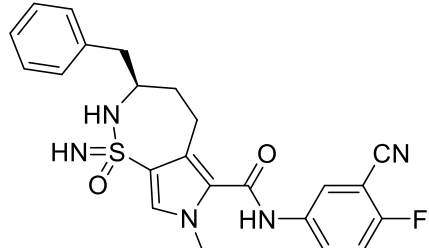
20x2		426	Peak2 (HPLC)
20y1		411	Peak1 (HPLC)
20y2		411	Peak2 (HPLC)
20z1		376	Peak1 (HPLC)
20z2		376	Peak2 (HPLC)
20aa1		419	Peak1 (HPLC)
20aa2		419	Peak2 (HPLC)

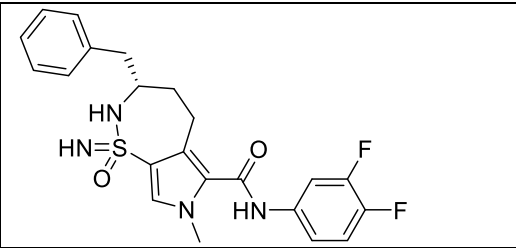
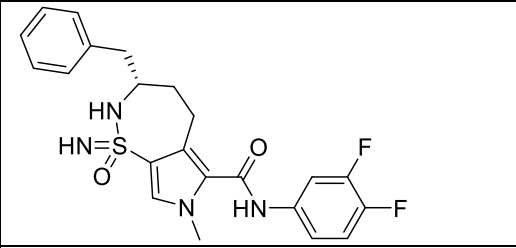
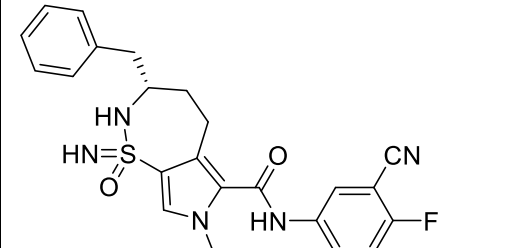
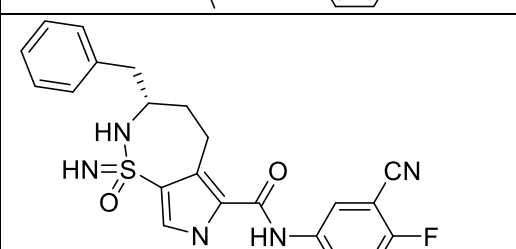
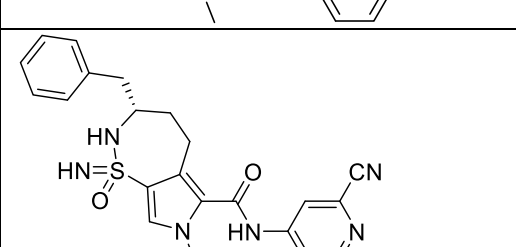
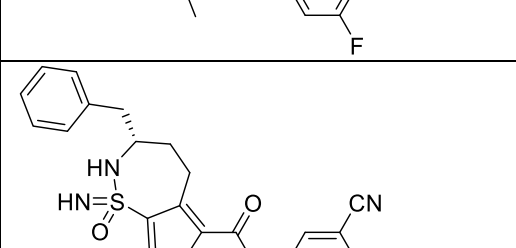
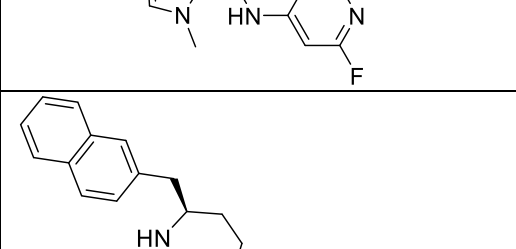
20bb1		437	Peak1 (HPLC)
20bb2		437	Peak2 (HPLC)
20cc1		444	Peak1 (HPLC)
20cc2		444	Peak2 (HPLC)
20dd1		445	Peak1 (HPLC)
20dd2		445	Peak2 (HPLC)

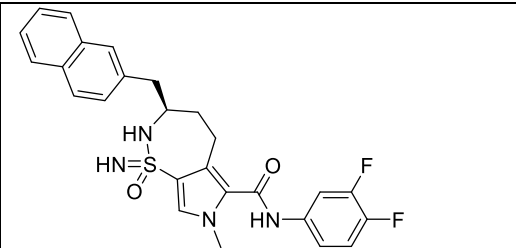
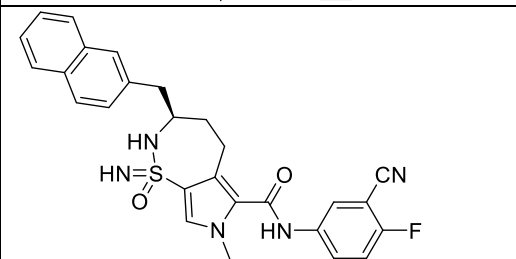
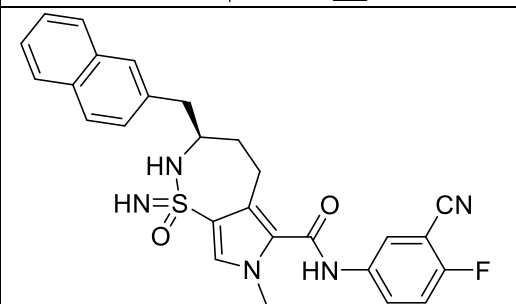
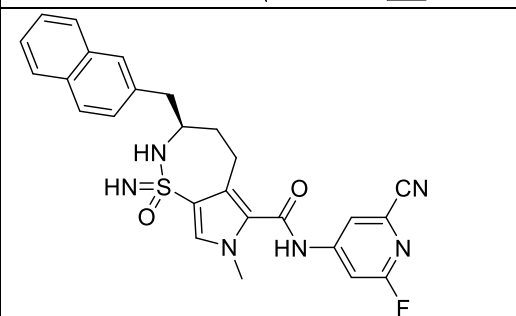
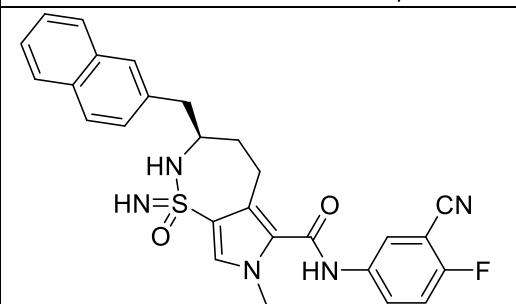
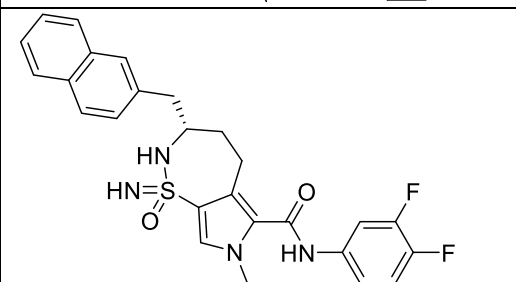
20ee1		452	Peak1 (HPLC)
20ee2		452	Peak2 (HPLC)
20ff1		437	Peak1 (HPLC)
20ff2		437	Peak2 (HPLC)
20gg1		402	Peak1 (HPLC)
20gg2		402	Peak2 (HPLC)

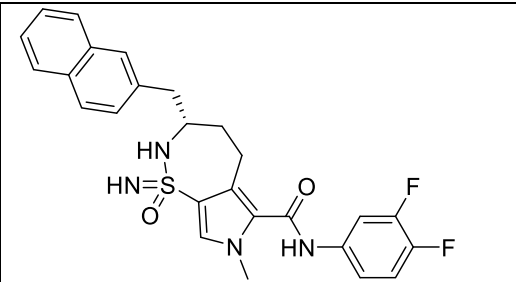
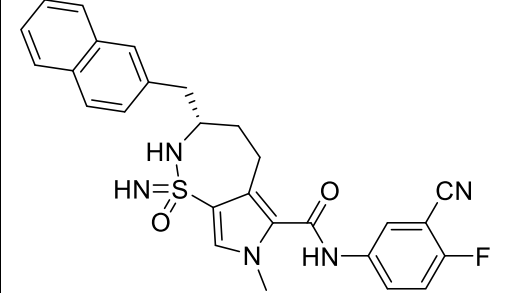
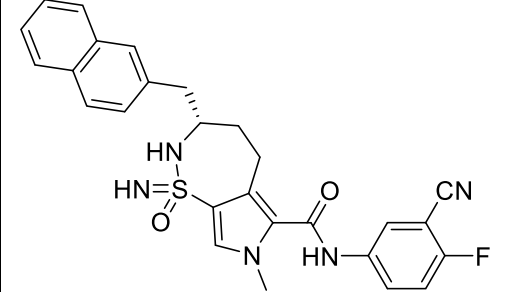
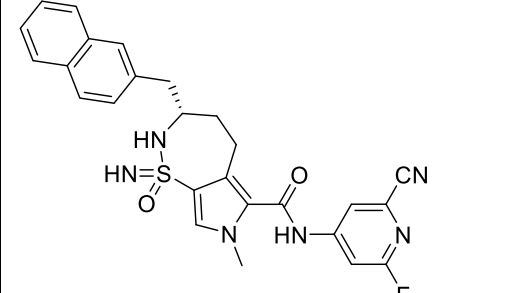
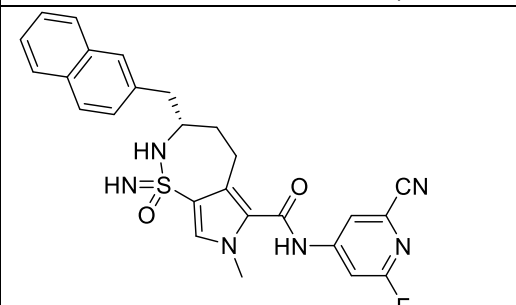
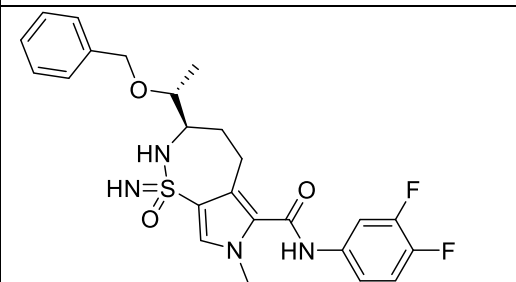
20hh1		445	Peak1 (HPLC)
20hh2		445	Peak2 (HPLC)
20ii1		431	Peak1 (HPLC)
20ii2		431	Peak2 (HPLC)
20jj1		438	Peak1 (HPLC)
20jj2		438	Peak2 (HPLC)
20kk1		439	Peak1 (HPLC)

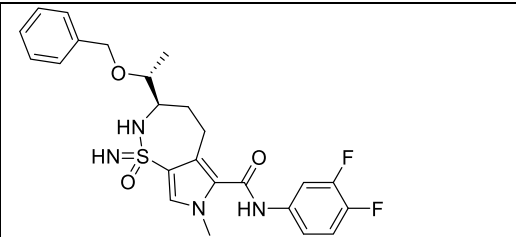
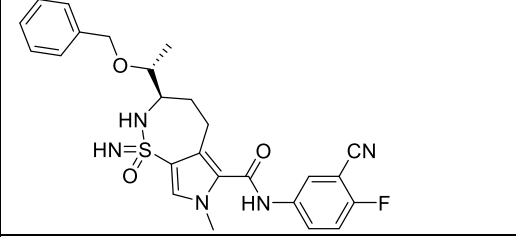
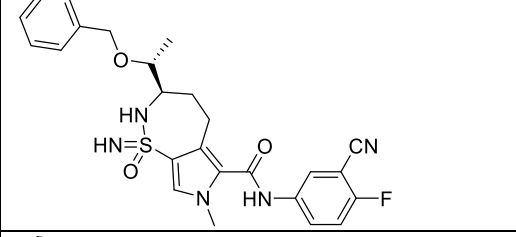
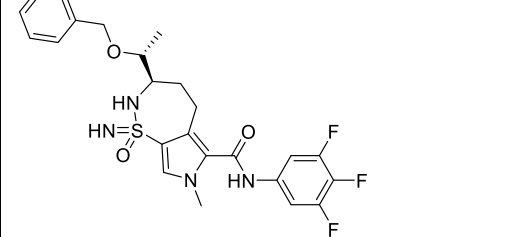
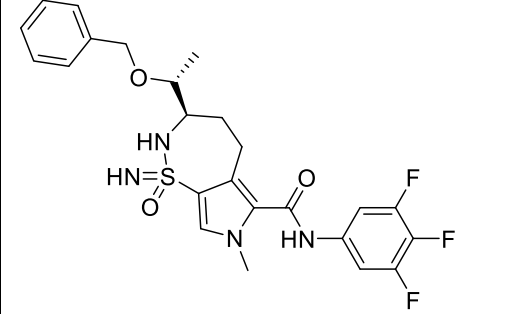
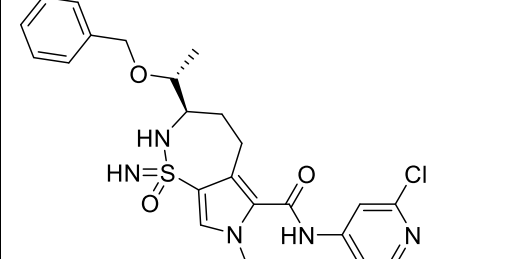
20kk2		439	Peak2 (HPLC)
20mm1		431	Peak1 (HPLC)
20mm2		431	Peak2 (HPLC)
20nn1		438	Peak1 (HPLC)
20nn2		438	Peak2 (HPLC)
20oo1		439	Peak1 (HPLC)

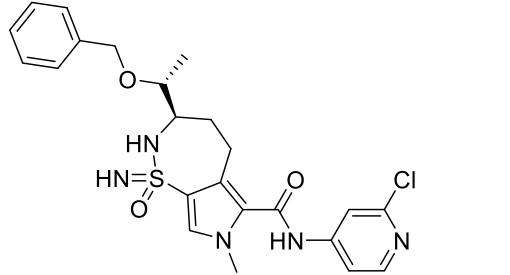
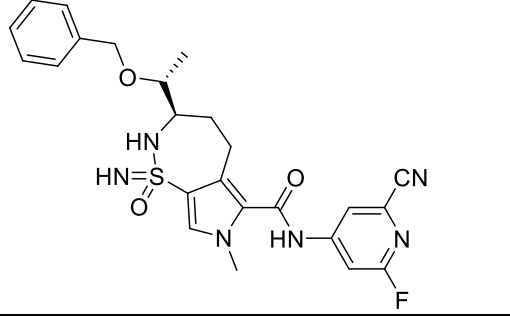
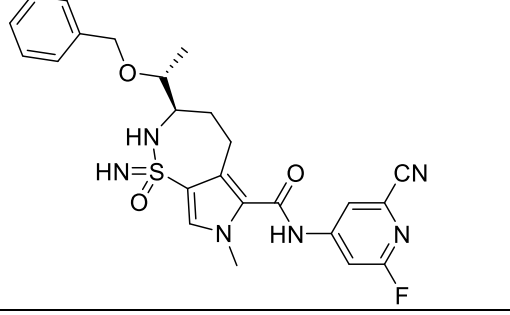
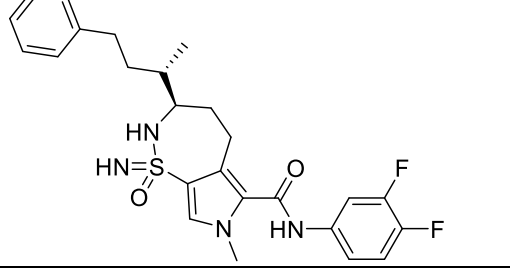
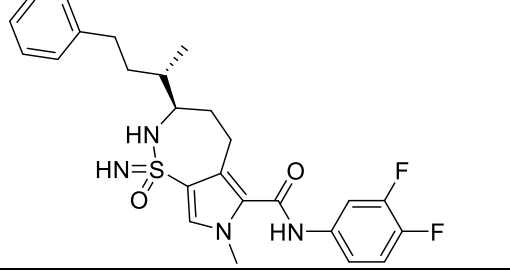
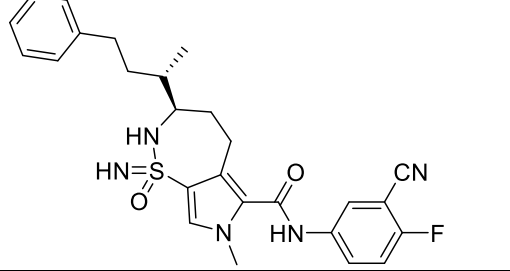
20oo2		439	Peak2 (HPLC)
20pp1		445	Peak1 (HPLC)
20pp2		445	Peak2 (HPLC)
20qq1		452	Peak1 (HPLC)
20qq2		452	Peak2 (HPLC)
20rr1		453	Peak1 (HPLC)
20rr2		453	Peak2 (HPLC)

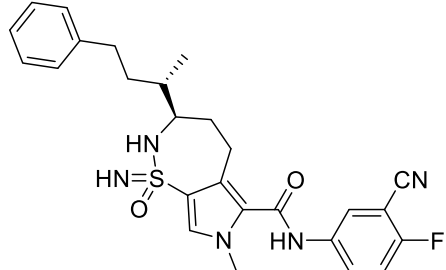
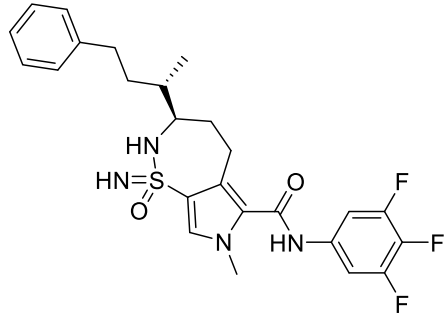
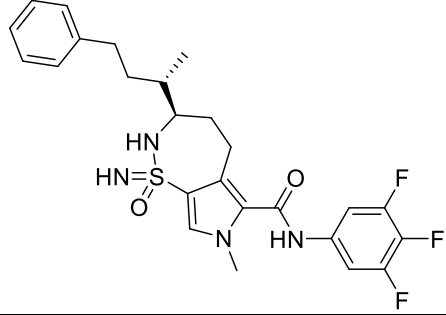
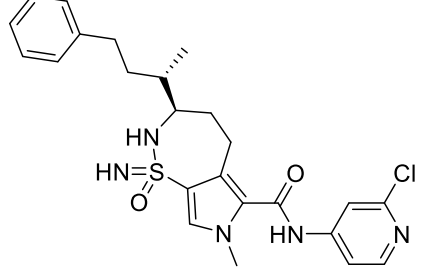
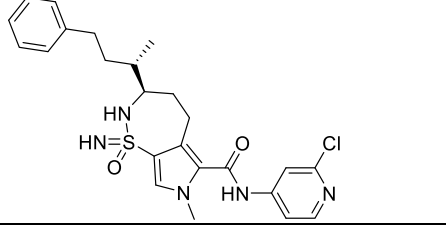
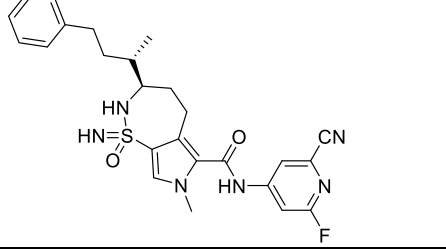
20ss1		445	Peak1 (HPLC)
20ss2		445	Peak2 (HPLC)
20tt1		452	Peak1 (HPLC)
20tt2		452	Peak2 (HPLC)
20uu1		453	Peak1 (HPLC)
20uu2		453	Peak2 (HPLC)
20vv1		495	Peak1 (HPLC)

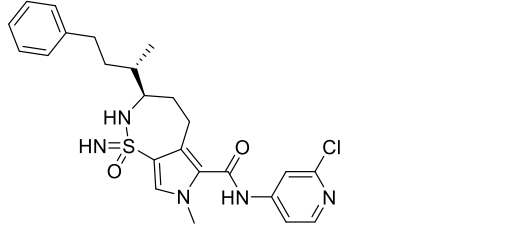
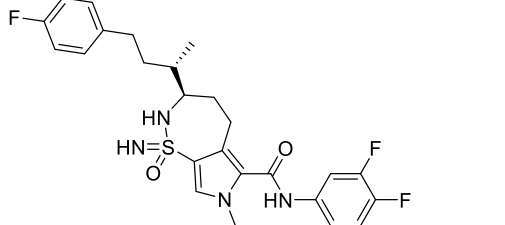
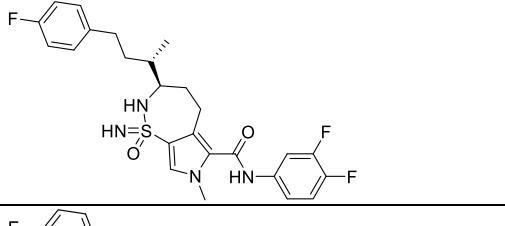
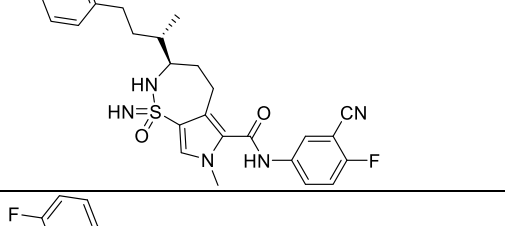
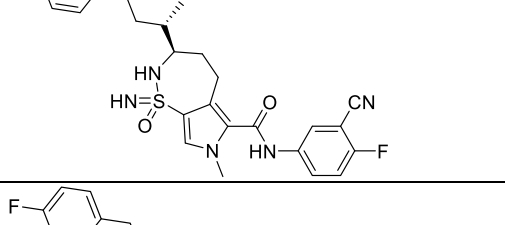
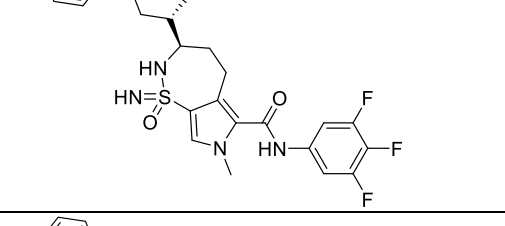
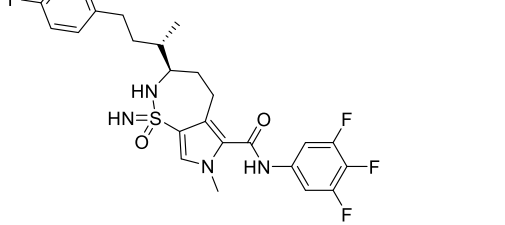
20vv2		495	Peak2 (HPLC)
20ww1		502	Peak1 (HPLC)
20ww2		502	Peak2 (HPLC)
20xx1		503	Peak1 (HPLC)
20xx2		503	Peak2 (HPLC)
20yy1		495	Peak1 (HPLC)

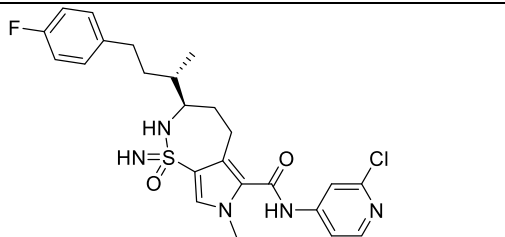
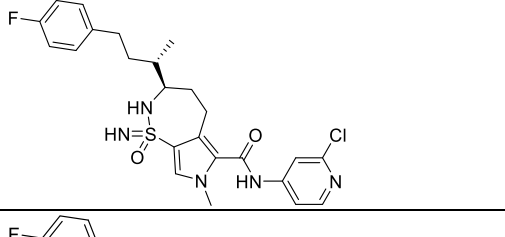
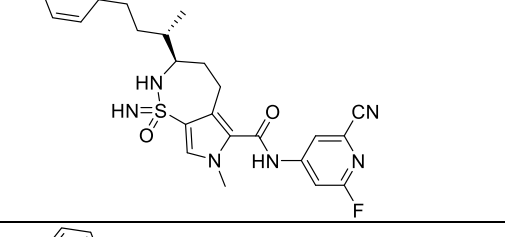
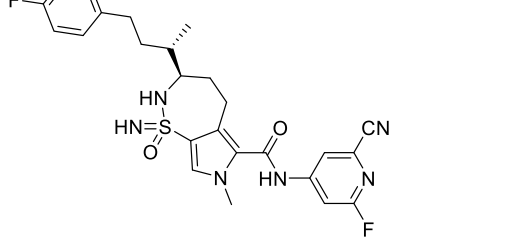
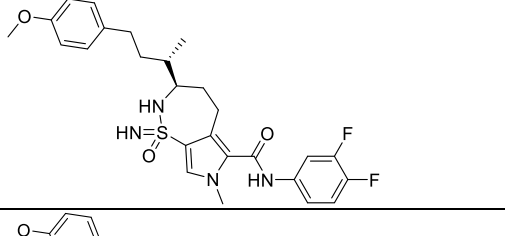
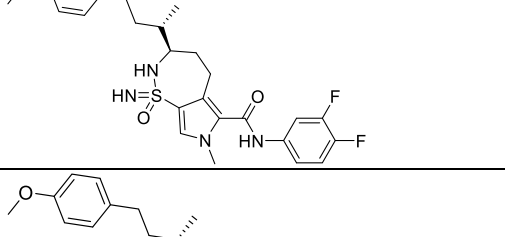
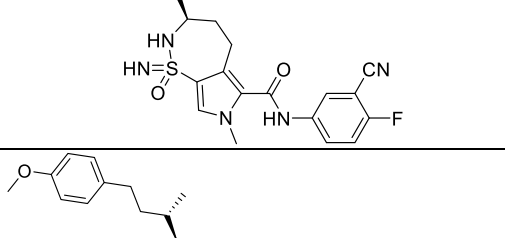
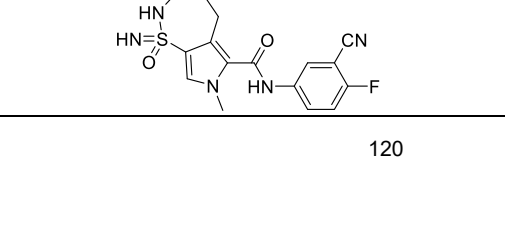
20yy2		495	Peak2 (HPLC)
20zz1		502	Peak1 (HPLC)
20zz2		502	Peak2 (HPLC)
20aaa1		503	Peak1 (HPLC)
20aaa2		503	Peak2 (HPLC)
20bbb1		489	Peak1 (HPLC)

20bbb2		489	Peak2 (HPLC)
20ccc1		496	Peak1 (HPLC)
20ccc2		496	Peak2 (HPLC)
20ddd1		507	Peak1 (HPLC)
20ddd2		507	Peak2 (HPLC)
20eee1		488	Peak1 (HPLC)

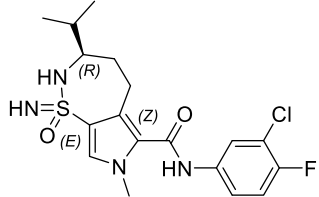
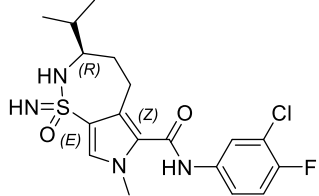
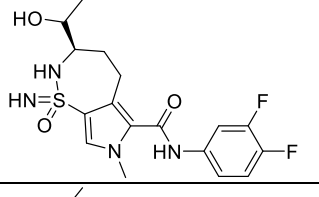
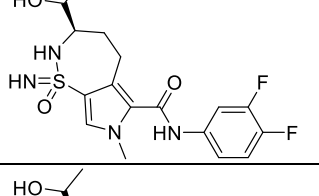
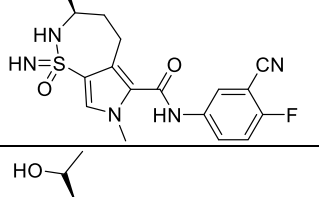
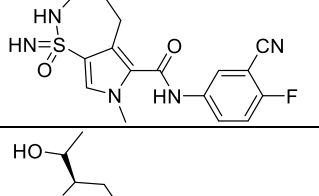
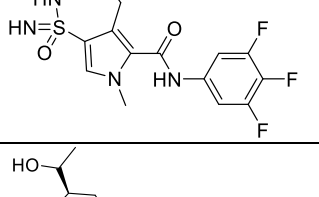
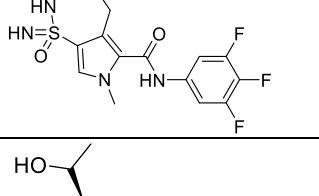
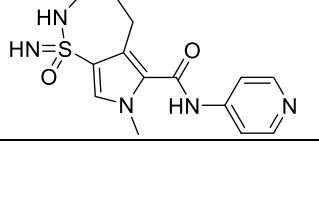
20eee2		488	Peak2 (HPLC)
20fff1		497	Peak1 (HPLC)
20fff2		497	Peak2 (HPLC)
20ggg1		486	Peak1 (HPLC)
20ggg2		486	Peak2 (HPLC)
20hhh1		494	Peak1 (HPLC)

20hhh2		494	Peak2 (HPLC)
20iii1		505	Peak1 (HPLC)
20iii2		505	Peak2 (HPLC)
20jjj1		486	Peak1 (HPLC)
20jjj2		486	Peak2 (HPLC)
20kkk1		495	Peak1 (HPLC)

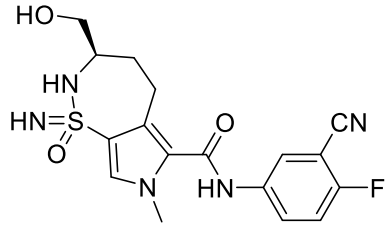
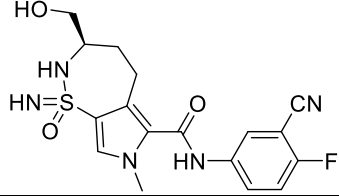
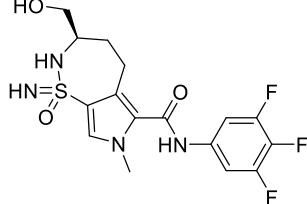
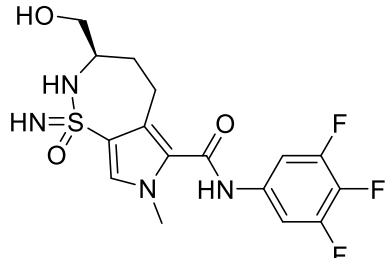
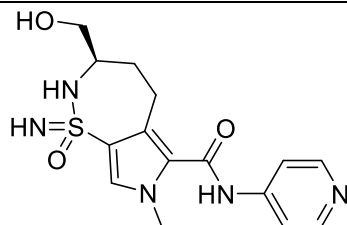
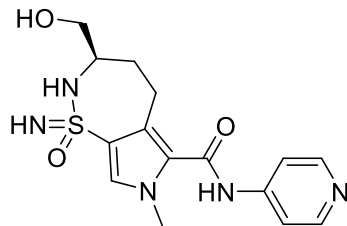
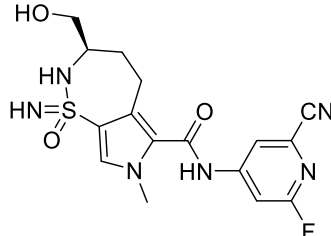
20kkk2		495	Peak2 (HPLC)
20mmm1		505	Peak1 (HPLC)
20mmm2		505	Peak2 (HPLC)
20nnn1		512	Peak1 (HPLC)
20nnn2		512	Peak2 (HPLC)
20ooo1		523	Peak1 (HPLC)
20ooo2		523	Peak2 (HPLC)

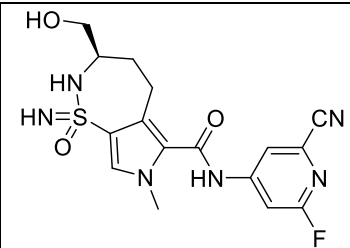
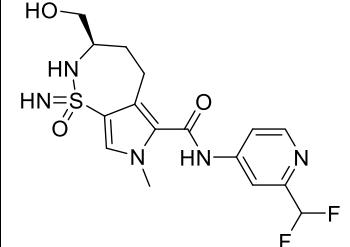
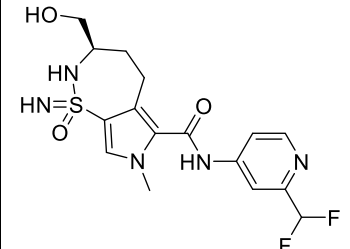
20ppp1		504	Peak1 (HPLC)
20ppp2		504	Peak2 (HPLC)
20qqq1		513	Peak1 (HPLC)
20qqq2		513	Peak2 (HPLC)
20rrr1		517	Peak1 (HPLC)
20rrr2		517	Peak2 (HPLC)
20sss1		524	Peak1 (HPLC)
20sss2		524	Peak2 (HPLC)

20ttt1		535	Peak1 (HPLC)
20ttt2		535	Peak2 (HPLC)
20uuu1		516	Peak1 (HPLC)
20uuu2		516	Peak2 (HPLC)
20vvv1		525	Peak1 (HPLC)
20vvv2		525	Peak2 (HPLC)
20www1		369	Peak1 (HPLC)
20www2		369	Peak2 (HPLC)

20xxx1		413	Peak1 (HPLC)
20xxx2		413	Peak2 (HPLC)
40a1		399	Peak1 (HPLC)
40a2		399	Peak2 (HPLC)
40b1		406	Peak1 (HPLC)
40b2		406	Peak2 (HPLC)
40c1		417	Peak1 (HPLC)
40c2		417	Peak2 (HPLC)
40d1		364	Peak1 (HPLC)

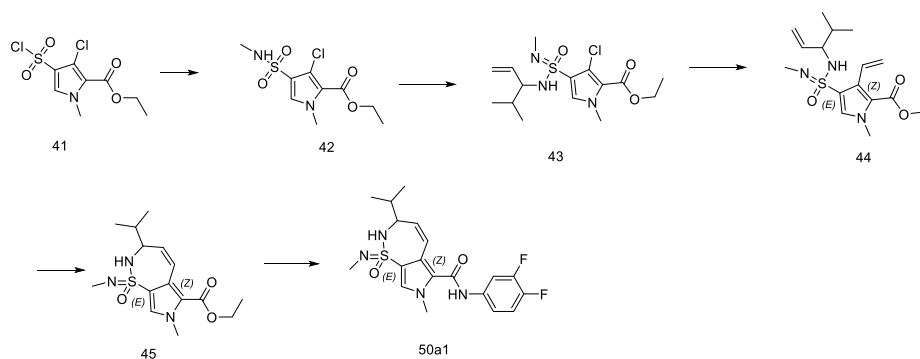
40d2		364	Peak2 (HPLC)
40e1		407	Peak1 (HPLC)
40e2		407	Peak2 (HPLC)
40f1		414	Peak1 (HPLC)
40f2		414	Peak2 (HPLC)
40g1		385	Peak1 (HPLC)
40g2		385	Peak2 (HPLC)

40h1		392	Peak1 (HPLC)
40h2		392	Peak2 (HPLC)
40i1		403	Peak1 (HPLC)
40i2		403	Peak2 (HPLC)
40j1		350	Peak1 (HPLC)
40j2		350	Peak2 (HPLC)
40k1		393	Peak1 (HPLC)

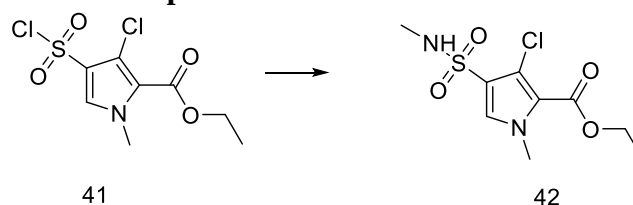
40k2		393	Peak2 (HPLC)
40m1		400	Peak1 (HPLC)
40m2		400	Peak2 (HPLC)

The following are the synthesis of 50 series compounds:

Example 167: Synthesis of compound 50a1

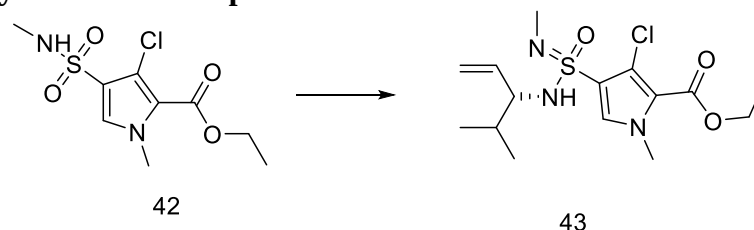


Step 1: Synthesis of Compound 42



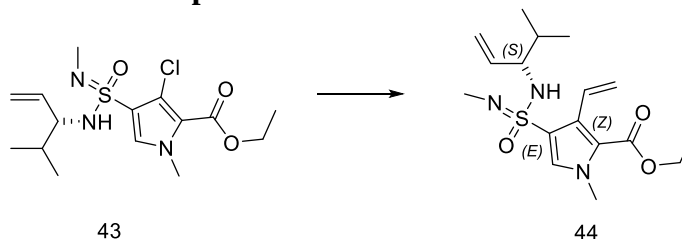
Compound 41 (10 g) was dissolved in dichloromethane (40 mL), and methylamine aqueous solution (30 mL) was added dropwise to the reaction system at room temperature. The reaction was carried out for 5 h at room temperature, then suction filtrated, and the filter cake was washed with water (5mL) to provide 5g of light yellow solid 42, MS ($M + 1 = 281$).

Step 2: Synthesis of Compound 43



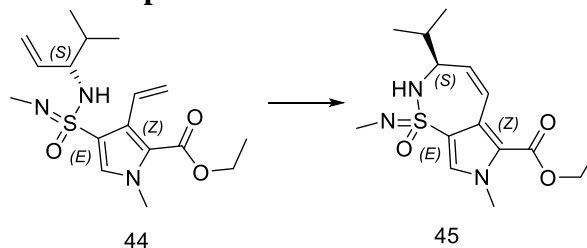
The PPh_3Cl_2 chloroform solution (80 mL) was cooled to 0 °C, and then triethylamine (7 mL) was added, stirred for 10 minutes and then compound 42 (5.0g) was added at 0 °C. After stirred for 20 minutes, 2-isopropyl-3-propenylamine (5g) was added to the reaction system and reacted at room temperature for 18h. Water (20 mL) and ethyl acetate (3 * 25mL) were added to the reaction system for extraction. The organic phase was dried and the solvent was evaporated in vacuum. Crude product was purified by column chromatography (n-heptane: ethyl acetate = 1: 5) to provide the product **43** (400 mg). MS ($M + 1 = 362$).

Step 3: Synthesis of Compound 44



Compound 43 (1.8 g), tetrakis (triphenylphosphine) palladium (100 mg), vinyl borate (900 mg), and cesium carbonate (2.7 g) were dissolved in DMF (410 mL), and the mixture was reacted at 100 °C under the protection of nitrogen for 15 h. The reaction was quenched with an aqueous solution, extracted with ethyl acetate, and the organic phase was dried and the solvent was evaporated in vacuum. The resulting crude product was purified by column chromatography (n-heptane: ethyl acetate = 1: 5) to provide compound 44 (0.5 g). MS ($M + 1 = 354$).

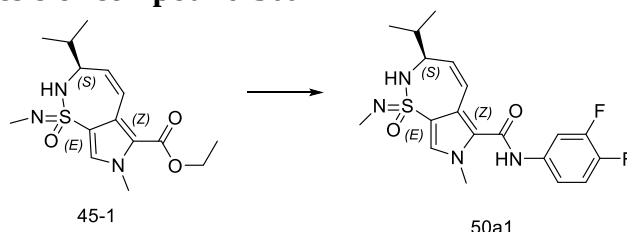
Step 4: Synthesis of Compound 45



Compound 44 (1.0 g) was dissolved in dichloromethane (500 ml), and then

the Zhan Catalyst (0.1 g) was added to the reaction system and stirred overnight. The reaction solution was evaporated in vacuum and crude product was column chromatography (n-heptane: ethyl acetate = 1: 3) purified to provide compound 45. The lower point of the TLC display was 45-1 (0.22 g), and the upper point of the TLC display was 45-2 (0.27 g), MS ($M + 1 = 312$).

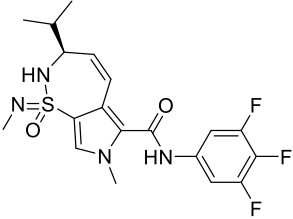
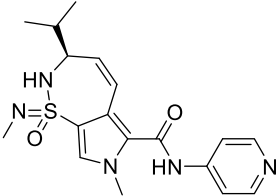
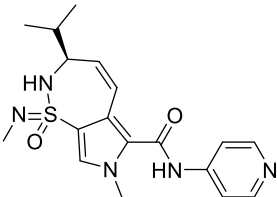
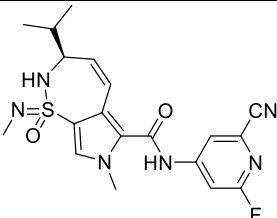
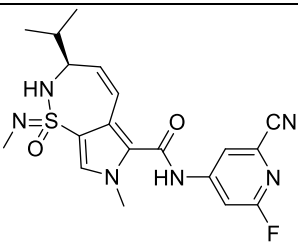
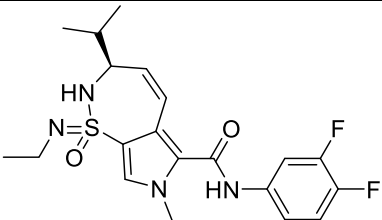
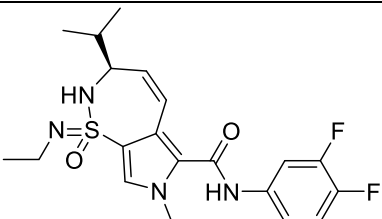
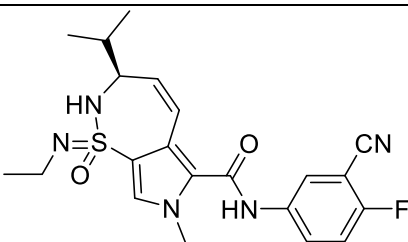
Step 5: Synthesis of compound 50a1

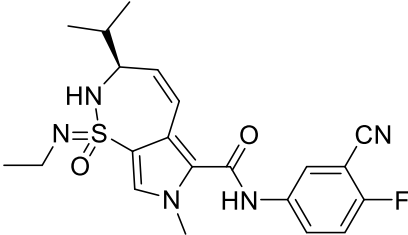
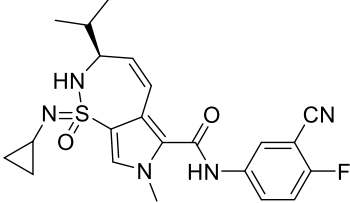
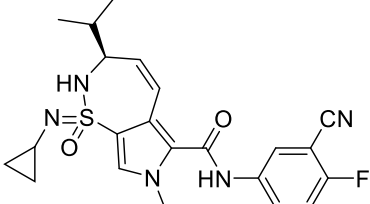
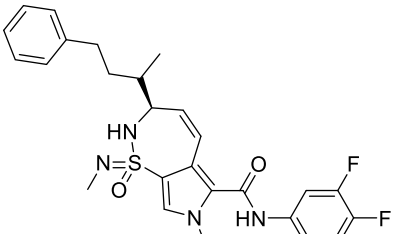
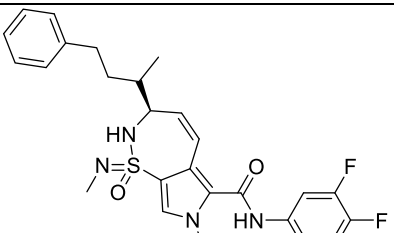
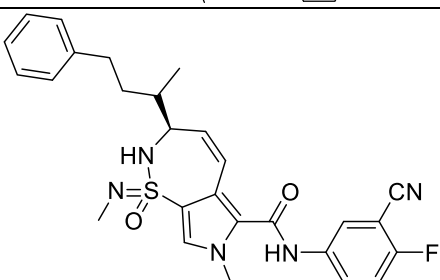
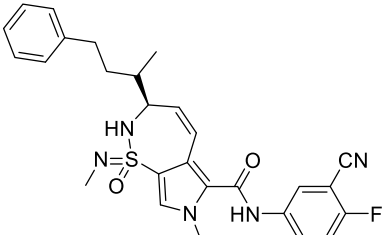


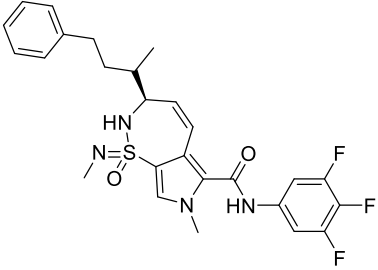
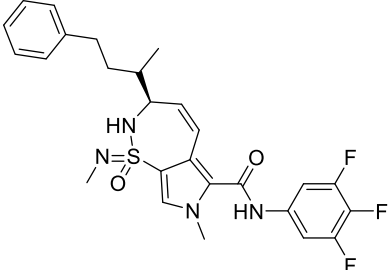
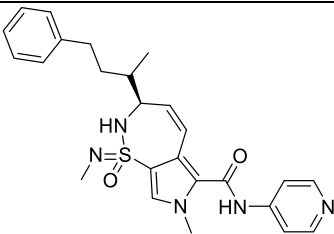
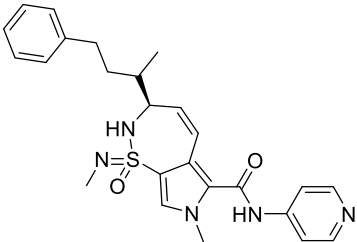
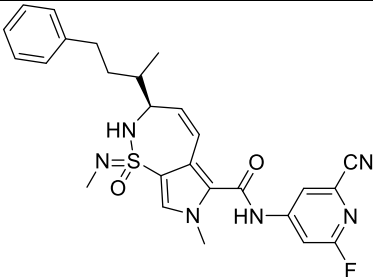
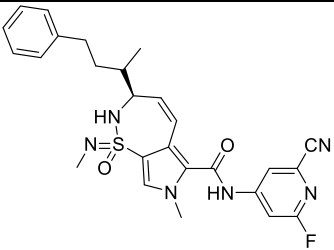
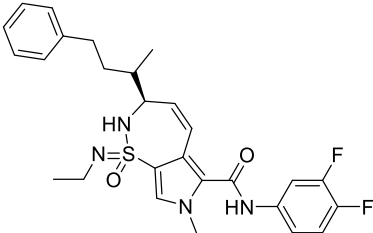
Compound 45-1 (30 mg) and 4-fluoro-3-cyanoaniline (20 mg) were dissolved in THF (5 mL), the system was cooled to 0 °C, and then NaHMDS (0.2 mL) was added to the reaction system. The reaction was stirred at room temperature for 16 h, and water was added to the reaction system. The mixture was extracted with ethyl acetate (3 * 15 mL). The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuum. The crude product was subjected to column chromatography (n-heptane: ethyl acetate = 1: 3) to provide target product 50a1 (11mg). MS ($M + 1 = 409$).

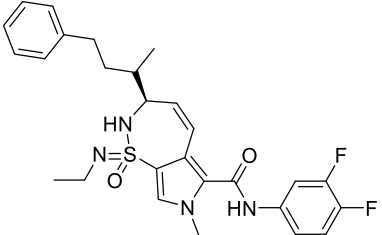
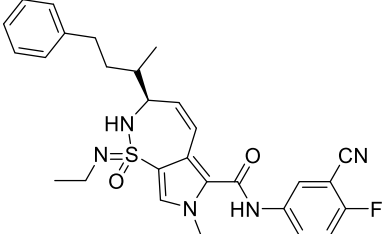
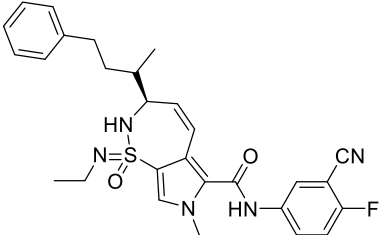
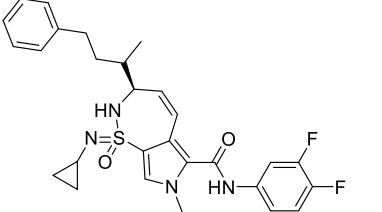
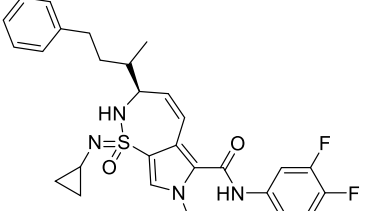
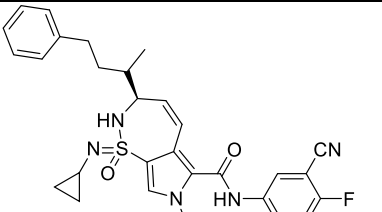
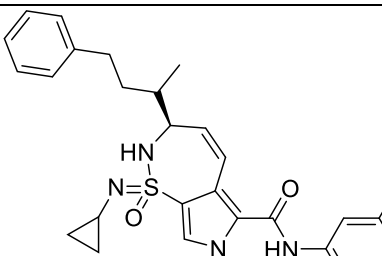
The following 50 series compounds are synthesized according to the method of example 167:

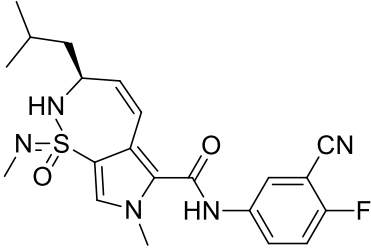
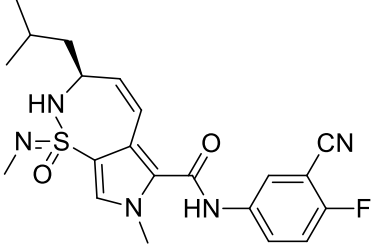
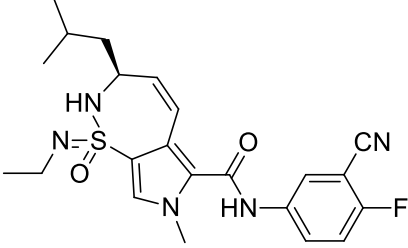
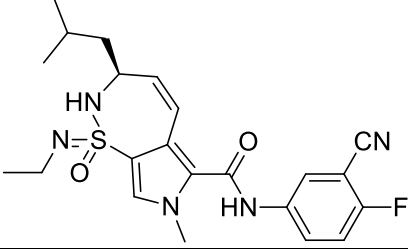
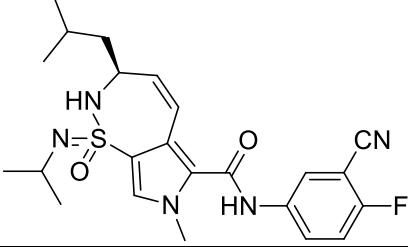
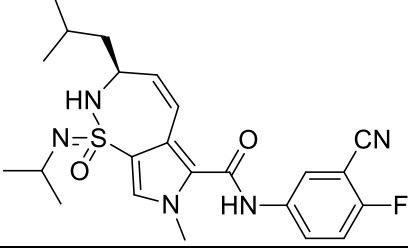
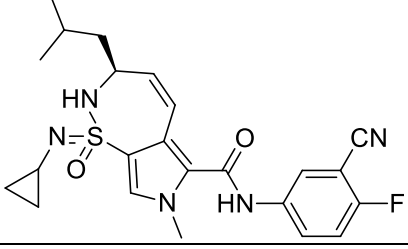
No.	Structure	Mass Spectrum ESI-MS, ($M + H$)	Remark
50b1		416	Peak1 (HPLC)
50b2		416	Peak2 (HPLC)
50c1		413	Peak1 (HPLC)

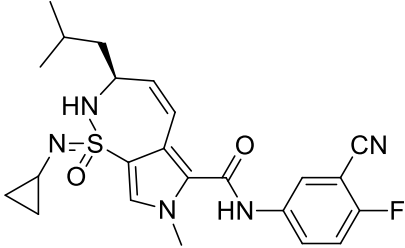
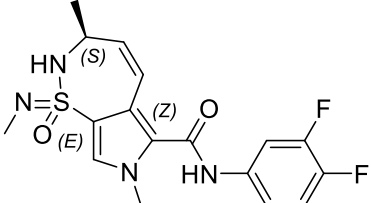
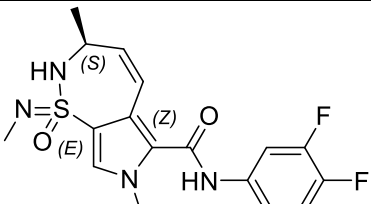
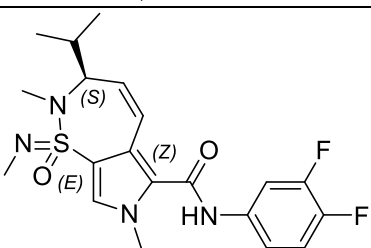
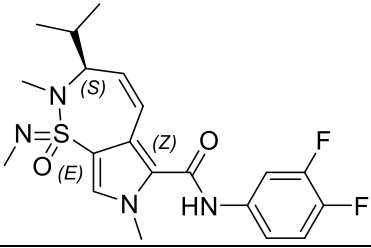
50c2		427	Peak2 (HPLC)
50d1		374	Peak1 (HPLC)
50d2		360	Peak2 (HPLC)
50e1		417	Peak1 (HPLC)
50e2		417	Peak2 (HPLC)
50f1		423	Peak1 (HPLC)
50f2		423	Peak2 (HPLC)
50g1		430	Peak1 (HPLC)

50g2		430	Peak2 (HPLC)
50h1		442	Peak1 (HPLC)
50h2		442	Peak2 (HPLC)
50i1		499	Peak1 (HPLC)
50i2		499	Peak2 (HPLC)
50j1		506	Peak1 (HPLC)
50j2		506	Peak2 (HPLC)

50k1		517	Peak1 (HPLC)
50k2		427	Peak2 (HPLC)
50m1		464	Peak1 (HPLC)
50m2		464	Peak2 (HPLC)
50n1		507	Peak1 (HPLC)
50n2		507	Peak2 (HPLC)
50o1		513	Peak1 (HPLC)

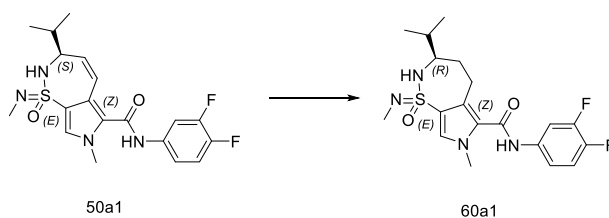
50o2		513	Peak2 (HPLC)
50p1		520	Peak1 (HPLC)
50p2		520	Peak2 (HPLC)
50q1		525	Peak1 (HPLC)
50q2		525	Peak2 (HPLC)
50r1		532	Peak1 (HPLC)
50r2		532	Peak2 (HPLC)

50s1		430	Peak1 (HPLC)
50s2		430	Peak2 (HPLC)
50t1		444	Peak1 (HPLC)
50t2		444	Peak2 (HPLC)
50u1		458	Peak1 (HPLC)
50u2		458	Peak2 (HPLC)
50v1		456	Peak1 (HPLC)

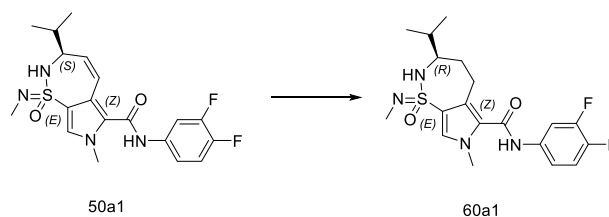
50v2		456	Peak2 (HPLC)
50w1		381	Peak1 (HPLC)
50w2		381	Peak2 (HPLC)
50x1		423	Peak1 (HPLC)
50x2		423	Peak2 (HPLC)

The following are the synthesis of 60 series compounds:

Example 186: Synthesis of compound 60a1



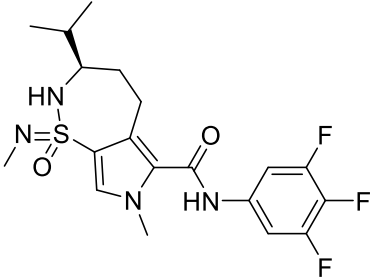
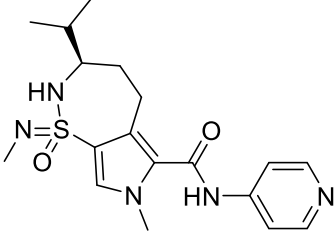
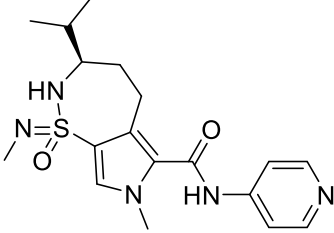
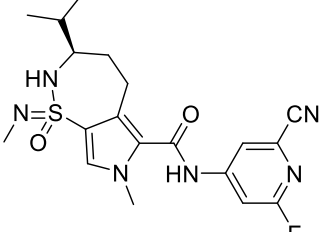
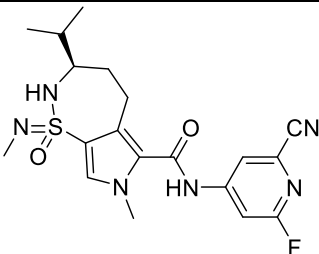
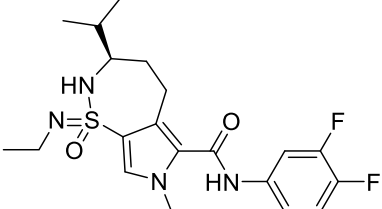
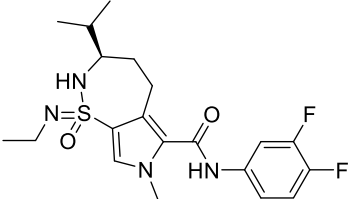
Step 1

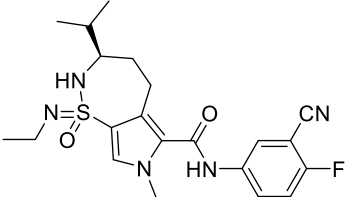
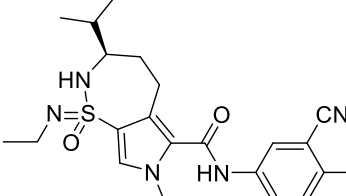
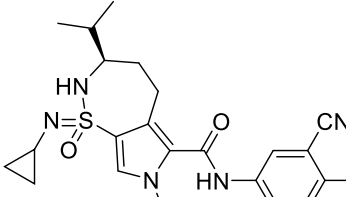
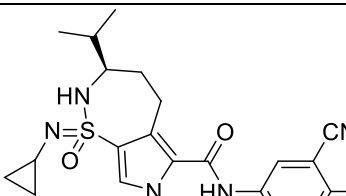
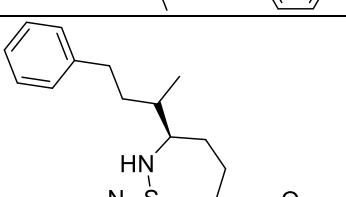
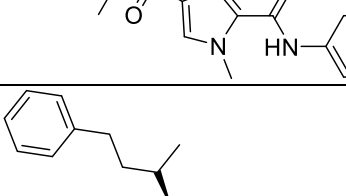
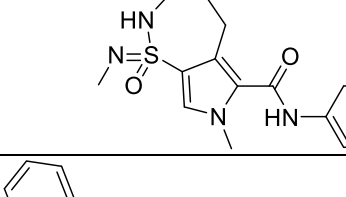


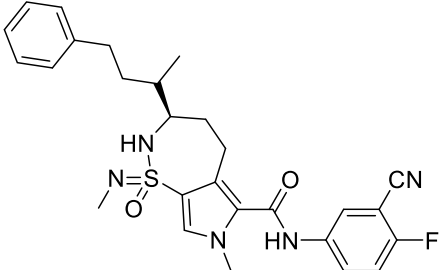
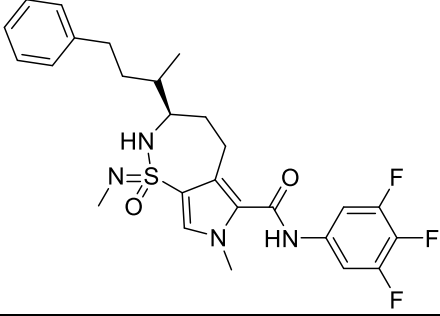
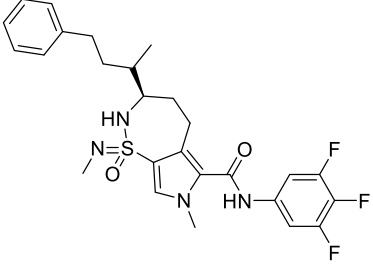
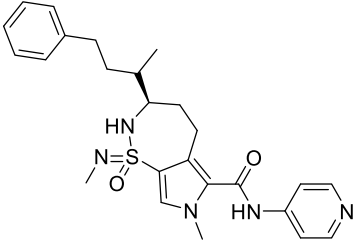
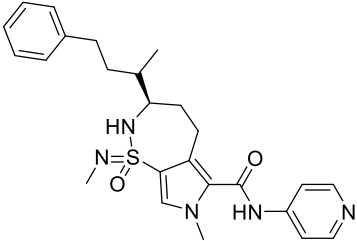
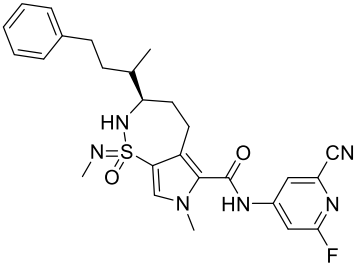
Compound 50a1 (20 mg) was dissolved in methanol (5 mL), and then palladium carbon (5 mg) was added to the reaction system. The reaction was performed at room temperature for 6 h under hydrogen. The crude product was purified by column chromatography (n-heptane: ethyl acetate = 1: 3) to provide the target product 60a1 (11 mg). MS ($M + 1 = 411$)

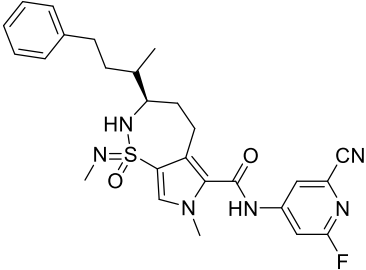
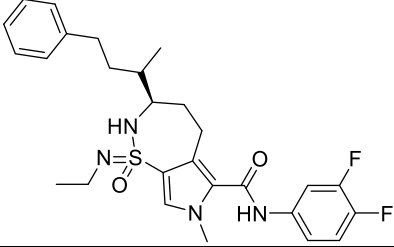
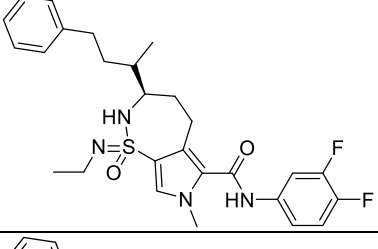
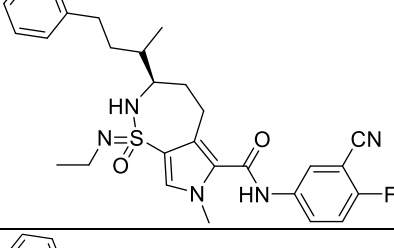
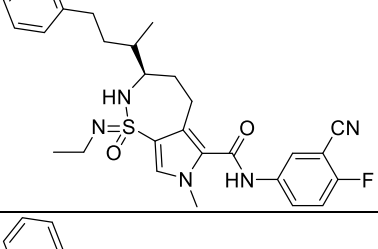
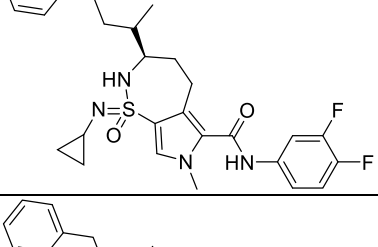
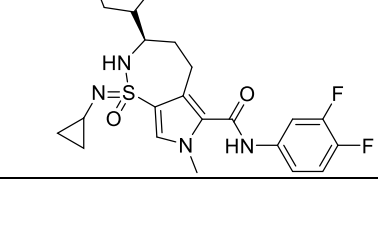
The following 60 series compounds are synthesized according to the method of example 186:

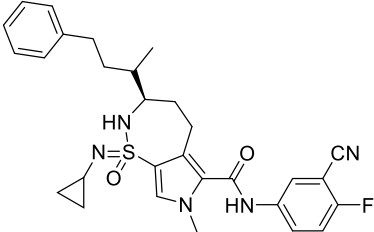
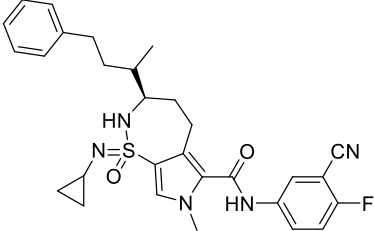
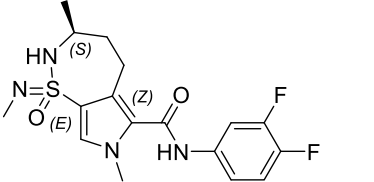
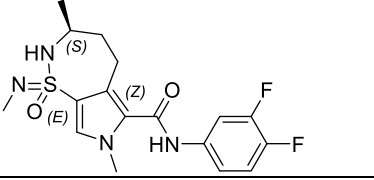
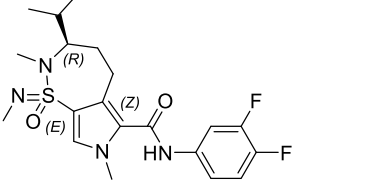
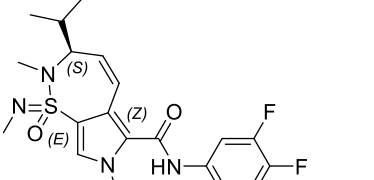
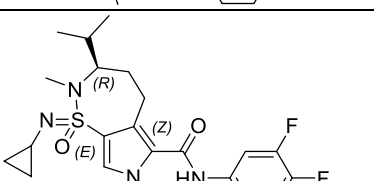
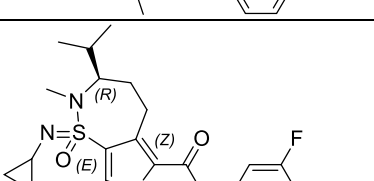
No.	Structure	Mass Spectrum ESI-MS, ($M + H$)	Remark
60a2		411	Peak2 (HPLC)
60b1		418	Peak1 (HPLC)
60b2		418	Peak2 (HPLC)
60c1		429	Peak1 (HPLC)

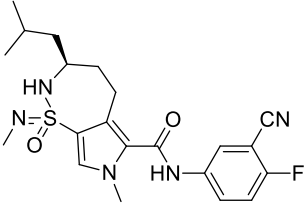
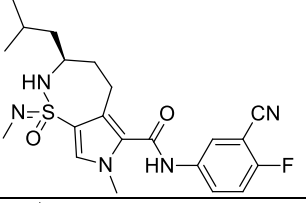
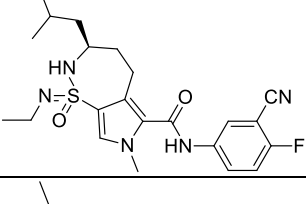
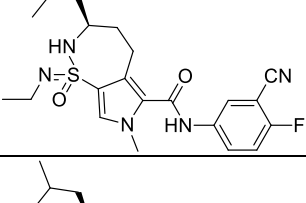
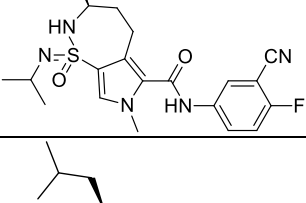
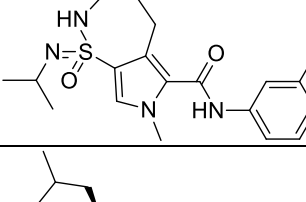
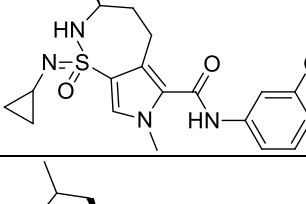
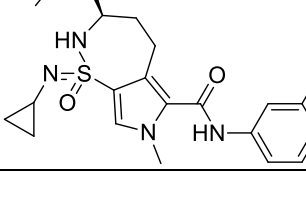
60c2		429	Peak2 (HPLC)
60d1		376	Peak1 (HPLC)
60d2		376	Peak2 (HPLC)
60e1		419	Peak1 (HPLC)
60e2		419	Peak2 (HPLC)
60f1		425	Peak1 (HPLC)
60f2		425	Peak2 (HPLC)

60g1		432	Peak1 (HPLC)
60g2		432	Peak2 (HPLC)
60h1		446	Peak1 (HPLC)
60h2		446	Peak2 (HPLC)
60i1		501	Peak1 (HPLC)
60i2		501	Peak2 (HPLC)
60j1		508	Peak1 (HPLC)

60j2		508	Peak2 (HPLC)
60k1		519	Peak1 (HPLC)
60k2		519	Peak2 (HPLC)
60m1		466	Peak1 (HPLC)
60m2		466	Peak2 (HPLC)
60n1		509	Peak1 (HPLC)

60n2		509	Peak2 (HPLC)
60o1		515	Peak1 (HPLC)
60o2		515	Peak2 (HPLC)
60p1		522	Peak1 (HPLC)
60p2		522	Peak2 (HPLC)
60q1		527	Peak1 (HPLC)
60q2		527	Peak2 (HPLC)

60r1		534	Peak1 (HPLC)
60r2		534	Peak2 (HPLC)
60s1		383	Peak1 (HPLC)
60s2		383	Peak2 (HPLC)
60t1		425	Peak1 (HPLC)
60t2		425	Peak2 (HPLC)
60u1		451	Peak1 (HPLC)
60u2		451	Peak2 (HPLC)

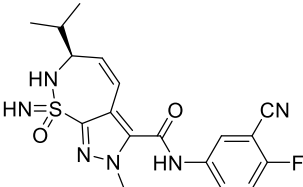
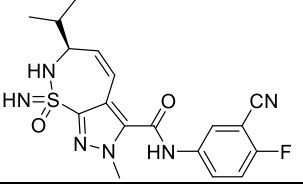
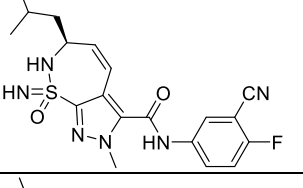
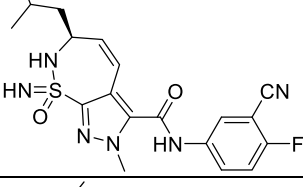
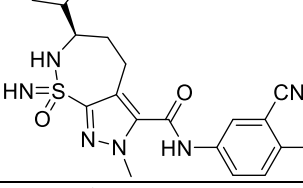
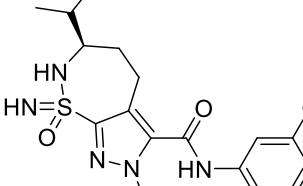
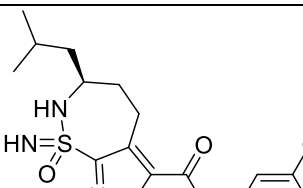
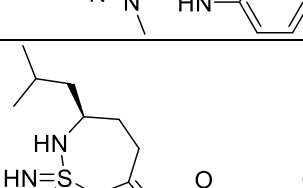
60v1		432	Peak1 (HPLC)
60v2		432	Peak2 (HPLC)
60w1		446	Peak1 (HPLC)
60w2		446	Peak2 (HPLC)
60x1		460	Peak1 (HPLC)
60x2		460	Peak2 (HPLC)
60y1		458	Peak1 (HPLC)
60y2		458	Peak2 (HPLC)

The following are the synthesis of 70, 80 and 90 series compounds:

Example 234: Synthesis of compound 70a1

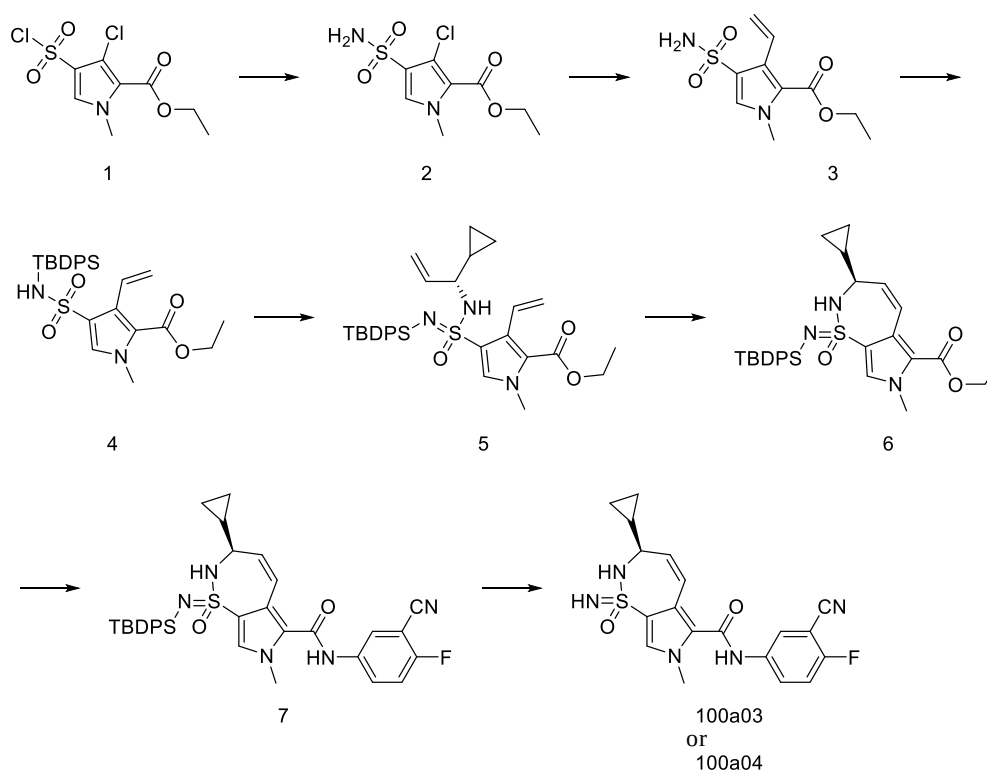
The reaction was carried out according to the example 74 and example 167,

while the pyrrole compounds were replaced with pyrazole compounds to obtain the compounds in the following list.

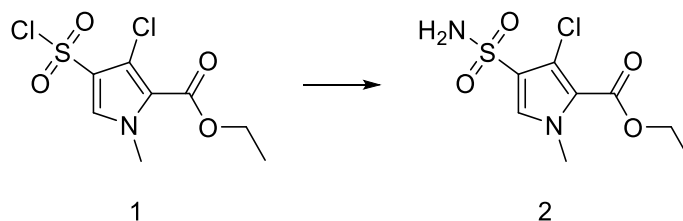
70a1		403	Peak1 (HPLC)
70a2		403	Peak2 (HPLC)
70b1		417	Peak1 (HPLC)
70b2		417	Peak2 (HPLC)
80a1		405	Peak1 (HPLC)
80a2		405	Peak2 (HPLC)
80b1		419	Peak1 (HPLC)
80b2		419	Peak2 (HPLC)

90a1		419	Peak1 (HPLC)
90a2		419	Peak2 (HPLC)
90b1		433	Peak1 (HPLC)
90b2		433	Peak2 (HPLC)

Example 235: Synthesis of compound 100a03 and compound 100a04

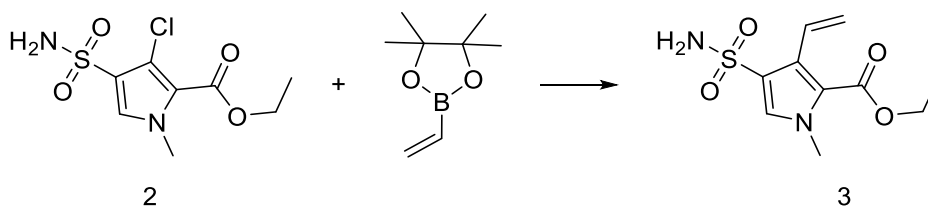


Step 1: Synthesis of compound 2



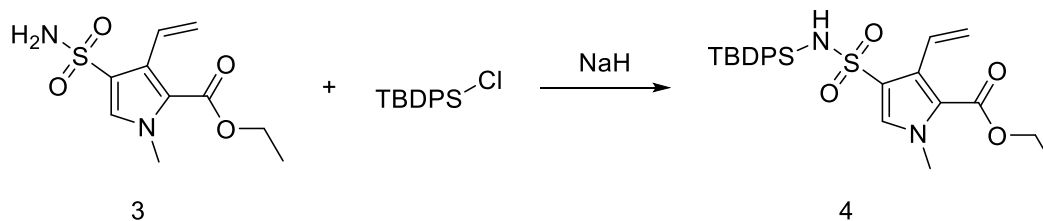
To a solution of compound 1 (10 g) in DCM (40 mL), aqueous ammonia (30 mL) was added dropwise at room temperature. The mixture was then reacted for 5 h, vacuum filtrated, and the residue was washed with water (5 mL) to afford 5 g light yellow solid 2, MS(M+1=267).

Step 2: Synthesis of compound 3



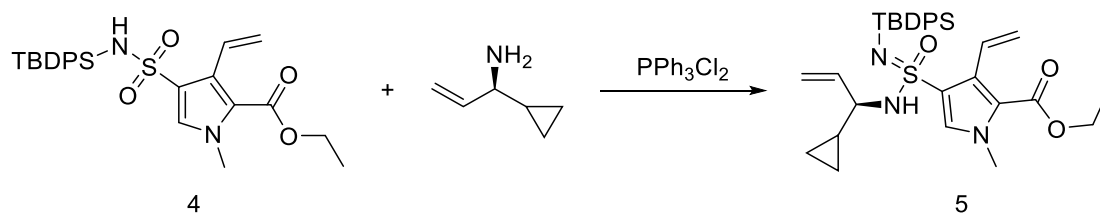
Compound 2 (1.8 g), XPhos PD G3 (100 mg), pinacolboronic acid (3.12 g) and cesium carbonate (2.7 g) were added into DMF (180 mL)/water (18 mL). The resulting solution was reacted under nitrogen protection for 15 h at 100 °C, and quenched with water and extracted with EtOAc. The organic phase was dried and spin-dried. The crude product was purified with column chromatography (n-heptane: ethyl acetate = 1:5) to afford 0.89 g compound 3, MS(M+1=259).

Step 3: Synthesis of compound 4



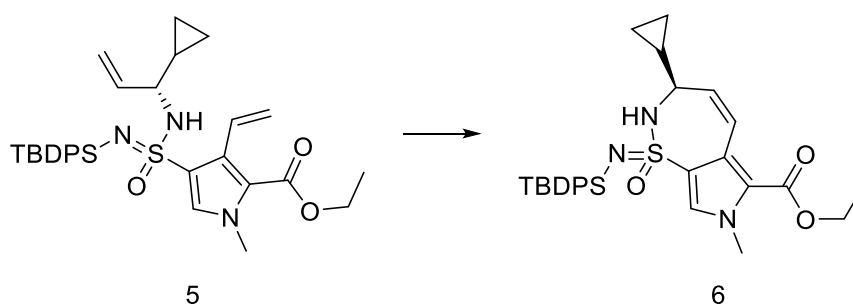
To a solution of substrate 3 (5.0 g) in DMF (50 mL) was added sodium hydride (560 mg) at 0 °C and stirred for 15 min. The mixture was added with TBDPSCl (6.38 g) and reacted for 18 h. The resulting solution was added into iced water and extracted with EtOAc (3*30 mL). The organic phase was dried and spin-dried. The crude product was purified with column chromatography (n-heptane: ethyl acetate = 1:4) to afford 9.03 g compound 4. ¹H NMR (400 MHz, DMSO-d₆) δ 10.78 (s, 1H), 7.62 – 7.59 (m, 1H), 7.45 – 7.41 (m, 1H), 7.33 – 7.29 (m, 3H), 7.13 (qd, J = 4.7, 4.2, 2.5 Hz, 2H), 6.16 (dd, J = 12.4, 2.7 Hz, 1H), 5.58 (dd, J = 12.4, 2.8 Hz, 1H), 5.09 (s, 1H), 4.35–4.40 (m, 2), 3.56 (s, 3H), 1.45–1.40 (m, 3), 1.04 (s, 9H). MS(M+1=497).

Step 4: Synthesis of compound 5



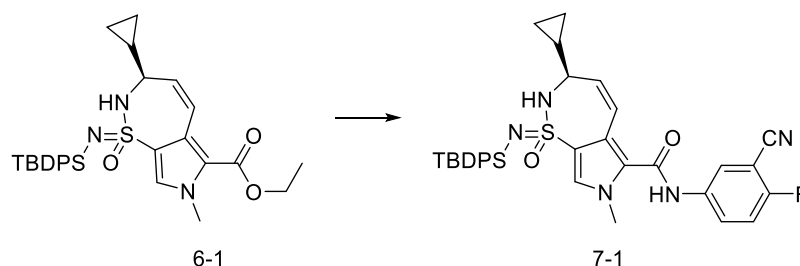
PPh_3Cl_2 (3.63 g) in chloroform (80 mL) was cooled to 0°C and trimethylamine (7 mL) was added and stirred for 10 min. The mixture was added with compound **4** (5.0 g) and stirred for 20 min at 0°C , then (R)-1-cyclopropylpropyl-2-en-1-amine (962 mg) was added. The resulting solution was reacted for 18 h at room temperature and added with water (20 mL) and extracted with EtOAc (3*30 mL). The organic phase was dried and spin-dried. The crude product was purified with column chromatography (n-heptane: ethyl acetate = 1:5) to afford 3.47 g compound **5** as a mixture of a pair of epimers, MS(M+1=585).

Step 5: Synthesis of compound 6



To a solution of compound **5** (1.0 g) in DCM (500 mL) was added Zhan catalyst (0.1 g). The mixture was stirred to reflux and reacted overnight. The reaction solution was spin-dried, and purified with column chromatography (n-heptane: ethyl acetate=1:3) to afford two compounds as chiral isomers of sulfur atom. The upper dot of TLC was compound **6-1** (0.35 g), MS(M+1=548), and the lower dot of TLC is compound **6-2** (0.35 g), MS(M+1=548).

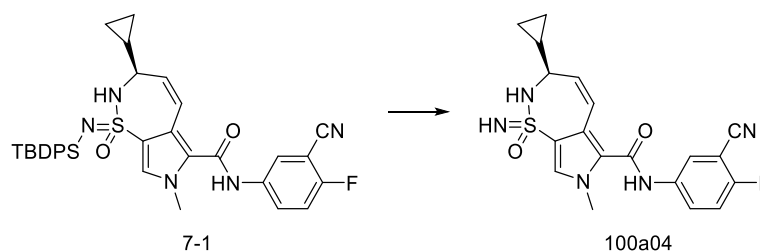
Step 6: Synthesis of compound 7-1



To a solution of compound **6-1** (30 mg), 4-fluoro-3-cyanoaniline (20 mg) in THF (5 mL) was cooled to 0°C , and NaHMDS (0.2 mL) was added and stirred for 16 h at room temperature. The resulting solution was added with water and extracted with EtOAc (3*15 mL). The organic phase was dried with anhydrous sodium sulfate and spin-dried. The crude product was purified with column chromatography (n-heptane: ethyl acetate=1:3) to afford compound **7-1** (11 mg), MS(M+1=638).

The target compound **7-2** was prepared by referring to the aforementioned procedure, by replacing compound **6-1** with compound **6-2**.

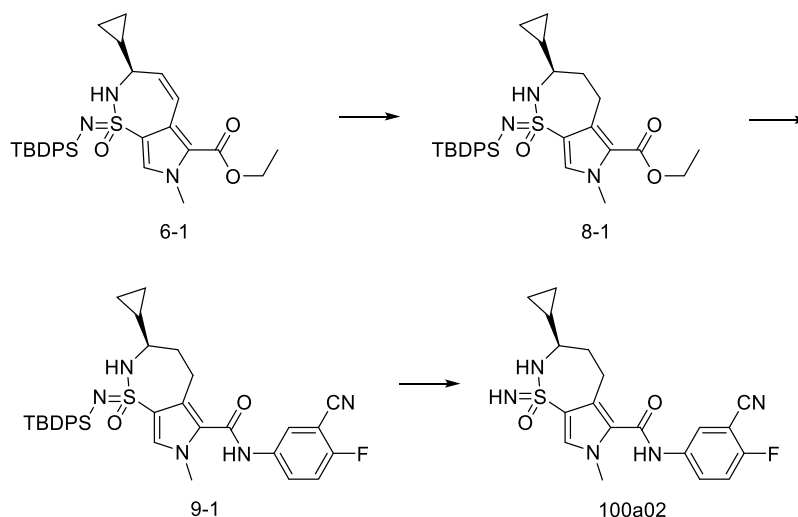
Step 7: Synthesis of compound **100a04**



To a solution of compound **7-1** (40 mg) in THF (3 mL) was added 3HF.TEA (1 mL) dropwise, and reacted for 3 days at room temperature. The resulting solution was separated and purified by preparation TLC to afford compound **100a04** (4.5 mg) as white solid, $m/z = 400(M+1)$.

The target compound **100a03** was prepared according to the aforementioned procedure, by replacing compound **7-1** with compound **7-2**.

Example 236: Synthesis of compound **100a2**



Step 1: Synthesis of compound **8-1**

To a solution of compound **6-1** (500 mg) in EtOAc (10 mL) was added Pd/C (200 mg), and reacted under H_2 at room temperature overnight. The solution was filtrated to remove Pd/C, and the filtrate was concentrated to afford 500 mg compound **8-1** and used directly in the following reaction.

Step 2: Synthesis of compound **9-1**

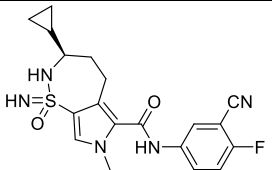
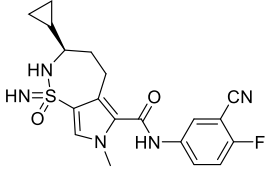
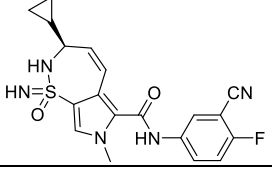
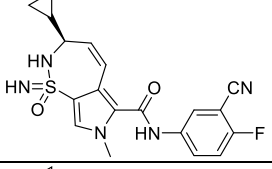
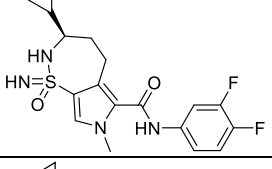
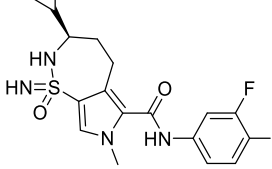
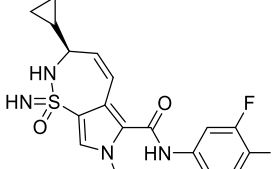
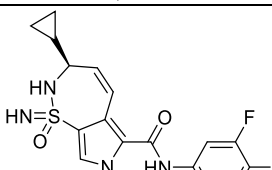
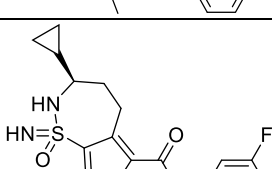
The target compound **9-1** was prepared according to example 1, step 6, by replacing compound **6-1** with compound **8-1**.

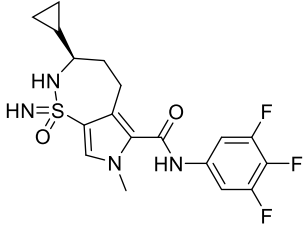
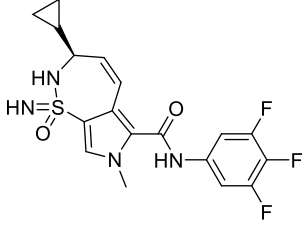
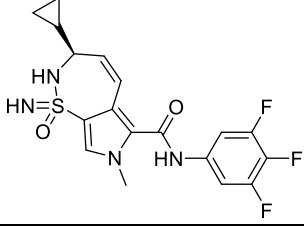
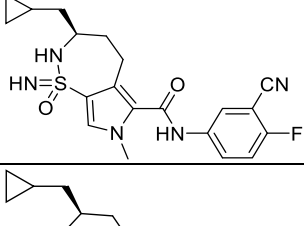
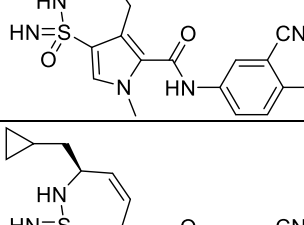
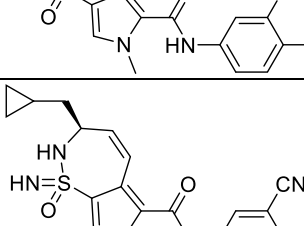
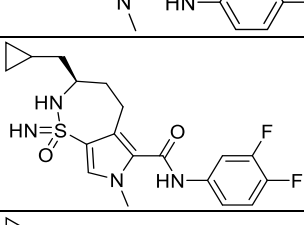
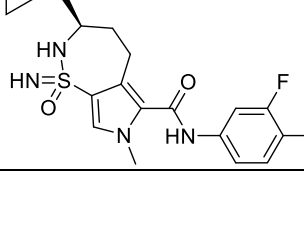
Step 3: Synthesis of compound **100a02**

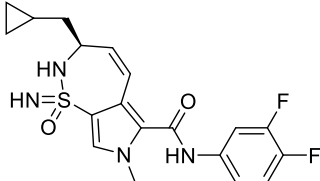
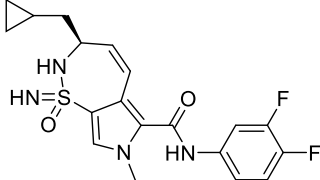
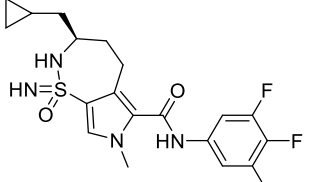
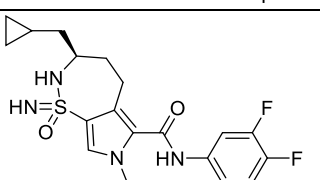
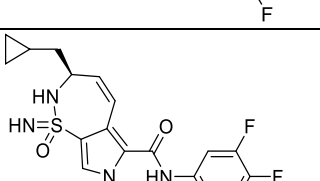
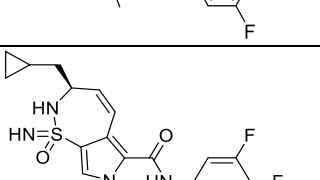
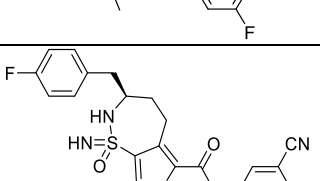
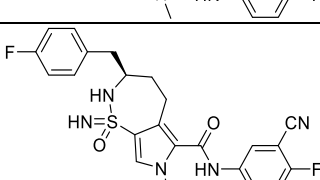
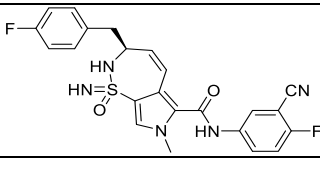
The target compound **100a02** was prepared according to example 1, step 7, by replacing compound **7-1** with compound **9-1**.

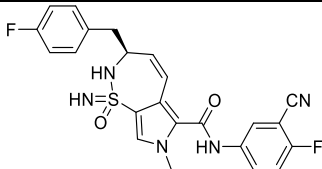
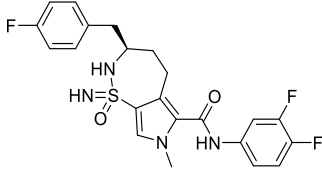
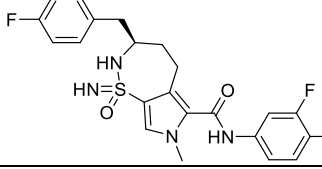
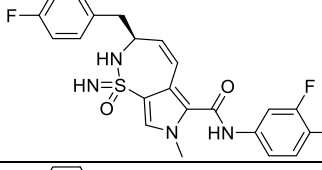
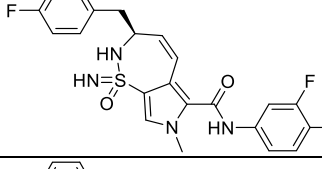
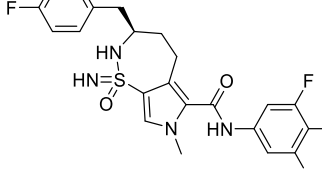
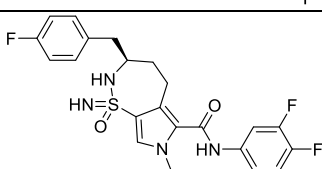
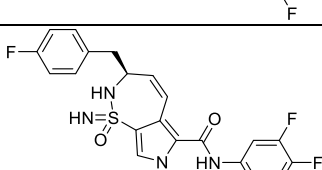
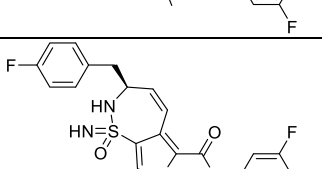
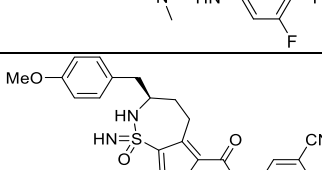
The target compound **100a01-100c20** shown below were prepared by substituting the corresponding ingredients under conditions similar to example

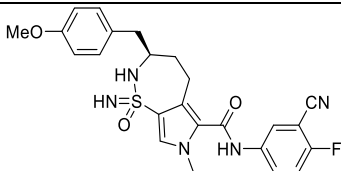
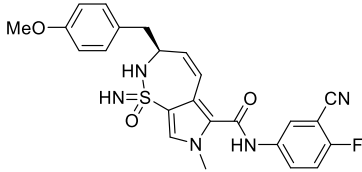
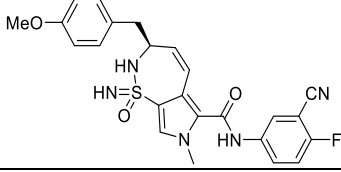
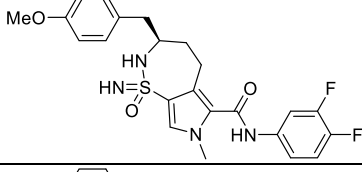
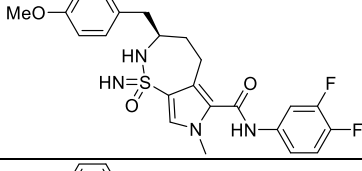
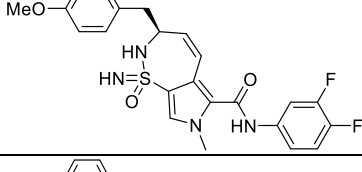
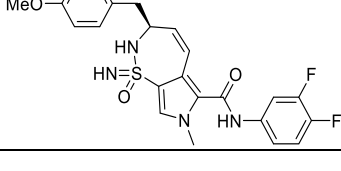
235-236:

100a01		402	Peak1 (HPLC)
100a02		402	Peak2 (HPLC)
100a03		400	Peak1 (HPLC)
100a04		400	Peak2 (HPLC)
100a05		395	Peak1 (HPLC)
100a06		395	Peak2 (HPLC)
100a07		393	Peak1 (HPLC)
100a08		393	Peak2 (HPLC)
100a09		413	Peak1 (HPLC)

100a10		413	Peak2 (HPLC)
100a11		411	Peak1 (HPLC)
100a12		411	Peak2 (HPLC)
100b01		416	Peak1 (HPLC)
100b02		416	Peak2 (HPLC)
100b03		414	Peak1 (HPLC)
100b04		414	Peak2 (HPLC)
100b05		409	Peak1 (HPLC)
100b06		409	Peak2 (HPLC)

100b07		407	Peak1 (HPLC)
100b08		407	Peak2 (HPLC)
100b09		427	Peak1 (HPLC)
100b10		427	Peak2 (HPLC)
100b11		425	Peak1 (HPLC)
100b12		425	Peak2 (HPLC)
100c01		470	Peak1 (HPLC)
100c02		470	Peak2 (HPLC)
100c03		468	Peak1 (HPLC)

100c04		468	Peak2 (HPLC)
100c05		463	Peak1 (HPLC)
100c06		463	Peak2 (HPLC)
100c07		461	Peak1 (HPLC)
100c08		461	Peak2 (HPLC)
100c09		481	Peak1 (HPLC)
100c10		481	Peak2 (HPLC)
100c11		479	Peak1 (HPLC)
100c12		479	Peak2 (HPLC)
100c13		482	Peak1 (HPLC)

100c14		482	Peak2 (HPLC)
100c15		480	Peak1 (HPLC)
100c16		480	Peak2 (HPLC)
100c17		475	Peak1 (HPLC)
100c18		475	Peak2 (HPLC)
100c19		473	Peak1 (HPLC)
100c20		473	Peak2 (HPLC)

HBV Activity Experiment

Experiment 1: *In vitro* anti-HBV nucleocapsid assembly activity test

Main reagents and raw materials:

C150 protein was expressed and purified by WuXi Apptec Co., Ltd;

BoDIPY® FL was purchased from Thermo Fisher Scientific.

Protein fluorescent label:

150 µL of 2% w/v skimmed milk was added into each well of 96-well plate, and incubated at room temperature for 2 hours. The skimmed milk was aspirated. The plate was washed with deionized water and dried, and stored at room temperature. C150 protein (3 mg per tube) was desalted with 5 ml Hitrap desalting column. The desalted C150 protein of each tube was added with 50 mM BoDIPY® FL Fluorescent Dye (20 µl), and incubated under 4 °C overnight in the dark after well mixed. Sephadex G-25 gel was used for filtration to remove fluorescent dyes

that were not bounded onto C150. The C150 fluorescent labeling efficiency was calculated according to the following equation:

$$[\text{BoDIPY@FL}] = A_{504} / 78,000 \text{ M}^{-1};$$

$$[\text{C150Bo}] = (A_{280} - [\text{BoDIPY@FL}] \times 1300 \text{ M}^{-1}) / 60,900 \text{ M}^{-1};$$

$$\text{Fluorescent Labeling Efficiency} = [\text{BoDIPY@FL}] / [\text{C150Bo}];$$

wherein,

[BoDIPY@FL] represents the concentration of the fluorescent label;

[C150Bo] represents the concentration of fluorescently labeled protein;

A₅₀₄ represents the absorbance value at 504nm wavelength;

A₂₈₀ represents the absorbance value at 280nm wavelength;

M⁻¹ represents the reciprocal of the molar concentration.

Compound dilution:

The mother liquor of compound was diluted with DMSO to 6 mM, then diluted to 600 μM with 50 mM HEPES, and then further 3-fold diluted with 10 DMSO / 50 mM HEPES to 8 concentrations.

C150Bo was diluted to 2 μM with 50mM HEPES. 37.5 μL of C150Bo and 2.5 μL of compound at each concentration were added into a 96 well plate and well mixed, then incubated at room temperature for 15 minutes. 10 μl of 750 mM NaCl / 50 mM HEPES were added into the each reaction well, and the final concentration of NaCl was 150 mM.

Into the control wells in the 0% protein group 10 μL of 50 mM HEPES was added, and the final concentration of NaCl was 0 mM.

Into the control wells in the 100% protein group 10 μL of 5 M/ 50 mM HEPES was added, and the final concentration of NaCl was 1 M.

The final concentration of DMSO was 0.5%, the maximum final concentration of the compound was 30 μM, and final concentration of C150Bo was 1.5μM. The mixture was incubated at room temperature for 1 hour. Fluorescence signal was measured (excitation light was 485 nm; emission light was 535 nm).

Data analysis

% protein assembly = [1 - (Sample fluorescence value – 1 M NaCl fluorescence value) / (0 M NaCl fluorescence value - 1 M NaCl fluorescence value)] x 100.

IC₅₀ value was calculated by prism software, and the equation was as follows:

$$Y = \text{Bottom} + (\text{Top}-\text{Bottom}) / (1+10^{((\text{LogIC}_{50}-X)*\text{HillSlope})});$$

wherein,

X represents the logarithm of the concentration, Y represents the effect value, and Y starts from the bottom and fits to the top by S type fitting.

Bottom represents the bottom of the curve;

Top represents the top of the curve;
HillSlope represents the absolute value of the maximum slope of the curve.

Experiment 2: Determination of Anti-HBV Activity in HepG2.2.15 Cell

Main reagents:

QIAamp 96 DNA Blood Kit (12) (Qiagen, Item No. 51162);

FastStart Universal Probe Master (Roche, Item No. 04914058001);

Cell-titer Glo Testing Reagent (Promega, Item No. G7573).

Compound dilution: all the compounds for *in vitro* anti-HBV activity assay and cytotoxicity assay were 3-fold diluted into 8 concentrations. The final starting concentration of the tested compound was 30 μ M, the final starting concentration of reference compound GLS4 was 1 μ M, and the final concentration of DMSO was 0.5%.

HepG2.2.15 cells (4×10^4 cells / well) was inoculated into 96-well plates and cultured overnight at 37 °C, 5% CO₂. On the second day, fresh culture medium containing different concentrations of compounds was added into the culture wells. On the fifth day, the old culture solution in the culture well was aspirated and fresh culture medium containing different concentrations of the compound was added.

On the eighth day, the supernatant in the culture well was collected for extraction of HBV DNA, and the content of HBV DNA in the supernatant of HepG2.2.15 was detected by qPCR. After the supernatant was collected, the medium and Cell-titer Glo reagent were added into the culture well, and the chemiluminescence value of each well was measured by microplate reader.

The activity calculation formula was as follows:

$$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogIC}_{50} - X) * \text{HillSlope})});$$

wherein,

X represents the logarithm of the concentration, Y represents the effect value, and Y starts from the bottom and fits to the top by S type fitting.

Bottom represents the bottom of the curve;

Top represents the top of the curve;

HillSlope represents the absolute value of the maximum slope of the curve.

Experiment 3: Determination of cytotoxicity

The cytotoxicity of the test compound was tested using HepG2 cells. The cells were incubated for 4 days in the presence of the test compound. Cell activity was assessed using the resazurin assay.

The results showed that the compound of the present invention had good anti-HBV nucleocapsid assembly activity and anti-HBV activity *in vitro*, and had low cytotoxicity.

The activity data of experiment 1 to 3 are shown in Table 1:

Table 1

Compound	Experiment 1	Experiment 2	Experiment 3
----------	--------------	--------------	--------------

No.	Protein experiment IC ₅₀ (μM)	Cell experiment EC ₅₀ (nM)	Cytotoxicity CC ₅₀ (nM)
10a1	++	++	>30000
10a2	++	+++	>30000
10b1	++	++	>30000
10b2	++	+++	>30000
10c1	++	++	>30000
10c2	++	+++	>30000
10e1	++	++	>30000
10e2	++	+++	>30000
10f1	++	++	>30000
10f2	++	+++	>30000
10g1	++	++	>30000
10g2	++	+++	>30000
10h1	++	+	>30000
10h2	++	+	>30000
10n1	++	++	>30000
10n2	++	+++	>30000
10o1	++	++	>30000
10o2	++	+++	>30000
10w1	++	++	>30000
10w2	++	+++	>30000
10bb1	++	++	>30000
10bb2	++	+++	>30000
10cc1	++	++	>30000
10cc2	++	+++	>30000
10ccc1	++	++	>30000
10ccc2	++	+++	>30000
10ddd1	++	++	>30000
10ddd2	++	+++	>30000
10vvv1	++	++	>30000
10vvv2	++	+++	>30000
20a1	++	++	>30000
20a2	++	+++	>30000
20b1	++	++	>30000
20b2	++	+++	>30000
20c1	++	++	>30000
20c2	++	+++	>30000
20dd1	++	++	>30000
20dd2	++	+++	>30000
20ee1	++	++	>30000
20ee2	++	+++	>30000
20ccc1	++	+++	>30000
20ccc2	++	+++	>30000
20ttt1	++	++	>30000
20ttt2	++	+++	>30000
30a1	++	++	>30000
30a2	++	++	>30000

30b1	++	++	>30000
30b2	++	++	>30000
30c1	++	++	>30000
30c2	++	++	>30000
30g1	++	++	>30000
30g2	++	++	>30000
40a1	++	++	>30000
40a2	++	++	>30000
40b1	++	++	>30000
40b2	++	++	>30000
40g1	++	++	>30000
40g2	++	++	>30000
50a1	++	++	>30000
50a2	++	+++	>30000
50s1	++	++	>30000
50s2	++	+++	>30000
50t1	++	++	>30000
50t2	++	+++	>30000
50u1	++	++	>30000
50u2	++	+++	>30000
50v1	++	++	>30000
50v2	++	+++	>30000
60a1	++	++	>30000
60a2	++	+++	>30000
60g1	++	++	>30000
60g2	++	+++	>30000
60h1	++	++	>30000
60h2	++	+++	>30000
60v1	++	++	>30000
60v2	++	+++	>30000
60w1	++	++	>30000
60w2	++	+++	>30000
60x1	++	++	>30000
60x2	++	+++	>30000
60y1	++	++	>30000
60y2	++	+++	>30000
70a1	++	++	>30000
70a2	++	+++	>30000
70b1	++	++	>30000
70b2	++	+++	>30000
80a1	++	++	>30000
80a2	++	+++	>30000
80b1	++	++	>30000
80b2	++	+++	>30000
90a1	++	++	>30000
90a2	++	+++	>30000
90b1	++	++	>30000
90b2	++	+++	>30000

100a01	+	++	>30000
100a02	++	+++	>30000
100a04	++	+++	>30000
100b02	++	+++	>30000
100b04	+	+++	>30000
100c02	++	+++	>30000
100c04	+	+++	>30000
100c14	++	+++	>30000
100c16	++	+++	>30000

Within table 1:

Test 1	Test 2
+++ represents IC ₅₀ <1μM; ++ represents IC ₅₀ being 1-100μM; + represents IC ₅₀ being >100μM.	++++represents EC ₅₀ <0.1nM; +++ represents EC ₅₀ being 0.1-100nM; ++ represents EC ₅₀ being 100-1000nM; + represents EC ₅₀ being >1000nM.

Thus, the compounds of the application have excellent anti HBV activity.

Meanwhile, for the compound of the present invention, after being separated by HPLC, the two configuration of compounds based on the chiral sulfur atom center (that is, the S atom in O=S=N-R6) can be effectively separated. The inventors have unexpectedly founded that, between the two configuration compounds based on the chiral sulfur atom center, the enantiomer with less polarity has significantly higher activity against HBV nucleocapsid than the enantiomer with greater polarity, and in some embodiments, and the difference in activity can reach up to several times.

Experiment 4 Example of mouse PK experiment:

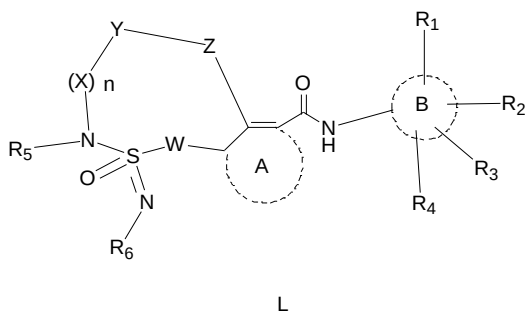
18 male C57 mice (9 intravenously administrated and 9 orally administrated) were randomly grouped according to body weight, and were administered with the test compounds at 2 mg / kg (intravenous) and 50 mg / kg (oral). 3 mice were taken at each time point in each group for a total of 8 time points (5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, and 24 hours). The calculation method of oral bioavailability F was $AUC_{po} / Dose_{po} / AUC_{iv} / Dose_{iv}$.

The compound of the present invention was administrated, and the result showed that each compound showed good bioavailability in *in vivo* experiments, and the bioavailability of some compounds have reached or exceeded 70%.

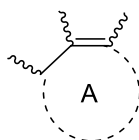
All literatures mentioned in the present application are incorporated herein by reference, as though each one is individually incorporated by reference. Additionally, it should be understood that after reading the above teachings, those skilled in the art can make various changes and modifications to the present invention. These equivalents also fall within the scope defined by the appended claims.

What we claim is:

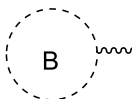
1. A compound represented by formula L, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof,



wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;



is a substituted or unsubstituted five or six membered ring, wherein the five or six membered ring optionally contains one or more heteroatoms selected from the group consisting of O, S, N or P; the substituted means that the hydrogen atoms on the group are substituted by one or more substituents selected from the group consisting of C1-C3 alkyl (especially methyl), C3-C4 cycloalkyl, cyano, or halogen;



is a substituted or unsubstituted five- or six-membered aromatic ring, or a substituted or unsubstituted five- or six-membered heteroaromatic ring;

X is $-CR^aR^b-$;

Y is substituted or unsubstituted C1-C7 alkylene, substituted or unsubstituted C2-C7 alkenylene, wherein, the substituent is selected from the group consisting of C1-C4 alkyl, hydroxyl;

Z is selected from the group consisting of O, S, N, P, or Z is C-C single bond (i.e. Z is none);

W is NR_c or none;

R₁, R₂, R₃ and R₄ are each independently selected from the group consisting of H, halogen, cyano, substituted or unsubstituted C₃-C₄ cycloalkyl, substituted or unsubstituted C₁-C₄ alkyl, substituted or unsubstituted C₁-C₄ alkoxy; wherein the substituted means that hydrogen atoms on the group are substituted by one or more substituents selected from the group consisting of halogen, C₁-C₄ alkyl (such as difluoromethyl, difluoroethyl, monofluoromethyl, trifluoromethyl, trifluoromethoxy);

R⁵, R⁶ are each independently selected from the group consisting of H, halogen, -CN, hydroxyl, amino, carboxyl, -(C=O)-substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₂-C₆ alkenyl, substituted or unsubstituted C₂-C₆ alkynyl, substituted or unsubstituted C₁-C₈ alkylamino, substituted or unsubstituted C₁-C₈ alkoxy, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted 3-10 membered heterocycloalkyl having 1-3 heteroatoms selected from the group consisting of N, S and O, substituted or unsubstituted C₆-C₁₀ aryl, and substituted or unsubstituted 5-10 membered heteroaryl having 1-3 heteroatoms selected from the group consisting of N, S and O;

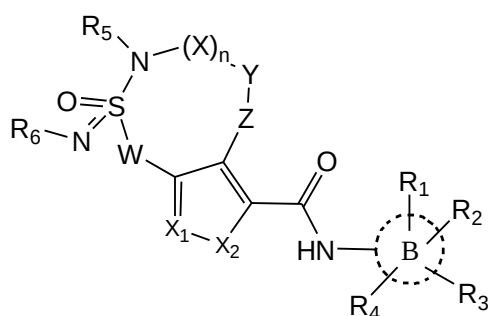
R^a and R^b are each independently H, halogen, -CN, hydroxyl, amino, carboxyl, -(C=O) -substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₂-C₆ alkenyl, substituted or unsubstituted C₂-C₆ alkynyl, substituted or unsubstituted C₁-C₈ alkylamino, substituted or unsubstituted C₁-C₈ alkoxy, substituted or unsubstituted C₁-C₆ alkoxy-alkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted 3-10 membered heterocycloalkyl having 1-3 heteroatoms selected from the group consisting of N, S and O, substituted or unsubstituted C₆-C₁₀ aryl, or substituted or unsubstituted 5-10 membered heteroaryl having 1-3 heteroatoms selected from the group consisting of N, S and O;

R_c is H, halogen, -CN, hydroxyl, amino, carboxyl, -(C=O)-substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₂-C₆ alkenyl, substituted or unsubstituted C₂-C₆ alkynyl, substituted or unsubstituted C₁-C₈ alkylamino, substituted or unsubstituted C₁-C₈ alkoxy, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted 3-10 membered heterocycloalkyl having 1-3 heteroatoms selected from the group consisting of N, S and O, substituted or unsubstituted C₆-C₁₀ aryl, or substituted or unsubstituted 5-10 membered heteroaryl having 1-3 heteroatoms selected from the group consisting of N, S and O;

unless otherwise specified, “substituted” means that the group substituted by one or more (such as 2, 3, 4, etc.) substituents selected from the group consisting of halogen, C₁-C₆ alkyl, halogenated C₁-C₆ alkyl, C₁-C₆ alkoxy, halogenated C₁-C₆

alkoxy, C₃-C₈ cycloalkyl, halogenated C₃-C₈ cycloalkyl, oxo, -CN, hydroxyl, amino, carboxyl, and the following groups unsubstituted or substituted by one or more substituents: C₆-C₁₀ aryl, halogenated C₆-C₁₀ aryl, 5-10 membered heteroaryl having 1-3 heteroatoms selected from the group consisting of N, S and O, halogenated 5-10 membered heteroaryl having 1-3 heteroatoms selected from N, S and O; and the substituent is selected from the group consisting of halogen and C₁-C₆ alkoxy.

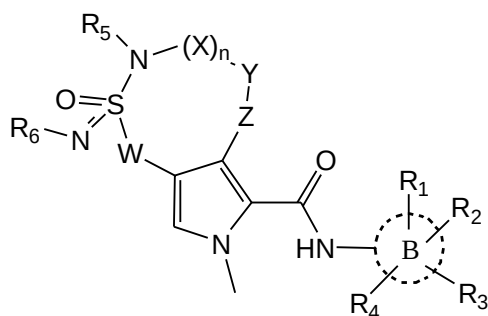
2. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein the compound has a structure according to Formula II:



II

wherein X₁ is -CR= or -N=, X₂ is -NR-; and R is H or C₁-C₄ alkyl.

3. The compound of claim 1, stereoisomers or tautomers thereof, or pharmaceutically acceptable salts, hydrates or solvates thereof, wherein the compound has a structure according to Formula III:



III

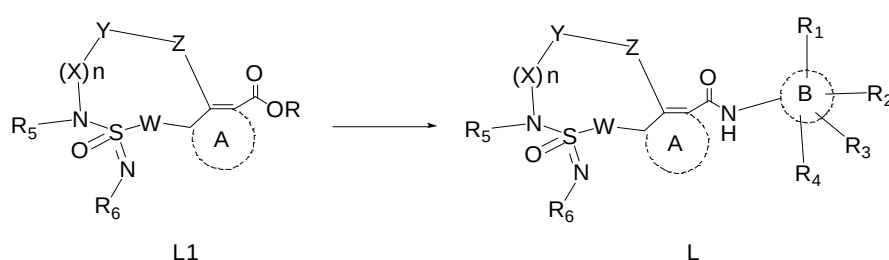
4. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein Ra is selected from the group consisting of substituted or unsubstituted C₁-C₈ alkyl,

substituted or unsubstituted C₁-C₈ alkoxy, substituted or unsubstituted C₁-C₆ alkoxy-alkyl; substituted or unsubstituted C₃-C₆ cycloalkyl, C₁-C₄ alkyl substituted by substituted or unsubstituted C₃-C₆ cycloalkyl, halogenated phenyl, substituted or unsubstituted C₁-C₆ alkoxy-phenyl;

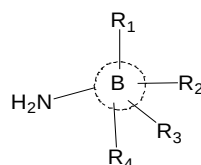
Rb is H.

5. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein the compound is the compound 10a1-100c20 as described in Table 1, wherein Peak 1 and Peak 2 refer to the order of the enantiomers' peaks in reversed-phase HPLC, wherein Peak 1 is the first peak in the enantiomer, and Peak 2 is the latter peak of the enantiomer.

6. A method for preparation of compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein the formula L compound is a compound represented by formula VII-1, and the method comprises the following steps:



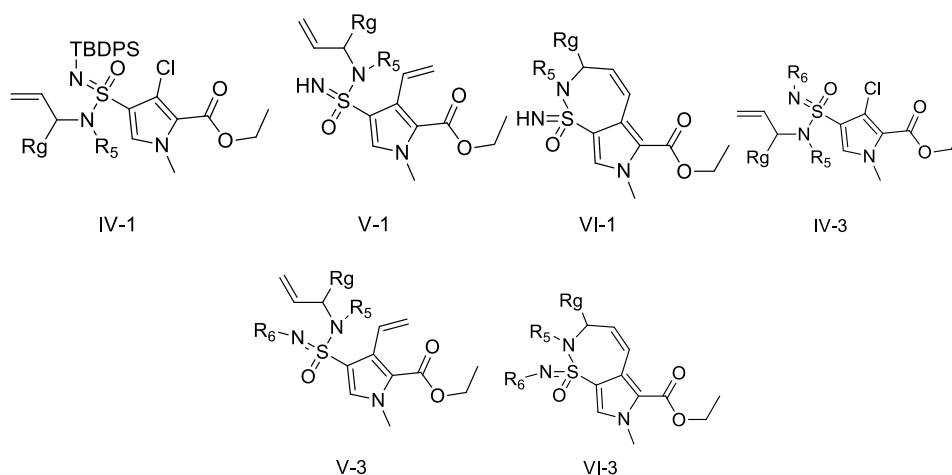
in inert solvents, compound L1 reacts with



to afford the compound according to formula L;

wherein, R is a leaving group, and the remaining groups are defined as described in claim 1.

7. A compound selected from the group consisting of:



in each formula, Rg is selected from the group consisting of H, halogen, -CN, hydroxyl, amino, carboxyl, -(C=O)-substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₂-C₆ alkenyl, substituted or unsubstituted C₂-C₆ alkynyl, substituted or unsubstituted C₁-C₈ alkylamino, substituted or unsubstituted C₁-C₈ alkoxy, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted 3-10 membered heterocycloalkyl having 1-3 heteroatoms selected from the group consisting of N, S and O, substituted or unsubstituted C₆-C₁₀ aryl, and substituted or unsubstituted 5-10 membered heteroaryl having 1-3 heteroatoms selected from the group consisting of N, S and O;

each group is defined as described in claim 1.

8. A pharmaceutical composition, wherein comprises (1) the compound, or the stereoisomer thereof, tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate of claim 1 and (2) pharmaceutically acceptable carriers.

9. A use of the compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof of claim 1, or the pharmaceutical composition of claim 11 in the preparation of a medicine for prevention and/or treatment of hepatitis B virus infection.

10. A hepatitis B virus inhibitor which comprises a compound, or a stereoisomer or a tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof of claim 1.

11. A method for in vitro inhibiting hepatitis B virus, which comprises the step: contacting the compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate or solvate thereof of claim 1 with hepatitis B virus so as to inhibit the replication of hepatitis B virus.